Systematic Review and Meta-Analysis

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The effectiveness and safety of preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Introduction: Because allogeneic blood transfusion carries a risk of serious complications, erythropoietin (EPO) has been used in patients scheduled for total hip or knee arthroplasty in an effort to reduce the need for allogeneic blood transfusion; however, its efficacy, cost-effectiveness, and safety are still controversial. The purpose of this review was to determine the hematopoiesis-promoting effect and potential complications, as well as the cost-effectiveness, of preoperative use of EPO in patients scheduled for total hip or knee arthroplasty.

Methods: : We searched MEDLINE, EMBASE, Cochrane, and ClinicalTrials.gov databases for relevant literature from 2000 to 2015. Risk of bias was assessed for all included studies and data were extracted and analyzed.

Results: Preoperative use of EPO was associated with lower exposure to allogeneic blood transfusion (odds ratio = 0.41) and higher hemoglobin concentration after surgery (standardized mean difference = 0.86, $P < 0.001$). Complications were not generally reported, but there was no significant difference between the group with and without EPO based on given data. Cost-effectiveness was also summarized but was not conclusive.

Conclusion: Preoperative administration of EPO reduces the requirement for allogeneic blood transfusion and increases hemoglobin level after surgery. The studies of cost-effectiveness were not conclusive. Further studies and guidelines specific to blood management in the perioperative stage of total knee and hip arthroplasty are expected.

Abbreviations: ABT = allogeneic blood transfusion, DVT = deep venous thrombosis, EPO = erythropoietin, PABD = preoperative autologous blood donation, PE = pulmonary embolism, RCT = randomized controlled trial, rHuEPO = recombinant human erythropoietin, SMD = standardized mean difference, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.

Keywords: allogeneic transfusion, erythropoietin, hemoglobin, total hip arthroplasty, total knee arthroplasty

1. Introduction

Losing a large volume of blood, enough to require an allogeneic blood transfusion (ABT), is inevitable in total hip arthroplasty (THA) or total knee arthroplasty (TKA) in many cases.[1] Despite its wide use, however, ABT has been reported to be associated with a risk of transmission of infectious disease,[2] increased cost,[3] an immunosuppressive effect,[4,5] and even a transfusion-associated graft-versus-host disease.[6] Consequently, several alternatives have been introduced to reduce the need for ABT, including perioperative use of erythropoietin (EPO), preoperative autologous blood donation (PABD),[7] and postoperative cell salvage.[8] PABD eliminates the risk of disease transmission and has shown promising results in some trials,[9] but was reported recently to be associated with a higher probability of perioperative transfusions and no reduction in the rate of ABT.[10]

Use of EPO is a potential solution to this problem. Compared to PABD, EPO can be administered conveniently with no requirement for special instruments. It has been reported that EPO may reduce the need for ABT,[11–13] but may not be cost-effective[14] and may increase the risk of thrombosis.[15]

A meta-analysis conducted in 2013 summarized the randomized controlled trials (RCTs) investigating the effect of preoperative erythropoiesis-stimulating agents in patients who underwent knee or hip arthroplasty. This analysis included studies conducted from 1993 to 2012[16] and concluded that EPO improved hemoglobin levels after surgery and decreased the need for ABT. Considering the progress in surgical techniques and procedures since the publication of this analysis, as well as new

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RCTs published in the past few years, we collected and analyzed the most recent trials, in hope of a more accurate and definitive conclusion.

2. Methods

2.1. Search strategy

We searched MEDLINE, EMBASE, Cochrane, and ClinicalTrials.gov databases for relevant publications dated from January 2000 to December 2015. The following terms were used for searching: total knee replacement, total knee arthroplasty, total hip replacement, total hip arthroplasty, erythropoietin, EPO, epoetin alfa, epoetin beta, recombinant human erythropoietin, and rHuEPO. In addition, we searched magazine articles by hand to supplement our database searches and contacted the authors for unpublished data if necessary. All searches were limited to human studies. There was no restriction on language.

