

Use of preoperative erythropoietin therapy to facilitate autologous blood donation in orthopedic surgery

A meta-analysis

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Abstract

Background: Autologous blood transfusion helps to avoid or reduce the need for allogeneic blood transfusion in patients undergoing major surgery. We examined the value of erythropoietin therapy to support preoperative autologous blood donation (PABD) in patients undergoing orthopedic surgery.

Methods: For this systematic review and meta-analysis, Medline, Cochrane, EMBASE, and Google Scholar databases were searched from October 26th, 1989 until September 30th, 2017. Primary outcomes were percentages of patients able to donate ≥ 4 units of blood for autologous transfusion, amount of allogeneic blood transfused, changes in hematocrit and hemoglobin levels from before PABD to immediately before surgery, and adverse events.

Results: Of 256 studies identified, 18 studies met the inclusion criteria with a total of 1914 patients (mean age 51–69 years), of whom 1153 were treated with erythropoietin. Erythropoietin was associated with a greater percentage of patients able to donate ≥ 4 units of blood for autologous use compared to controls (OR=6.00, 95% CI=3.97 to 9.09, $P < .001$). Patients receiving preoperative erythropoietin had significantly less of a reduction in hematocrit and hemoglobin levels from before PABD to immediately before surgery compared with controls (hematocrit: mean differences = -1.438 , 95% CI = -2.14 to -0.73 , $P < .001$; hemoglobin: mean differences = -1.426 , 95% CI = -1.78 to -1.07 , $P < .001$). No significant differences were observed in the amount of allogeneic blood transfused between patients receiving erythropoietin and controls (difference in means = -0.220 , 95% CI = -0.536 to 0.097 , $P = .174$). Patients who received erythropoietin were less likely to experience dizziness than controls, but the incidence of nausea or fatigue were similar between groups.

Conclusion: Erythropoietin therapy during the PABD period results in less of a reduction in hematocrit and hemoglobin levels and an increase in the percentage of patients able to donate blood preoperatively.

Abbreviations: 95% CI = 95% confidence intervals, ABT = allogeneic blood transfusions, AE = adverse event, EAS = erythropoiesis-stimulating agent, OR = odds ratio, PABD = preoperative autologous blood donation, RBC = red blood cell, RCT = randomized controlled trial, rHuEPO = recombinant human erythropoietin.

Keywords: autologous blood donation, erythropoietin, orthopedic surgery, transfusion

1. Introduction

Allogeneic blood transfusions (ABT) are often necessary in major orthopedic surgery such as hip replacement and complex spine procedures because of perioperative blood loss. While donor screening and advances in blood testing

have reduced risk of ABT-carried infection, ABT is still associated with other risks, including transfusion reactions, allo-immunization, and transfusion-related immunomodulation that may increase the risk of infection in the postoperative period.^[1]

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The preventive use of erythropoietin during preoperative autologous blood donation in patients undergoing orthopedic surgical procedures is associated with less of a reduction in hemoglobin and hematocrit levels after autologous blood donation and a greater proportion of patients able to donate blood preoperatively. However, erythropoietin therapy does not appear to significantly reduce the need for allogeneic blood transfusion or the incidence of adverse events in this population.

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Autologous blood transfusion has become an important method by which to avoid or reduce the need for ABT in patients undergoing major surgery when significant blood loss is expected and transfusion is likely.^[2] Autologous blood transfusion typically involves preoperative autologous blood donation (PABD) by the patient and then reinfusion of the patient's own blood during surgery.^[3] The amount of PABD, however, is limited by the body's ability to replenish the blood withdrawn from circulation.^[4] Study has shown that the body's endogenous erythropoietin response to autologous blood donation is not sufficient to stimulate maximal erythropoiesis in the marrow.^[4] The availability of iron has also been shown to be a limiting factor in red blood cell (RBC) production after phlebotomy.^[5]

Erythropoietin, a hormone that stimulates erythropoiesis, was discovered in 1953^[6] and recombinant human erythropoietin (rHuEPO) was developed in the 1980s. Erythropoietin is widely used to treat anemia in patients with chronic renal failure. It is also used for correcting anemia in patients who undergo PABD.^[2,7-12] A previously published study showed that patients undergoing PABD who were treated with rHuEPO were able to donate a higher RBC volume than patients who received placebo.^[13] Though the use of PABD is increasing,^[2] concerns remain such as donor anemia, wastage of donated autologous blood, a lower transfusion threshold, and indications that autologous donors are more likely to require perioperative blood transfusions than those who do not undergo PABD.^[14-17] A prior systematic review concluded that currently available evidence is insufficient and that adequately powered prospective trials with low risk of bias are necessary to provide evidence for the utility of erythropoietin in reducing the need for perioperative blood transfusions in patients.^[18] However, that particular review did not specifically examine the use of erythropoietin in facilitating PABD.

The purpose of the current study was to perform a systematic review and meta-analysis to determine whether preoperative erythropoietin therapy increased the percentage of patients able to give ≥ 4 units of blood for autologous transfusion before surgery and decrease the amount of allogeneic blood transfused. Safety was also assessed.

