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Review

Clinical Impact of Preoperative Anemia in Patients Undergoing Peripheral Vascular Interventions: A Systematic Review

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Abstract: Introduction: This systematic review aims to summarize the existing evidence relating to preoperative anemia and clinical outcomes in peripheral vascular surgery patients. Methods: The following databases were searched—PubMed, COCHRANE, LILACS, and Science Research—from 1 January 2010 up to 8 May 2020, with the last search performed on 1 January 2021. An additional manual search for potential primary studies was conducted on major journals (e.g., *Anesthesiology*, the *British Journal of Anesthesia* and the *European Journal of Anaesthesiology*) and reference lists of included studies. Google Scholar was also checked for additional eligible studies. Reviewers independently screened potentially eligible articles and extracted data from included studies on populations, interventions, comparisons, and outcomes. This review was registered at PROSPERO as CRD 180954. Results: In total, 6 observational studies with a combined total of 87,327 participants were analyzed. Data collected in this review suggest that preoperative anemia, especially when hemoglobin is <10 g/dL, is associated with an increased risk of red blood cell transfusions (OR: 7.5; 95% CI 6.3–8.9, $p < 0.0001$), limb amputation (OR: 5.2; 95% CI 3.1–8.6, $p < 0.0001$), and death ($p < 0.0031$). Conclusions: These data suggest an association between preoperative anemia, blood transfusion requirements, and other adverse clinical outcomes among patients subjected to peripheral vascular interventions. However, further investigations, particularly randomized controlled trials, are warranted to better understand the association between preoperative anemia and patients' prognosis.

Keywords: preoperative anemia; peripheral vascular interventions; anesthesia; vascular surgery; blood transfusion

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1. Introduction

Anemia is a frequent condition among patients undergoing surgery for peripheral arterial disease (PAD) [1]. The World Health Organization defines anemia as a hemoglobin (Hb) level < 13 g/dL in men and <12 g/dL in women [2]. Anemia has multifactorial causes, including iron deficiency, vitamin deficiency, inflammation, and chronic kidney disease [3]. There is an association between preoperative anemia and adverse clinical outcomes, such as prolonged hospital length of stay and death [4,5]. However, preoperative anemia is frequently unrecognized as a risk factor and, therefore, not corrected before surgical procedures, particularly those associated with major bleeding.

Peripheral arterial disease has been reported to affect more than 200 million individuals worldwide [6], and perioperative data from these patients have demonstrated anemia prevalence rates ranging from 47 to 75% [1–3]. Thus, anemia is a significant problem for the healthcare system, and literature is scant regarding the impact of adequate treatment of anemia during the perioperative period in peripheral vascular surgical patients.

Patients with symptomatic PAD and critical limb ischemia (CLI) have an increased risk of death and cardiovascular events. Advances in medical, surgical, and endovascular techniques have improved these patients' outcomes; however, an optimal management paradigm has not been established [7]. A large retrospective study demonstrated that anemia's prevalence is high among patients undergoing percutaneous peripheral vascular intervention (PVI) and is associated with a significantly greater likelihood of amputation, adverse events, and major cardiovascular complications [8].

Patient Blood Management (PBM) program is a patient-centered interdisciplinary with the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss [9]. Strategies to improve anemia, such as PBM programs, are associated to improved outcomes in various surgical settings [9]. It remains to be determined whether the preoperative clinical optimization of anemic patients can decrease post-PVI adverse events [8,10]. This systematic review summarizes the existing evidence relating to preoperative anemia and clinical outcomes in peripheral vascular surgery patients.

2. Methods

This systematic review of the literature was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [11]. This review was registered at PROSPERO as CRD 180954.

2.1. Eligibility Criteria

We considered all case reports, clinical studies, clinical trials (Phase III and IV), randomized controlled trials (RCTs), pragmatic clinical trials, controlled clinical trials, comparative studies, and multicenter studies. We exclusion criteria were <18 years of age and patients who received red blood cell concentrate transfusion in the preoperative period.

The inclusion criteria for data were as follows: adults, anemic patients with PAD, and preoperative period for peripheral vascular surgery.

The eligible studies reported one or more of the following: number of transfusion packs, the amount of blood transfusion, threshold for transfusion, number of amputations, death 3 months after surgery, hospital length of stay (number of days/weeks), ICU length of stay (number of days/weeks), and bleeding during and or after surgery (volume).