2.2. Inclusion and exclusion criteria

2.2.1. Type of studies. Only RCTs were included.

2.2.1.1. Subjects. Patients were included in this review if they were diagnosed with osteoarthritis or rheumatoid arthritis, scheduled for TKA or THA, and gave informed consent. Patients were excluded because of severe hematologic disease, thromboembolic disease, hepatic or renal disease, coagulation disorder, infection, malignancy, pregnancy, anticoagulant therapy, hypersensitivity to iron sucrose or rHuEPO, or a history of a blood transfusion within the previous 1 month.

2.2.1.2. Intervention. Patients allocated to the experimental group received injections of EPO or its equivalents in the perioperative stage. In the control group, patients did not receive EPO. Iron was supplied in most studies. In several studies, PABD protocols were utilized.

2.2.1.3. Outcomes. Studies reporting the following primary or secondary outcomes were included. Primary outcomes were those related to ABT, including the number of patients who needed ABT and the volume of allogeneic blood used. Secondary outcomes pertained to the hematological response to EPO or control method, including reticulocyte counts or percentage, and levels of hemoglobin at discharge or at the last time measured after surgery, as well as complications from the use of EPO. Economic evaluation was also summarized.

2.3. Quality assessment

The assessment tool developed by the Cochrane Collaboration[17] was applied to assess selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias arising from RCTs. The assessment was performed by 2 independent authors and disagreement was resolved by discussion with a third author.

2.4. Data extraction

Data were extracted with a collection form designed by 2 investigators independently (See Collection Form, Supplemental Collection Form, http://links.lww.com/MD/B103). Data presented only in graphs and figures were extracted to numerical values whenever possible, but were included only if 2 reviewers had the same results. Unpublished data were acquired by contact with the original investigators and if that failed, calculated with available data. If only hematocrit was available, concentration of hemoglobin was calculated by dividing hematocrit by 3.[18]

2.5. Statistical analysis

We employed Revman 5.3 software[19] (the Cochrane Collaboration, UK) to perform the meta-analysis. The number of patients who received ABT was regarded as a discontinuous variable, whereas the volume of blood transfused and the levels of hemoglobin were considered continuous variables. Odds ratios and standard mean differences were calculated for discontinuous and continuous variables, respectively. The results were presented as mean difference with 95% confidence intervals. Furthermore, χ^2 and I^2 were calculated to evaluate the heterogeneity between studies according to the Cochrane Handbook.[20] Any difference of outcomes with a P value <0.05 was considered significant.

3. Results

3.1. Search results

A total of 169 articles were retrieved from the initial search. After removing duplicates and articles published before 2000, 105 articles were screened based on the titles and abstracts, and 18 were assessed for eligibility. After full-text screening, 3 articles were excluded, 2 of which were not RCTs[21,22] and 1 of which recruited patients who underwent operations not restricted to THA/TKA and failed to report the outcomes separately.[23] In the end, 15 RCTs involving 2155 patients were included in this meta-analysis[11–13,24–35] (Fig. 1).

3.2. Characteristics of the included trials

The characteristics of the included trials are summarized in Table 1.[11–13,24–35] Four trials compared the outcomes of patients who received EPO with those who did not receive EPO. Six studies focused on the difference in outcomes between patients receiving EPO and those receiving PABD. Five RCTs investigated the effects of EPO plus PABD versus PABD alone. Almost all patients included in this review had a preoperative hemoglobin level of over 100 g/L (with a few exceptions from the studies by Bezwada et al[30] and Feagan et al[24]). The risk of bias in the included RCTs is demonstrated in Fig. 2.

The trials were divided into 3 subgroups: EPO versus no EPO, EPO versus PABD, and EPO plus PABD versus PABD alone. Subgroup analysis was performed accordingly.