2. Materials and methods

2.1. Literature search strategy

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.^[19] Medline, Cochrane, EMBASE, and Google Scholar databases were searched from October 26th, 1989 until September 30th, 2017 using combinations of the following search terms: autologous blood transfusion, erythropoietin, and orthopedic surgery, as follows: ((orthopedic) AND ((autologous OR blood OR transfusion))) AND erythropoietin. Reference lists of relevant studies were hand-searched. Patients' raw data and private information were not required nor were used in the present study, and thus approval from the institutional review board and patients' informed consent were waived.

2.2. Selection criteria and data extraction

Inclusion criteria were:

- 1) Randomized controlled trials (RCTs);
- 2) Patients received orthopedic surgery and underwent PABD;

- 3) Comparisons between patients who received preoperative erythropoietin and those who did not receive erythropoietin (control group);
- 4) Quantitative outcome data of hemoglobin or hematocrit levels during the preoperative, perioperative, and postoperative periods;
- 5) Published in English or Chinese. Cohort studies, letters, comments, editorials, case reports, proceedings, personal communications and retrospective studies were excluded.

Studies that included patients who received anticoagulants, who had congenital anemia/thalassemia, or who were not eligible for erythropoietin therapy were further excluded. Studies were also excluded if the variables of interest were not reported or presented quantitatively. Studies were identified by the above search strategy by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted.

From studies that met the inclusion above selection criteria, the following information/data were extracted: the name of the first author, year of publication, number of participants in each group, participants' age and gender, intervention protocol, mean unit blood collected per patient, percentage of patients able to donate ≥ 4 units of blood for autologous use, as previously described, hematocrit/hemoglobin level before PABD and immediately before surgery, the amount of allogeneic blood transfused and adverse events (AEs).

2.3. Quality assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)^[20] by 2 reviewers.

2.4. Outcome measures and data analysis

The outcomes included the percentage of patients able to donate ≥ 4 units of blood for autologous transfusion, as previously described^[21]; amount of allogeneic blood transfused; changes in hematocrit and hemoglobin levels from PABD to immediately before surgery; and occurrence of adverse events. Outcomes were compared between the erythropoietin-treated PABD and PABD alone (control) groups. For amount of allogeneic blood transfused and hematocrit/hemoglobin change from PABD to immediately before surgery, means with standard deviations were calculated and compared between the 2 groups; the combined effect size, difference in means between groups with 95% confidence intervals (95% CI) were calculated for each individual study, and for the studies combined. For percentage of patients able to donate ≥ 4 units of blood for autologous transfusion and the occurrence of AEs, the rates were summarized for each group; the combined effect size, odds ratios (ORs) with 95% CI were calculated for each individual study and for the studies combined. A χ^2 -based test of homogeneity was performed, and the inconsistency index (I^2) and Q statistics were determined. For the Q statistic, $P < .10$ was considered to indicate statistically significant heterogeneity.^[22] The I^2 statistic indicates the percentage of the observed between-study variability caused by heterogeneity, and a value $> 50\%$ was established as indicating significant heterogeneity.^[23] If heterogeneity existed between studies (a Q statistic with $P < .1$ or an I^2 statistic $> 50\%$), a random-effects model (DerSimonian-Laird method) of analysis was used.^[24] Otherwise, a fixed-effect model was used (Mantel-Haenszel method). Pooled effects were

calculated, and a 2-sided P value $< .05$ was established as statistical significance. Sensitivity analysis was carried out using the leave one-out approach. Publication bias was not assessed for ≤ 10 studies because > 10 studies are required to detect funnel plot asymmetry. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

3. Results

3.1. Literature search results and study characteristics

A flow diagram of study selection is shown in Figure 1. A total of 256 studies were identified by the database searches. After removal of duplicates and non-relevant studies as determined by title and abstract review, 56 studies were fully reviewed for eligibility. Thirty-eight studies were deemed ineligible due to control group design (13 studies), reported outcomes (12 studies), study type (6 studies), duplicate trials (2 studies), publication language (3 studies), and publication type (2 studies).

Eighteen studies with a total of 1914 patients were included in the meta-analysis (Table 1).^[10,13,25-40] All included studies were RCTs. Overall, 1153 patients were treated with erythropoietin and 761 were not. Patients' mean age across studies was 60 years, ranging from 51 to 69 years. Patients received hip or knee replacement, or spine surgeries, including laminectomy. The protocols for administering erythropoietin varied considerably between the studies, but the drug was typically given for 3 to 4 weeks before surgery and during the period of PABD. In all protocols, oral iron was given but, as with erythropoietin, the

dosage varied between studies. A summary of outcomes, including baseline and preoperative hemoglobin and hematocrit levels of the included studies are shown in Table 2.

3.2. Percentage of patients able to donate ≥ 4 units of blood for autologous use

Six studies^[27,30,35-38] that reported the percentage of patients able to donate ≥ 4 units of blood for autologous use were included for analysis. No evidence of heterogeneity ($I^2=0\%$, Q statistic = 3.677, $P=.597$) was found, thus a fixed-effects model was used. The combined effect indicated that the erythropoietin group had a higher percentage of patients being able to donate ≥ 4 units of blood for autologous use compared to that in the control group (OR=6.00, 95% CI=3.97 to 9.09, $P<.001$) (Fig. 2).