2.2. Data Source and Searches

The search was performed in the following electronic databases from 1 January 2010 to 8 May 2020: PubMed, Cochrane Library, LILACS, and Web of Science. Research filters were applied restricting searches to humans, adults (older than 18 years), and the English language. The last search was performed on 1 January 2021.

The terms used for the search were anemia, iron, erythropoietin, and peripheral arterial disease, peripheral arterial surgery or peripheral vascular intervention, including all synonyms.

In addition, a manual search of the reference lists of potential primary studies was conducted, and several major journals (e.g., *Anesthesiology*, *British Journal of Anesthesia*, and *European Journal of Anaesthesiology*) were hand-searched for additional eligible studies.

2.3. Selection of Studies

Using prestandardized screening forms and protocols, two authors (RML and JEGP) independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated the studies for eligibility.

The software Abstrackr beta (Center for Evidence Synthesis in Health. Brown University, Scholl of Public Health) was used for independent analyses of abstracts. Reviewers resolved disagreement through discussion, with third party adjudication (CDAB) if necessary.

2.4. Data Extraction, the Risk of Bias Assessment, and Certainty of Evidence

The data extraction form included the following characteristics: study design, participants, interventions, outcome event rates, and follow-up. We planned to assess the risk of bias using the risk of bias approach for Cochrane reviews modified by Guyatt [12]. However, this assessment was not possible because no RCTs were completed before the end of our review. For incomplete outcome data, we considered a loss to follow-up of less than 10% and a difference of 5% or less in missing data between the intervention and control groups as a low risk of bias. There was no RCT to be included for GRADE assessment [13–17].

3. Results

3.1. Search Results

We identified a total of 4079 citations (Figure 1). After screening by title, and then by abstract and excluding duplicates, we obtained full-text copies for seven citations that were potentially eligible for inclusion in the review. Of the seven citations, three did not fulfill our eligibility criteria and were excluded. Two additional studies, one study [18] found in the Google Scholar database and another [19] in the *British Medical Journal Open*, were identified and included in this review. No other additional eligible studies were identified on the basis of hand-searching of major anesthesia journals or manual review of reference lists of relevant primary studies and systematic reviews.

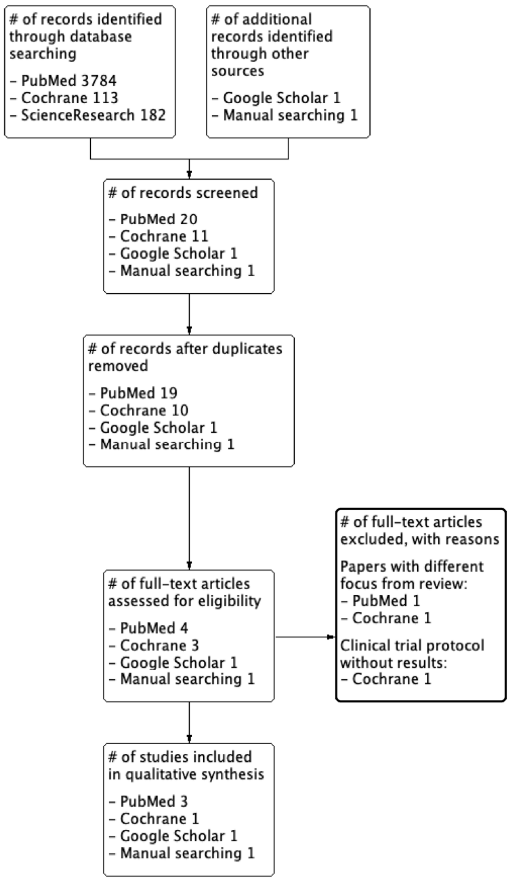

Figure 1. PRISMA graph detailing search results.

3.2. Characteristics of the Included Studies

Our analysis included six observational studies [1,18–22]. Three studies [1,18,19] took place in Europe and three [20–22] were conducted in the USA (Table 1). The total average age was impossible to calculate because three studies excluded age data [1,18,19]. The other three studies had a weighted average of 68.72 years [20–22]. Males represented 58.2%, 59.2%, and 80.1% of the participants in three of the studies [1,20,21], and the other three studies [18,19,22] did not report the percentage of genders. All studies included both men and women.

Table 1. Study characteristics related to population.