3.3. Requirements for allogeneic blood transfusion

In the subgroup of EPO versus no EPO, EPO was associated with a lower proportion of patients who needed ABT (OR = 0.30, $P < 0.001$) and with a lower volume of allogeneic blood transfused ($P = 0.01$). In the subgroup of EPO plus PABD versus PABD alone, use of EPO was associated with lower exposure to ABT (OR = 0.39, $P = 0.03$), but no decrease in the average volume of allogeneic blood transfused. In the subgroup of EPO versus PABD, however, injection of EPO caused no significant difference either in the proportion of patients receiving ABT (OR = 0.65, $P = 0.25$), or in the average volume of allogeneic blood transfused ($P = 0.64$). After taking all studies into consideration, EPO reduced exposure to ABT (OR = 0.41, $P < 0.001$), but there was no significant difference in the average volume of allogeneic blood transfused ($P = 0.10$) (Figs. 3 and 4).

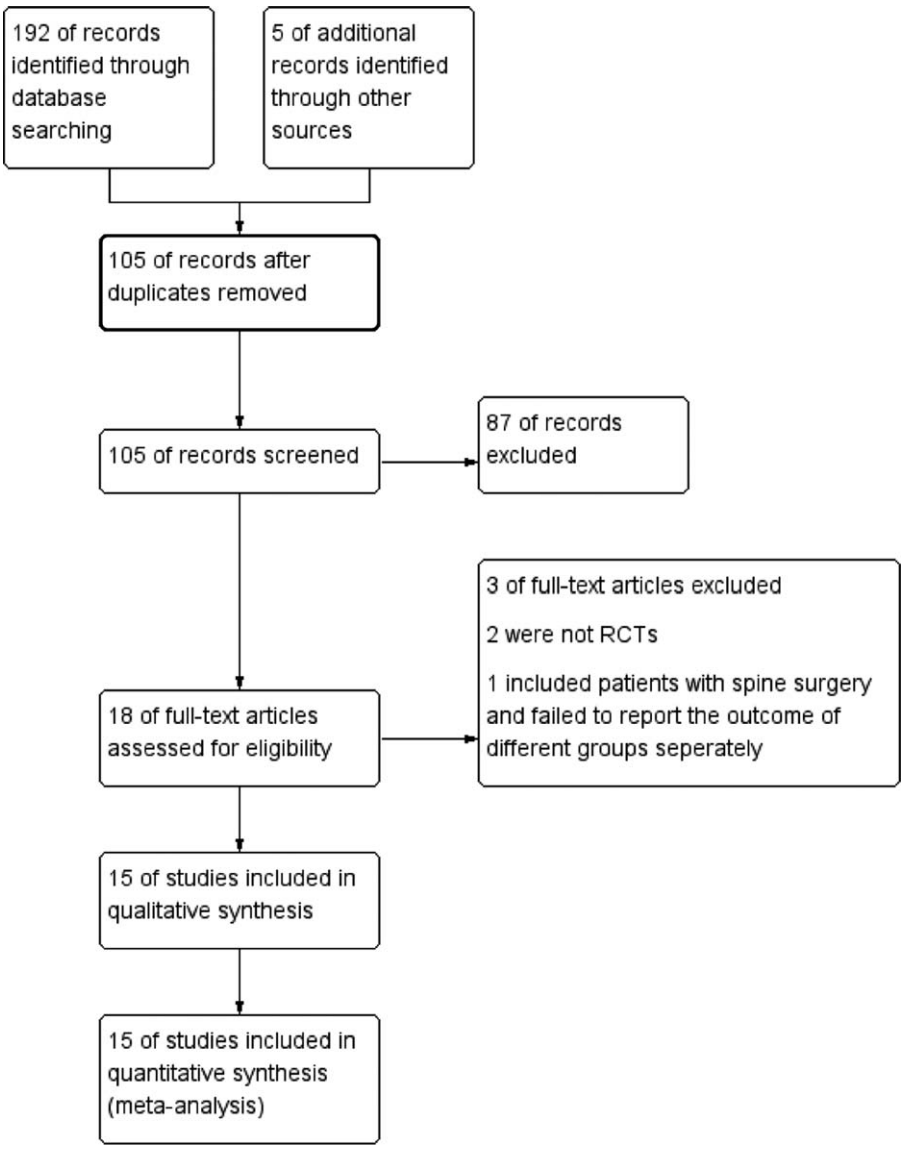

Figure 1. Study flow diagram.