3.3. Changes in hematocrit and hemoglobin levels from before PABD to immediately before surgery

Only 2 studies, Adamson et al^[27] and Mercuriali et al^[28] reported complete data for hematocrit, while another 2 studies, Beris et al^[40] and Schlaeppli et al,^[29] reported full outcomes for hemoglobin. These four studies were used in the analysis. A fixed-effects model was applied for both outcomes because no evidence of heterogeneity was found (hematocrit: $I^2=0\%$, Q statistic = 0.932, $P=.334$; hemoglobin: $I^2=0\%$, Q statistic = 0.004, $P=.949$). The combined effect indicated that the erythropoietin group had less of a reduction in hematocrit and hemoglobin levels after PABD compared to levels in the control group (hematocrit: difference in means = 1.438, 95% CI = 0.73 to 2.14, $P<.001$;

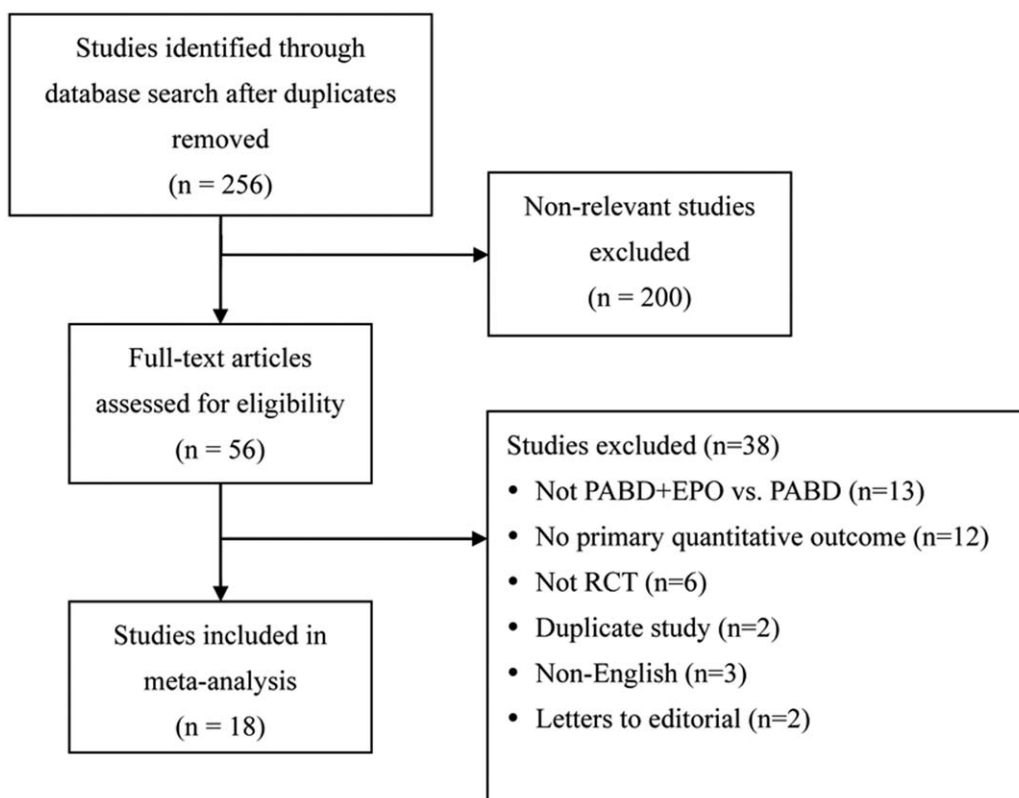


Figure 1. Flow diagram of study selection.