Author Year	Country	Type of Study	Number of Randomized Participants or Observational Participants	Mean Age (Years) Per Group Being Studied	Male Gender per Group	Inclusion Criteria	Exclusion Criteria	Follow-up Time (Days)
Mensel (2019) [18]	Denmark	Observational intervention study; ongoing	I: NA C: NA	I: NA C: NA	I: NA C: NA	Iron-deficiency anemic patients in the interventional group; Vascular anemic patients;	NA	Perioperative period
Chau (2017) [19]	UK	Observational intervention study; ongoing	I: 144 C: 288	I: NA C: NA	I: NA C: NA	Patients $\geq$ 18 years old; Undergoing elective cardiac or vascular surgery; Written informed consent	Patients who are pregnant or lactating; Undergoing renal dialysis (current or planned within the next 12 months); Prisoners; Patients with history of learning disabilities; Adults without mental capacity to consent for themselves.	30 days
Henke (2017) [20]	USA	Prospective, multicenter observational	Total of 23,273; cases between 2010 and 2014 at 47 hospitals	No transfusion patients: 68.3 $\pm$ 11.4 Transfusion patients: 71.5 $\pm$ 12.2	No transfusion patients: 13,152 (59%) Transfusion patients: 413 (41.9%)	All patients undergoing elective, urgent, or emergent percutaneous vascular interventions	Age < 18 years old; Critical missing variables; Patients under primary renal, mesenteric, and carotid artery stenting; Hybrid open surgical–endoluminal therapy	Measure until hospital discharge (median of 24 h)
Esteban (2019) [1]	Spain	Retrospective multicentric observational	A total of 518; cases between 1 February 2014 and 31 March 2014 at 12 vascular surgery units	NA	414 (80.1%)	Patients under vascular surgery, in 12 vascular surgery units within the 2 months preceding the study	Emergency surgery; carotid surgery; surgery under ischemic stroke; Patients who had been readmitted to the clinic, to avoid duplicate cases	At least 1 year
Kolte (2017) [21]	USA	Retrospective observational	60,998; 2013 to 2014 cases of Nationwide Readmissions Database	68.9 $\pm$ 11.9	36,110 (59.2%)	Readmissions after critical limb ischemia hospitalization Between 2013 and 2014	Discharge month: December; The patient died during the index hospitalization; Carotid surgery; Discharge was unknown or patient left against medical advice; No endovascular or surgical revascularization or amputation was performed during hospitalization; The patient had two hospitalizations within a 30 day period	Readmissions. 30-day readmissions were 20.4%
Kougias (2017) [22]	USA	Retrospective observational	2106 patients; 2508 surgeries	67 $\pm$ 8.1	NA	Elective open procedures for occlusive vascular disease; Open or endovascular aneurysm repair; From May 2008 to December 2015	Patients undergoing peripheral endovascular only interventions; Hemodialysis; Venous interventions	Postoperative period

NA: Not Available. UK: United Kingdom. Hb: hemoglobin.

3.3. Observational Prospective Studies

Three prospective studies involved preoperative anemia [18–20]. Mensel et al. conducted a study in Denmark [18], Chau et al. conducted a study in the United Kingdom [19], and Henke et al. conducted a study in the USA [20].

The Mensel et al. trial was on preoperative anemia optimization to reduce blood transfusions during surgery and postoperative complications, in vascular patients [18]. This observational interventional study had a 3-month controlled period followed by a 3-month intervention period. There were no data regarding the demographics of the population included in the preliminary results. The authors described anemia in 24% of all vascular patients and, specifically, in 27% of patients admitted for peripheral surgery. Iron-deficiency anemia was demonstrated in 18% of peripheral surgery patients. Packed red blood cells were administered to 16% of peripheral surgery patients. The total number of transfusions was higher among anemic patients, although details were not provided. The study concluded that vascular surgery patients have a high prevalence of anemia and myocardial injury, and red blood cell transfusions were frequent during and after surgery.

Chau et al. conducted a multicenter observational study in patients awaiting major cardiac or vascular surgery. The manuscript is in the submission process for publication, but the data were not available for review. The information focuses on the protocol [19]. Two cohorts were present. In the first cohort, the researchers examined the effect of anemia and outcomes (cohort 1, control arm), and the effect of treatment with intravenous iron on anemia (cohort 2, study arm) was assessed. The researchers expected to recruit 72 cardiac and 72 vascular surgery patients for the study arm (cohort 2). A control arm consisting of 288 patients (anemic and nonanemic) was planned. This study examined different hematologic variables (especially hepcidin), functional capacity, and patient outcomes. Patients were compared based on their anemia status, whether they received intravenous iron according to the hospital's preoperative pathway, and the disease group. The primary outcomes were the change in hemoglobin level from baseline (before treatment) to before surgery, the number of successful patients who were recruited and who consented, and the feasibility of studying patients for a future planned RCT. The secondary outcomes included changes in iron-deficiency biomarkers (hepcidin, ferritin, and transferrin saturation), length of stay, quality of life, and postoperative recovery.