3.4. Reticulocyte counts or percentage

Eight of 15 RCTs reported the counts or percentages of reticulocytes. Owing to the insufficiency of data available, quantitative analysis was not conducted, but the general pattern was observed. The reticulocyte counts (or percentage) increased within a week after injection of EPO and were maintained at a higher level than placebo or PABD as the injections were continued.[12,24–26,28,29,31,33]

3.5. Hemoglobin concentration

In the comparison between EPO versus no EPO, EPO plus PABD versus PABD alone, and EPO versus PABD, use of EPO was associated with higher hemoglobin level after surgery ($P < 0.001$, $P = 0.006$, $P = 0.008$, respectively) and the overall difference between the 3 subgroups was also significant ($P < 0.001$) (Fig. 5).

3.6. Complications

Data regarding complications were reported in only 5 trials[24,32–35] and the manifestations were diverse, which made them impossible to quantitatively analyze (Table 2).[12,13,24,26,28,30–35] Feagan et al[24] reported the occurrence of deep venous thrombosis (DVT) and pulmonary embolism (PE). In the placebo, low-dose (80000 IU EPO in total) and high-dose (1,60,000 IU EPO in total) groups, the rate of DVT or PE was 7.7%, 6.3%, and 4.5%, respectively. Rosencher et al[32] found there was no significant difference between the occurrence of DVT and PE between the EPO group and the PABD group. Other complications reported included fatigue, hypotension, dizziness, tachycardia, decreased urine output, cerebrovascular accident, fever, hypokalemia, urinary tract infection, nausea, hypoxia, vomiting, perforated sigmoid colon, diabetes mellitus instability, periprosthetic fracture, hematoma, prolonged wound discharge, and superficial wound infection.[33–35]

3.7. Economic evaluations

Only 2 of the 15 trials evaluated the economics of EPO. In the study conducted by Hardwick et al,[31] 80,000 IU of epoetin alfa was used, and the total cost was $978, whereas a unit of

Table 1

Characteristics of studies included.