Table 1**Characteristics of the studies included in the meta-analysis.**

First author (year)	Group	Number. of patients	Age (year)	Male (%)	Erythropoietin dose/frequency	Iron supplement	PABD protocol	Mean unit blood collected per patient
Sharma	Erythropoietin	33	55*	70	600 unit/kg rHuEPO every 5 days intravenously for 3–4 wk	Iron sulfate tablet (325 mg) orally 3 times a day	Study patients were adults for whom ≥ 2 units of blood was requested.	4.33 \pm 0.4
(2013) Bujan	Placebo EPO	35 30	52* NR	69 NR	15,000 IU (average 200 IU/kg) rHu-EPO i.v. twice a week	ferrous-2 sulphate 3 \times 65 mg	Hb level \leq 80g/L and/or clinical symptoms of anaemia (increased heart rate or lower blood pressure despite fluid i.v. bolus).	3.05 \pm 0.71
(2012)	EPO	31			30,000 IU (average 400 IU/kg) rHu-EPO i.v. once a week			
Weber	Control Erythropoietin	32 467	67	10	only iron perorally 40,000 IU Epoetin- α subcutaneously once weekly for 3 weeks before surgery and on the day of surgery	Oral iron daily for 3 weeks.	Blood transfusions were only given according to an Hb-based transfusion trigger, as described in the hospital transfusion protocol.	
(2005) Shapiro	Control Erythropoietin	237 25	67 51	11 20	40,000 units Epoetin- α subcutaneously weekly for 4 wk.	Ferrous sulfate 325 mg 3 times a day	HCT < 24 asymptomatic; HCT < 30 with symptoms	
(2002) Hasegawa	Control rHuEPO	23 20	52 53 \pm 13	17 0	6000 U i.v. twice weekly for 3 weeks	Ferrous sul-fate, 105 mg/day, p.o. for 1 month before and after surgery.		
(1999) Mercuriali	no EPO Epoetinalfa 75 IU/kg	17 9	46 \pm 16 63.5 \pm 8.5	0 1	untreated 75 IU/kg i.v.	iron saccharate 200 mg during each treatment visit		
(1998)	Epoetinalfa 150 IU/kg Epoetinalfa 300 IU/kg Placebo	10 10 9	59.2 \pm 11.2 61.0 \pm 4.5 64.6 \pm 7.7	0 0 2	150 IU/kg i.v. 300 IU/kg			
Goodnough (1997)	EPO (RA patients) EPO (non-RA patients) Placebo (RA patients) Placebo (non-RA patients)	4 32 6 28	63.5 \pm 7.7 60.7 \pm 17 62.2 \pm 10.6 60.1 \pm 14	NR	600IU/kg i.v. 600IU/kg i.v.			
Adamson	Epoetinalfa	86			600 IU/kg twice a week for 3 wks; iv			4.5 \pm 1.0
(1996)	Placebo	87	NR	NR		oral ferrous sulfate 325 mg 3 times daily (approximately 180 mg elemental iron/d) 200 mg elemental iron		3.0 \pm 1.1
Nydegger	EPO	19	NR	NR	100 IU/kg sc		patients were transfused if Hct level was \leq 32%	
(1996)	EPO Placebo	22 21			200 IU/kg sc			
Price (1996)	rHuEPO Placebo	86 87	62 \pm 15 61 \pm 17	11 11	600 IU/kg			
Sans	Erythropoietin	11	67	55	100 IU/kg rHuEPO sc twice a week	Iron sulfate 270 mg orally twice daily	Patient receiving hip or knee replacement for whom ≥ 3 units of blood was requested	3.3 \pm 1.0
(1996) Tryba	Placebo Epoetinalfa 50 + i.v. iron	13 125	69	54	Epoetin alfa 50 IU/kg twice a week for 3 weeks; sc	iron saccharate 200 mg i.v. twice a week for 3 weeks	1 unit of AB (450ml) was donated at each of the six preoperative visits if Hct \geq 34%	3.0 \pm 0.7 4.3
(1996)	Epoetinalfa 100 + i.v. iron Epoetinalfa 150 + i.v. iron Untreated control i.v. Iron only				Epoetin alfa 100 IU/kg twice a week for 3 weeks; sc Epoetin alfa 150 IU/kg twice a week for 3 weeks; sc	iron saccharate 200 mg i.v. twice a week for 3 weeks iron saccharate 200 mg i.v. twice a week for 3 weeks		4.5 4.6 3.8 3.9
Goodnough	Erythropoietin	18	NR	NR		iron saccharate 200 mg i.v. twice a week for 3 weeks		4.6 \pm 1.1

(continued)

Table 1
(continued).

First author (year)	Group	Number of patients	Age (year)	Male (%)	Erythropoietin dose/frequency	Iron supplement	PABD protocol	Mean unit blood collected per patient
(1994) Schlaeppli	Placebo	23			600 IU/kg rHuEPO i.v. every 3–4 days for 6 doses	Oral iron supplement 325 mg 3 times a day	Elective orthopedic surgical procedure requiring ≥ 2 units Minimum age: 12 years	5.6 \pm 0.8
(1994)	EPO	19	64.0 \pm 6.7	10	100 IU/kg once a week; sc		Hct 32%	
	EPO	22	64.3 \pm 11.0	12	200 IU/kg once a week; sc			
	placebo	21	64.8 \pm 8.3	14				
Beris	rhEPO	49		24	150–180 U/kg given three times per week as a subcutaneous injection 4 and 2 weeks before surgery; sc			
(1993) Mercuriali	Control	52	NR	25				
	rhHuEPO 300	19	55 (30–68)	0	300IU/kg on days 1, 4, 7, total 6 doses in 3 wks; i.v.			
(1993)	rhHuEPO 600	20	56 (39–67)	0	600IU/kg on days 1, 4, 7, total 6 doses in 3 wks; i.v.			
	Placebo	9	58 (41–63)	0	saline; i.v.			
Tasaki (1992)	r-HuEPO	4	41.3 \pm 24.3	2	3000 U twice a week; i.v.	iron sulphate		
	r-HuEPO	5	46.2 \pm 17.6	1	6000 U twice a week; i.v.			
	r-HuEPO	4	31.3 \pm 24.7	0	9000 U twice a week; i.v.			
	Control	12	44.9 \pm 7.4	3				
Goodnough	Erythropoietin	23	55	52	600 IU/kg rHuEPO i.v. twice a week for 3 weeks	Oral iron sulfate 325 mg 3 times a day	Elective orthopedic surgical procedure requiring ≥ 3 units	4.1 \pm SE 0.2
(1989) =>1990	Placebo	24	54	38				5.4 \pm SE0.2

Hb = hemoglobin; HCT = hematocrit; i.v. = intravenous; NR = not response; rHuEPO = recombinant human erythropoietin; sc = subcutaneous; SE = standard error.

hemoglobin: difference in means = -1.426 , 95% CI = -1.78 to -1.07 , $P < .001$ (Fig. 3).

3.4. Amount of allogeneic blood transfused

Five studies, Bujan,^[10] Goodnough,^[36] Goodnough,^[26] Goodnough,^[37] and Mercuriali,^[32] reported the amount of allogeneic blood transfused. A random effects model was applied due to the presence of heterogeneity in the data ($I^2 = 63.23\%$, Q statistic = 10.878, $P = .028$). No differences in the amount of allogeneic blood transfused were observed between the 2 groups (difference in means = -0.220 , 95% CI = -0.536 to 0.097 , $P = .174$) (Fig. 4).