Henke et al. analyzed data from 23,273 male and female patients between 2010 and 2014 at 47 hospitals [20]. The mean age was 71.5 years in the patients who were transfused and 68.3 years in those who were not. All patients underwent elective, urgent, or emergency PVI surgery. This study investigated the association of periprocedural blood transfusion with morbidity and mortality in patients undergoing percutaneous lower extremity vascular intervention. A total of 4.2% (n = 985) of the patients received periprocedural blood transfusions, and of these, 93.5% were given transfusions postprocedurally. Patients who received transfusions had multiple baseline differences compared to those not receiving a transfusion. Transfused patients were more likely to be older, females, African Americans, and have a lower BMI. Of note, nonsmokers were more likely to be transfused than current smokers. The medical conditions associated with blood transfusion requirement included preprocedural anemia, hypertension, diabetes mellitus, congestive heart failure, valve disease, chronic lung disease, coronary artery disease, current GI bleeding, atrial fibrillation, history of a cerebrovascular accident or transient ischemic attack, and renal failure requiring hemodialysis. Hyperlipidemia was uncommon among transfused patients. The results revealed that preprocedural anemia was an independent factor for perioperative blood transfusion.

We retrieved data from the Henke study and performed a post hoc analysis calculating the OR between preoperative anemia and blood transfusion. We found a 7.5-fold increase (95% CI, 6.3–8.9; $p < 0.0001$) in the risk of blood transfusion requirements among patients presenting with anemia preoperatively (Table 2) [20]. The OR was calculated using the MedCalc software® (MedCalc software Ltd. Ostend, Belgium).

Table 2. Adapted from Henke Study [20] comparing periprocedural transfusion between preoperative anemic and nonanemic patients.

	Transfusion	No Transfusion	Total
Anemic	820	8851	9671
Nonanemic	165	13,437	13,602

Post hoc analysis: the odds ratio between preoperative anemia and blood transfusion demonstrated a 7.5-fold (95% CI 6.3–8.9, $p < 0.0001$) increase in risk of transfusion.

3.4. Observational Retrospective Studies

Three retrospective studies involved perioperative anemia [1,21,22]. A total of 63,622 patients were distributed across two countries (USA and Spain), with average ages of 68.9 ± 11.9 [21] and 67 ± 8.1 years [22]. No data were provided about age in the Esteban study [1]. The gender distribution in the studies was as follows: 80.1% males in the Esteban study, 59.2% males in the Kolte study [21], and no data available from the Kougias study [22].

The Esteban et al. study included 518 patients and studied the correlation between vascular surgery, preoperative anemia, and cardiovascular outcomes. The global prevalence of preoperative anemia was 54.4% (282/518), 63.6% (255/401) among patients with lower limb ischemia, and 23.1% (27/117) in patients with aneurysms. The prevalence of anemia significantly increased one year after surgery (total prevalence of 64.7% [335/518], 68.8% [276/401] in patients with lower limb ischemia, and 50.4% [59/117] in patients treated for an aneurysm).

Preoperative anemia, especially when the Hb was <10 g/dL, was associated with an increased risk of death and amputation. An analysis with ROC curves was performed to calculate the Hb level that better discriminated patient survival. This value was calculated to be 10 g/dL. Patients presenting with Hb levels ≤ 10 g/dL at the preoperative period represented 15.1% of the total, and 63% (49/78) of them had to undergo amputation. In contrast, among those with Hb levels > 10 g/dL, only 25% (108/440) required amputation (OR: 5.2; 95% CI, 3.1–8.6; $p < 0.0001$—post hoc analysis, MedCalc software®). The survival curve analyzing the time elapsed between the vascular surgery and the last follow-up visit or death was significantly different based on the Hb levels (≤10 g/dL vs. >10 g/dL). Specifically, Hb concentrations ≤ 10 g/dl were associated with decreased survival rates ($p < 0.0031$)—90.5% versus 96.4%, 30 days after the procedure and 78.6% versus 86.2% at one year.