Author, year	Method	Number of patients	Intervention		Baseline Hb (g/L)	Transfusion criteria	Outcomes reported
			Experimental	Control			
Feagan et al, 2000[24]	EPO vs. no EPO	201	Epoeitin alfa: 40,000 IU or 20,000 IU sc per week beginning from 4 weeks before operation	Placebo	98–137	—	Need for ABT, reticulocytes, complications
Gombotz et al, 2000[25]	EPO vs. PABD	40	rHuEPO: 600 U/kg sc on day 14 and, if needed, on day 7 before surgery	PABD: starting 4 weeks before surgery (goal: 3 U per donor)	120–150	—	Need for ABT, hemoglobin, reticulocytes
Aksoy and Tokgozoglu, 2001[26]	EPO + PABD vs. PABD	40	rhuEPO: 300 IU/kg twice a week for 2 weeks, then once 3 days before operation PABD: 1 unit at 4 days interval until Hb <100 g/L	PABD same as EPO group	≥120	Hb <80 g/L or hemodynamically unstable	Need for ABT, hemoglobin, reticulocytes
Matsuda et al, 2001[27]	EPO + PABD vs. PABD	37	rhuEPO: 12,000 or 24,000 IU PABD: 1 U	PABD: 1 U	≥100	—	Hemoglobin
Olijhoek et al, 2001[28]	EPO vs. no EPO	110	Epoeitin alfa: 600 IU/kg weekly for 3 weeks	Placebo	100–130	—	Hemoglobin, reticulocytes
Avall et al, 2003[29]	EPO + PABD vs. PABD	38	EPO: 10000 IU sc for 5 times PABD: 1 U before 3, 2, and 1 week before surgery	PABD: 1 U before 3, 2 and 1 week before surgery	>110	Hb <85 g/L or when in danger of inadequate oxygenation	Need for ABT, reticulocytes
Bezwada et al, 2003–1[30]	EPO + PABD vs. PABD	160	EPO: 600 IU/kg weekly for 4 weeks PABD: 1 U for unilateral arthroplasty and 2U for bilateral arthroplasty	PABD: same as EPO group	93–140	Hb <80 g/L and/or persistent or hemodynamically unstable	Need for ABT
Bezwada et al, 2003–2[30]	EPO vs. PABD	160	EPO: 600 IU/kg weekly for 4 weeks	PABD: 1 U for unilateral arthroplasty and 2U for bilateral arthroplasty	83 – 140	Hb <80 g/L and/or persistent or hypotension requiring administration of large volume of crystalloid	Need for ABT
Hardwick et al, 2004[31]	EPO vs PABD	40	Epoeitin alfa: 40000 IU weekly for 2 weeks	PABD: 1 or 2 U before operation	120 -150	—	Need for ABT, hemoglobin, reticulocytes
Rosencher et al, 2005[32]	EPO vs. PABD	86	Epoeitin alfa: 40000 IU sc per week beginning 3 weeks before operation	PABD: Once a week starting 3 weeks before surgery, as long as Hct >3%	100–130	Hct between 21% and 30%	Need for ABT, hemoglobin, complications
Deutsch et al, 2006[33]	EPO vs. PABD	50	Epoeitin alfa: 40000 IU sc 14 days and 7 days before operation	PABD: 2 U if Hb between 110 and 130 g/L	100–130	Hct <25%	Need for ABT, hemoglobin, reticulocytes, complications
Keating et al, 2007[34]	EPO vs. PABD	279	EPO: 600 IU/kg weekly for 3 weeks and with 24 h postoperatively	PABD: 1 U before TKA, 2U before THA	110–140	Hb <80 g/L	Need for ABT, hemoglobin, complications
Moonen et al, 2008[35]	EPO vs ABR	100	Epoeitin alfa: 40000 IU weekly for 4 weeks	Autologous blood retransfusion	100–130	—	Need for ABT, hemoglobin, complications
Na et al, 2011[11]	EPO vs. no EPO	108	rhuEPO-β: 3000 IU sc 3 times	No EPO	>100	Hb <70 g/L	Need for ABT, hemoglobin
Buljan et al, 2012[12]	EPO + PABD vs. PABD	93	rhuEPO: 15000 IU or 30000 IU IV twice weekly for 3 weeks PABD: 12% of total blood volume donated on the 10th and 3rd preoperative days	PABD: 12% of total blood volume donated on the 10th and 3rd preoperative days	105–130	Hb ≤80 g/L and/or clinical symptoms of anaemia	Need for ABT, reticulocytes
So-Osman et al, 2014[13]	EPO vs. no EPO	613	EPO group: EPO 40000 IU sc weekly for 3 weeks before operation EPO + AUTO group: EPO 40000 IU sc weekly for 3 weeks before operation and autologous blood reinfusion	Control group: No treatment AUTO group: autologous blood reinfusion	100–130	—	Need for ABT, hemoglobin

ABR = autologous blood retransfusion, ABT = allogeneic blood transfusion, EPO = erythropoietin, PABD = preoperative autologous blood donation, rhuEPO = recombinant human erythropoietin.