3.5. Adverse events

The commonly encountered AEs of nausea, fatigue, and dizziness were analyzed individually. Only perioperative in-hospital AEs were included; long-term sequelae of the intervention were not evaluated. Three studies reported data of nausea,^[13,37,39] and a fixed-effects model was used as there was no evidence of heterogeneity ($I^2 = 0\%$, Q statistic = 1.714, $P = .424$). Analysis revealed no significant differences in the incidence of nausea between the erythropoietin and control groups (pooled OR = 1.12, 95% CI: 0.45 to 2.76, $P = .807$, Fig. 5A).

Two studies reported data of fatigue.^[13,36] Moderate heterogeneity was found in the data ($I^2 = 53.5\%$, Q statistic = 2.15, $P = .143$), thus a random-effects model was used. Analysis revealed no significant differences in the incidence of fatigue between the two groups (pooled OR = 1.27, 95% CI: 0.20 to 7.99, $P = .800$, Fig. 5B).

Four studies reported data of dizziness.^[13,36,37,39] No significant heterogeneity was present in the data ($I^2 = 0\%$, Q statistic =

1.368, $P = .713$), thus a fixed-effects model was used. Analysis revealed that patients treated with erythropoietin were less likely to experience dizziness compared with those who did not receive the drug (pooled OR = 0.39, 95% CI: 0.18 to 0.83, $P = .014$, Fig. 5C).

3.6. Sensitivity analysis

Sensitivity analysis was performed using the leave-one-out approach for the percentage of patients able to donate ≥ 4 units of blood for autologous use and amount of allogeneic blood transfused (Supplemental Fig. 1, <http://links.lww.com/MD/D573>). The direction and magnitude of combined estimates did not vary markedly with the removal of individual studies, indicating that the meta-analysis had good reliability and the data were not overly influenced by any single study.

3.7. Quality assessment

Results of the quality assessment of the included studies are shown in Supplemental Figure 2, <http://links.lww.com/MD/D574>. Overall, an unclear or high risk of bias was present for 16 of the studies that did not include an intent-to-treat analysis. In $> 50\%$ of the studies, it was unclear or a high risk of performance (blinding of participants or personnel) and/or detection bias (blinding of outcome assessment) was noted. Overall the included articles were of adequate quality.

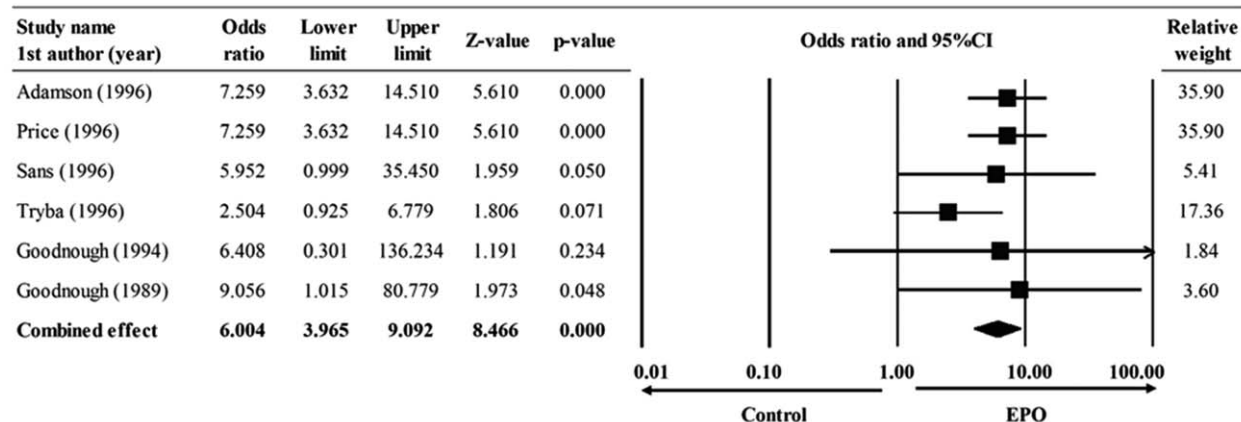
4. Discussion

The present review evaluated the impact of erythropoietin on improving the ability of patients to donate autologous blood

Table 2
Summary of study outcomes.