Kolte et al. [21] demonstrated that anemia was an independent risk factor for the 30-day hospital readmission rate after surgical treatment of critical limb ischemia. The study included 60,998 index CLI hospitalizations (mean age, 68.9 ± 11.9 years; 40.8% women; 24.6% for rest pain, 37.2% for ulcers, and 38.2% for gangrene). The 30-day readmission rate was 20.4%. Independent predictors of 30-day readmission were the presence of ulcers or gangrene, age greater than or equal to 65 years, female sex, large hospital size, teaching hospital status, known coronary artery disease, heart failure, diabetes mellitus, chronic kidney disease, anemia, coagulopathy, obesity, major bleeding, acute myocardial infarction, vascular complications, and sepsis.

Kougias et al. analyzed the effect of postoperative anemia and baseline cardiac risk on adverse outcomes after major vascular interventions in patients who underwent elective open procedures for occlusive vascular disease and open or endovascular aneurysm repair [22]. A total of 2508 operations performed during 8 years in 2106 patients with a mean age of 67 years (range, 45–90 years) were analyzed.

A fully adjusted multivariable model demonstrated that low values of Hb increased the risk of the composite of mortality or major ischemic events (myocardial infarction, stroke, acute kidney injury, or coronary revascularization) within 90 days from the primary surgery (odds ratio (OR), 1.24; $p < 0.001$), representing a 24% increase in the odds of the composite end point for each 1 g/dL decrease in Hb. No interaction term between transfusion and Hb was statistically significant, indicating that anemia's harmful effect was independent of blood transfusion. Low values of Hb also increased the risk of respiratory

complications (OR, 1.41; $p = 0.002$) and ICU length of stay (LoS) (average, 2.6-day increase per 1 g/dL decrease in Hb; $p < 0.0001$).

4. Discussion

This systematic review showed that preoperative anemia in patients subjected to peripheral vascular surgery confers an increased risk of perioperative blood transfusion, limb amputation, and death. Our analysis of six observational studies strongly suggests that low levels of Hb in the postoperative period increase the risk of the composite of mortality or major ischemic events. These findings agree with data from studies investigating the association between anemia and adverse outcomes in other surgical specialties, such as orthopedics and major surgery [23–25]. The authors found that preoperative anemia and perioperative allogeneic blood transfusion (ABT) were independent risk factors for postoperative mortality, ischemia, and infections. Moreover, in one study analyzed in this review, anemia was an independent risk factor for 30-day hospital readmission in CLI patients.

Preoperative anemia is a risk predictor of perioperative transfusion of allogeneic blood products, which carries a significant risk of adverse events and mortality [26,27]. In critically ill and surgical patients, transfusion of a single unit of packed [26,27] red blood cells increased the multivariate risk of mortality, wound problems, pulmonary complications, postoperative renal dysfunction, systemic sepsis, composite morbidity, and prolonged postoperative LoS compared to propensity-matched patients who did not receive intraoperative ABT (Figure 2). Further concerns have been raised that ABT is associated with recurrence in cancer surgery [5]. Data from an observational cohort of 2,087,423 primary total hip arthroplasties showed that ABT was independently associated with an extended length of hospital stay, increased costs, and worse surgical and medical outcomes without affecting the in-hospital mortality rate. Moreover, the adverse effects of blood loss, ABT, and preoperative anemia are synergistic [5]. Orthopedic patients, similarly to vascular disease patients, are, to a great extent, a frail population. They both present a similar array of comorbidities, and therefore, this interesting correlation of worse outcomes and anemia is clearly evident across both our systematic review and Munõz's observational study [5].