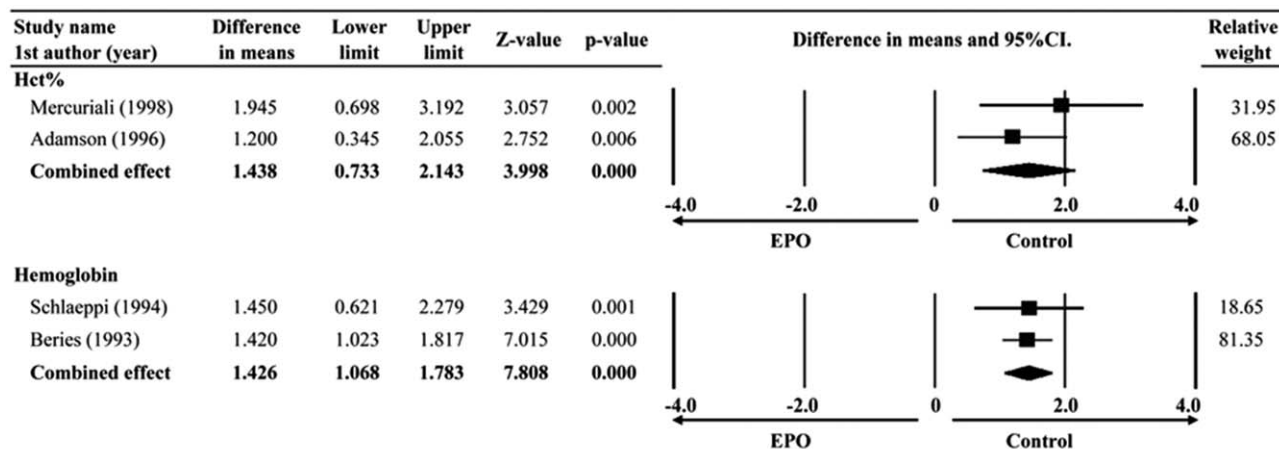
First author (year)	Group	Number of patients	% of patients able to donate >= 4 units of blood for autologous use	Allogeneic blood transfusion	Hematocrit (%)		Hemoglobin		Adverse Events (%)		
					Before PABD	Immediately before surgery	Before PABD	Immediately before surgery	Nausea	Fatigue	Dizziness
Sharma (2013)	Erythropoietin	33			37.78				9	6	9
	Placebo	35		0.1 ± 0.4 unit/pts	35.8				11	11	20
	Bujian (2012)	30		0.23 ± 0.49			122.37 (g/L)				
	EPO	31		0.13 ± 0.51			122.69				
Weber	control	32		0.69 ± 1.23			123.08				
	Erythropoietin	467					12.3 ± 0.7 g/dL				
(2005)	Control	237					12.2 ± 0.7				
	Erythropoietin	25		0.5 unit/pts.	41.85				78	NR	20
(2002)	Control	23		2.9 unit/pts.	41.12				82	NR	29
	rHuEPO	20									
Hasegawa (1999)	no EPO	17									
Mercuriali (1998)	Epoetin alfa 75 IU/kg	9									
	Epoetin alfa 150 IU/kg	10	88.8% (8/9)		decrease by 3.0 ± 1.9%						
	Epoetin alfa 300 IU/kg	10			decrease by 1.7 ± 2.5%						
	Placebo	9			decrease by 0.4 ± 2.5%						
Goodnough (1997)	Placebo	9		0.5 ± 1.0	36.1						
	EPO (RA patients)	4		0.3 ± 0.8	32.4						
(1996)	EPO (non-RA patients)	32		0.3 ± 1.6	32.6						
	Placebo (RA patients)	6		0.5 ± 1.2	39						
Nydegger (1996)	Placebo (non-RA patients)	28			36.4 ± 2.2						
	Epoetin alfa	86	81%		36.4 ± 2.3						
Price (1996)	Placebo	87	37%								
	rHuEPO	19									
Sans (1996)	Placebo	22									
	rHuEPO	21									
Tryba (1996)	Placebo	86	81%								
	Erythropoietin	87	37%								
(1996)	Placebo	13		1 unit	42.04						
	Epoetin alfa 50 + i.v. iron	125			42.77						
Goodnough (1994)	Placebo	18									
	Erythropoietin	23		0.4 (1.0) unit/pts	40.02						
Schleppi (1994)	Placebo	19		0.1 (0.5) unit/pts	40.02						
	EPO	22									
Beris (1993)	Placebo	21									
	rHuEPO	49									
Mercuriali (1993)	Control	52		0.5							
	rHuEPO 300	19		0.2							
Tasaki (1992)	rHuEPO 600	20		0.4 ± 0.8							
	Placebo	9		1.2 ± 1.4							
Goodnough (1989)	r-HuEPO	4									
	r-HuEPO	5									
Goodnough (1989)	Control	12									
	Erythropoietin	23	95.65%	0.1 (0.1)	40.83						
	Placebo	24	70.83%	0.2 (0.7)	39.58						

NR = non-responder; pts = patients.



Heterogeneity test: Q-value=3.677, df=5, p-value=0.597, I-squared=0%

Figure 2. Meta-analysis of percentage of patients able to donate ≥4 units of blood for autologous transfusion. CI=confidence intervals.

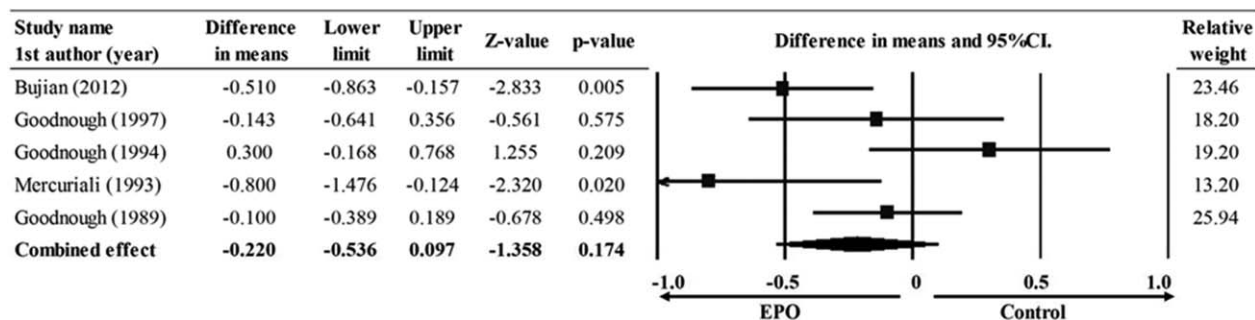


Heterogeneity test:

Hct%: Q-value=0.932, df=1, p-value=0.334, I-squared=0%

Hemoglobin: Q-value=0.004, df=1, p-value=0.949, I-squared=0%

Figure 3. Meta-analysis of changes in hematocrit and hemoglobin from before PABD to immediately before surgery. CI=confidence intervals.



Heterogeneity test: Q-value=10.878, df=4, p-value=0.028, I-squared=63.23%

Figure 4. Meta-analysis of amount of allogeneic blood transfused. CI=confidence intervals.

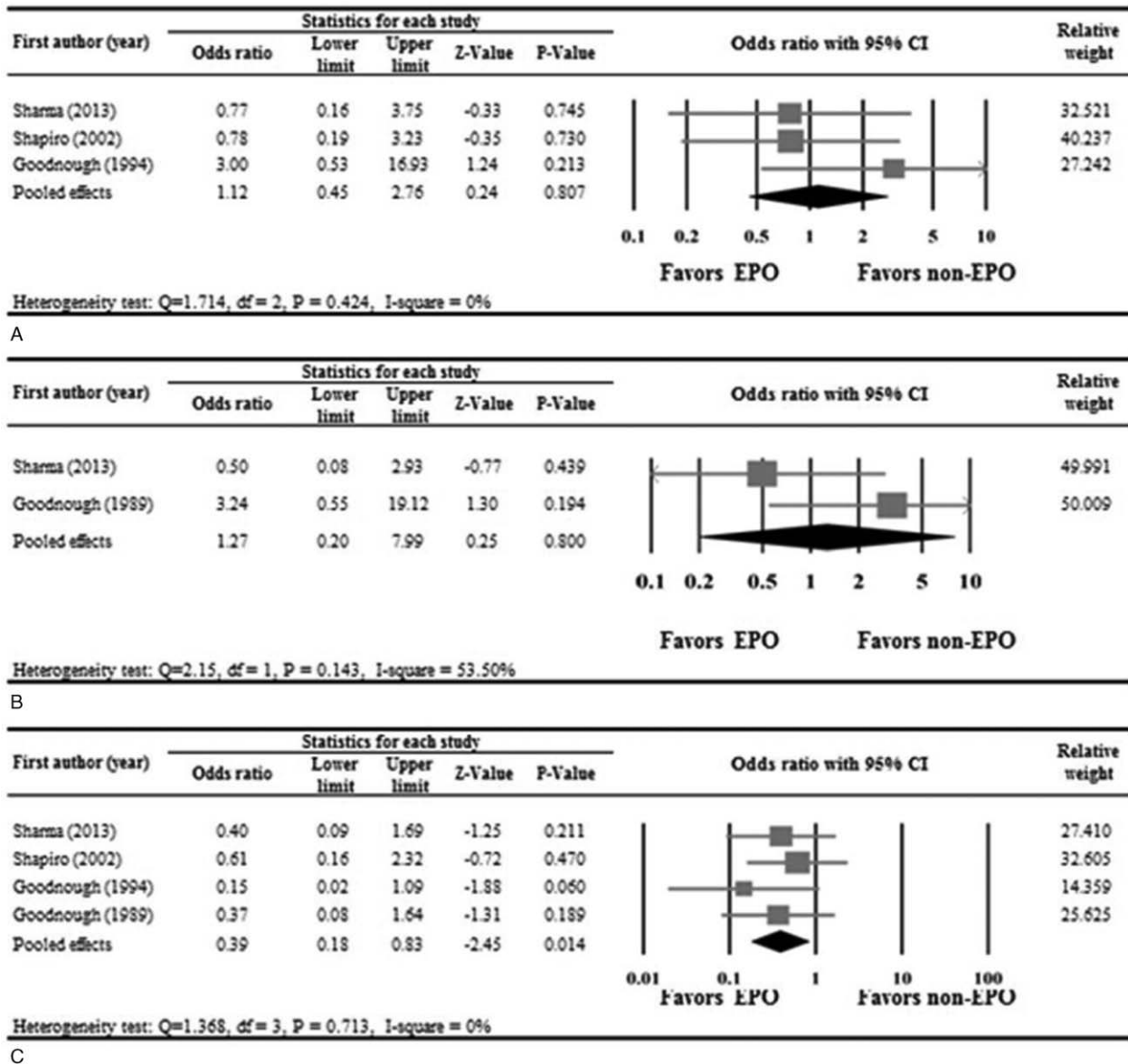


Figure 5. Meta-analysis of adverse events of (A) nausea, (B) fatigue, and (C) dizziness.

prior to orthopedic surgery and thereby help to reduce patients' need for ABT peri- or postoperatively. In 18 studies with a total of 1153 patients, our meta-analysis revealed that erythropoietin therapy was associated with a greater percentage of patients able to donate ≥ 4 units of blood preoperatively and less of a reduction in patients' hematocrit and hemoglobin levels following PABD compared to controls. The amount of allogenic blood transfused and the incidence of nausea and fatigue were similar between erythropoietin and control groups. Although a greater percentage of control patients experienced dizziness compared with erythropoietin treated patients, the results were not significant. These results suggest that erythropoietin therapy does not significantly reduce the need for ABT or related incidence of AEs.