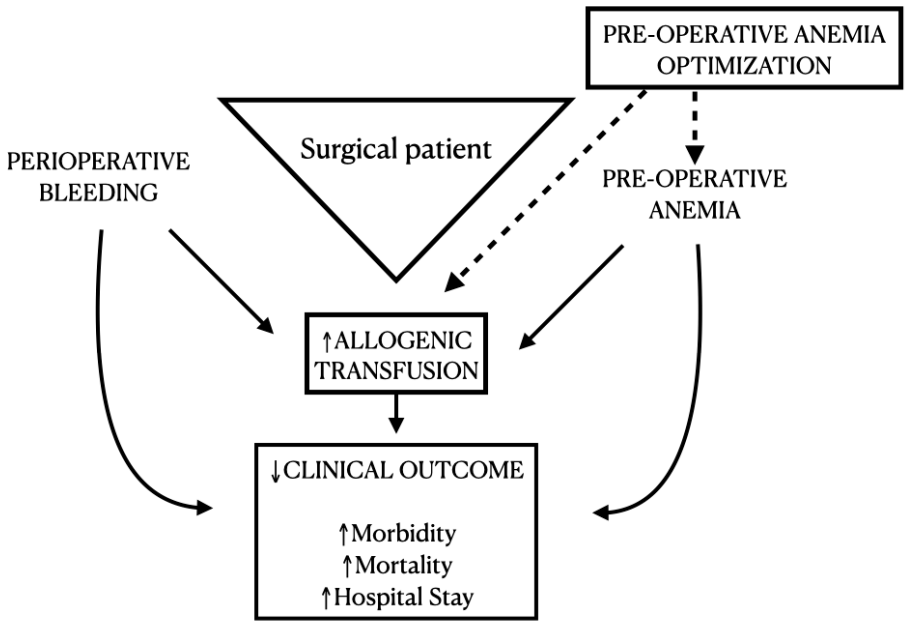

Figure 2. Effects of anemia, bleeding, and allogeneic transfusion on clinical outcomes in patients undergoing major surgery. Preoperative anemia optimization may have positive effects (dashed line). Adapted from Muñoz et al. [2].

The European Society of Anaesthesiology recommends that patients at risk of bleeding should be assessed for anemia 3–8 weeks before surgery. Although it is possible to investigate and address anemia preoperatively, it should be noted that many surgical patients require urgent intervention. Therefore, the time available for the assessment and correction of anemia is limited at times [26,27]. Anemia prevalence due to iron or vitamin deficiency among patients with critical limb ischemia is high. Therefore, we recommend a systematic approach in preoperative management to measure biomarkers of iron deficiencies, such as ferritin, transferrin saturation, iron, iron-binding capacity, vitamin B12, and folate. The cause of anemia should be assessed and treated before the intervention, and therefore, blood transfusion might be minimized [28,29]. Advances in pharmaceutical technologies results newer iron formulations, which in turn decrease problems inherent with traditional approaches [30]. New oral preparations as effective as standard ferrous sulfate, but better tolerated, are in active research. In other hand, new preparations have entered the clinical scenario, which can be collectively named as "third generation" IV iron compounds. These preparations share common technical features conferring superiority over the older products, allowing giving the total replacement dose (usually 1–1.5 g) in just one or two infusions [30].

A study from Diez [31] is ongoing, and its results can clarify certain aspects of anemia optimization and clinical outcomes in endovascular or vascular patients. This trial is measuring outcomes (red blood cell requirements, changes, and evolution of hemoglobin, establishing the optimal preoperative timing for intravenous iron administration to yield the ideal increase in Hb; the impact of anemia and its treatment on the length of hospital stay, morbidity, mortality, and quality of life) in anemic patients with chronic lower limb ischemia. These patients will undergo endovascular or open surgical techniques, and revascularization surgery scheduled ≥ 1 week from the inclusion data. The intervention group receives a single dose of carboxymaltose (1000 mg intravenously) 1 week before surgery. The control group receives standard care or oral iron in severe iron-deficiency anemia at the time of hospital admission. Chau et al., in a partial publication, investigated the impact of intravenous iron treatment in anemic patients undergoing cardiac and vascular surgeries, and valuable information can be yielded from their study [19].

Limitations

Our study encompassed a comprehensive literature search and a systematic approach to assess the studies' eligibility independently and in duplicate.

Our findings show a strong correlation between preoperative anemia and blood product requirements and between preoperative anemia and adverse outcomes in PVI patients.

Our search did not retrieve clinical prospective trials or observational studies addressing preoperative anemia optimization, or other PBM treatment, in patients undergoing peripheral vascular interventions. This fact highlights the urgent need for clinical trials addressing the clinical impact of anemia optimization in patients undergoing lower limb revascularization.

5. Conclusions

Our study confirms that the screening and clinical evaluation of anemia should be considered a key objective in patients with peripheral arterial vascular disease during the preoperative period. Preoperative anemia, blood transfusion requirement, and adverse outcomes have a strong association in this setting. Our systematic review revealed the scarcity of data regarding anemia correction and outcome in patients submitted to lower limb revascularization. Thus, large multicenter randomized controlled trials are necessary to provide consistent evidence about anemia correction in patients with peripheral vascular disease submitted to percutaneous vascular interventions.

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