Erythropoietin has been used to increase the hematocrit level in patients undergoing PABD prior to surgery. It is also given in patients not providing autologous blood prior to surgery so as to possibly reduce the need for allogenic blood transfusions. Results

of the present meta-analysis are consistent with prior findings suggesting that the use of erythropoietin does not significantly reduce the need for ABT in patients undergoing orthopedic surgery. A recent review by Cherian et al^[41] of preoperative blood management strategies for total hip arthroplasty, including preoperative iron therapy, intravenous erythropoietin, and autologous blood donation, concluded that no single strategy was superior to another in reducing the need for allogenic transfusions; however, the authors suggested that a combinational approach may result in improved blood loss outcomes. In a report not included in the present analysis, Deutsch et al^[42] randomized patients undergoing primary total knee arthroplasty to receive either epoetin- α 40,000 U at preoperative days 14 and 7 or a standard PABD protocol, and baseline hematologic parameters were similar between the groups. In that study, by the day of surgery, the erythropoietin group had significantly higher hemoglobin/hematocrit levels and reticulocyte counts compared

to controls, and the differences remained significant for 1 to 2 days postoperatively. However, those authors found no significant differences in the incidence of allogeneic transfusions between groups, comparable to results of the present study.

In contrast, a meta-analysis conducted by Alsaleh et al^[43] pooled the results from 26 studies with 3560 patients undergoing knee or hip arthroplasty to evaluate the effectiveness of erythropoiesis-stimulating agents (ESAs, including erythropoietin) on reducing ABT and maintaining hemoglobin levels. That study found that the use of preoperative ESAs reduced the need for ABT, and a significant difference was found in mean hemoglobin between the ESA and control groups postoperatively. A more recent meta-analysis performed in 2016 by Zhao et al^[44] evaluated the preoperative use of erythropoietin in reducing ABT and complications in patients scheduled for total hip or knee arthroplasty. Those authors found that preoperative use of erythropoietin was associated with lower exposure to ABT and higher postoperative hemoglobin concentrations. A systematic review by Lin et al^[18] also found that erythropoietin reduced the need for ABT in patients from four RCTs. Those authors found that a short preoperative erythropoietin regimen or a single dose of erythropoietin plus IV iron in the pre- or peri-operative period reduced allogeneic transfusion rates (the number of patients needed to treat to avoid any transfusion ranged from 3 to 6).

Although no significant differences were observed in complications between patients who did or did not receive erythropoietin, Zhao et al^[44] did suggest that venous thromboembolism (VTE) was a major concern associated with erythropoietin therapy and, although some patients in that study had received VTE prophylaxis, no significant differences were found in VTE incidence in groups treated with and without erythropoietin. Also, Alsaleh et al^[43] found no increased risk of thromboembolism in the ESA group compared with the control group. In contrast, other authors reported that erythropoietin was likely to increase the risk of thromboembolism in spine surgery patients who received only mechanical anti-thrombosis prophylaxis.^[18] In the present review, VTE was not evaluated as an endpoint, given the studies included did not provide such data.

Cost-effectiveness is important considerations in blood management strategies. On the cost side, several studies evaluated the advantages of erythropoietin in treating patients. Based on data from a German hospital, Tomeczkowski et al^[45] concluded that erythropoietin reduced ABT and associated complications in anemic patients undergoing elective hip or knee surgery, and thus was considered cost effective by a cost analysis model. Green et al^[46] found that preoperative erythropoietin was significantly less costly than ABT using a cost minimization analysis, and savings of \$800 per patient undergoing total hip arthroplasty and \$392 per patient undergoing total knee arthroplasty could be realized through administering preventive erythropoietin. In contrast, the studies of Coyle et al^[47] and Bedair et al^[48] concluded that the use of erythropoietin was not cost-effective, even though it reduced ABT. Despite these findings, results of the present review and others still report that preventive use of erythropoietin is not associated with substantial reduction in peri-operative allogeneic blood transfusion, and thus estimating cost benefits may not be relevant.

4.1. Limitations

Several important limitations of the present analysis must be considered. Marked variation was present among the studies

with respect to the dosage and administration of erythropoietin and blood transfusion protocols. Although 18 studies were included in the present study, only a few studies contributed to the individual subsections of meta-analysis. For example, while 11 studies reported allogeneic blood transfused, only 5 studies provided all variables of interest and only two studies were included for evaluating changes in hematocrit or hemoglobin from pre-PABD to postoperative status. In addition, most studies were performed in the 1990s. Only perioperative in-hospital AEs were reviewed. We did not evaluate the possible long-term AEs linked to erythropoietin therapy. For example, tumor growth is previously reported to be accelerated by EPO therapy.^[49,50] Nevertheless, the results of the present review must be interpreted with caution since adequately powered studies focusing on this topic are currently lacking. A lack of relevant studies in the medical literature clearly indicates that further research on the value of erythropoietin therapy in preparing for orthopedic surgery is highly warranted.

5. Conclusions

The use of erythropoietin prior to PABD results in less of a reduction in hemoglobin and hematocrit levels in patients undergoing orthopedic surgical procedures and a greater proportion of patients being able to donate blood preoperatively. However, erythropoietin administration does not appear to be associated with reductions in the use of ABT or the incidence of AEs.

Author contributions

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