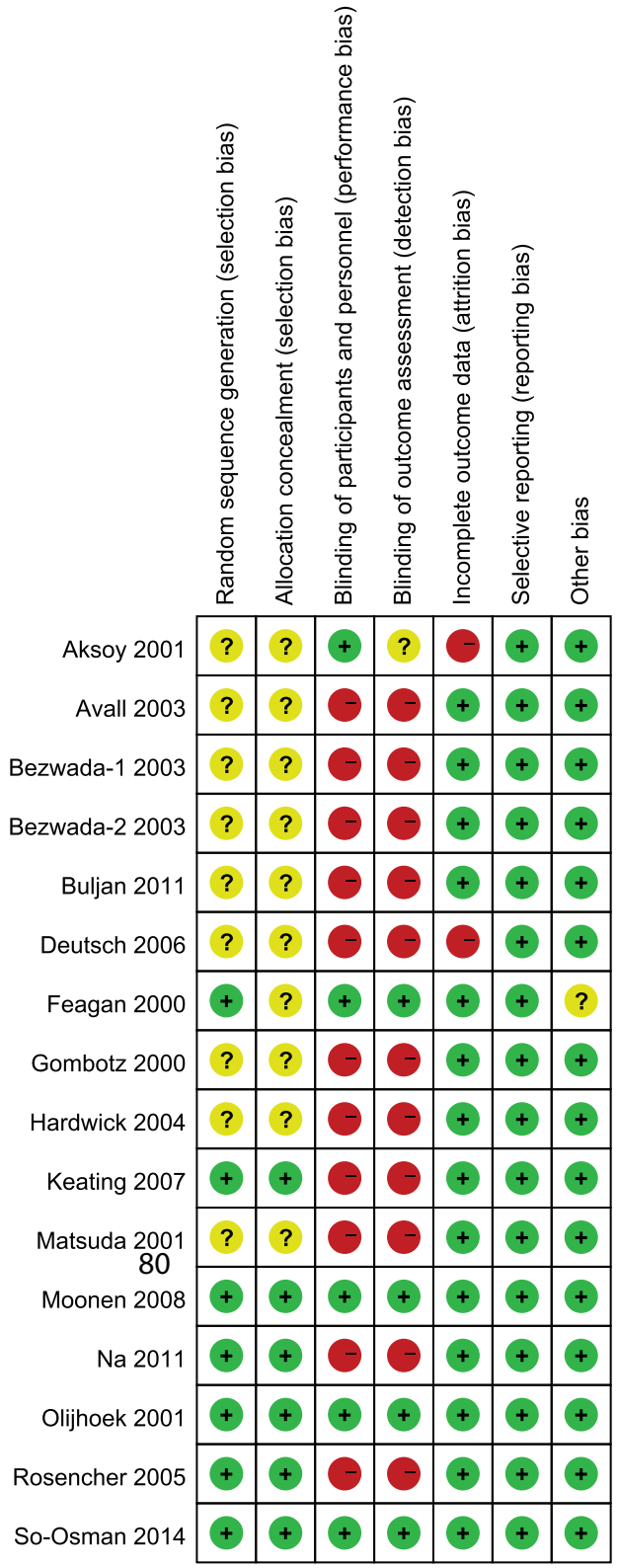

Figure 2. Risk of bias.

autologous blood was $391 and a unit of allogeneic blood was $514. This implied that the patients would have to receive ≥2 units of blood to equal the cost of epoetin alfa. Upon calculation, the average cost per patient in the EPO and PABD group was $1032 and $345, respectively. In the study performed by So-Osman et al,[13] the additional cost for the EPO strategy was €785 per patient and the cost per avoided transfusion was €7300.

4. Discussion

This systematic review and meta-analysis summarized the RCTs published in 2000 or later. The effect and safety of preoperative use of EPO in patients scheduled for total hip or knee arthroplasty were evaluated. Subgroup analysis was introduced to detect the difference between EPO versus no EPO, EPO versus PABD, and EPO plus PABD versus PABD alone.

The major finding of this review was that use of EPO reduced the need for allogeneic transfusion by approximately 60%, which is promising considering the possible complications of ABT.[2–6] Apart from EPO, several strategies have been proposed to decrease ABT, one of which is PABD. Our results indicated that EPO had no advantage over PABD, with respect to exposure to allogeneic blood; however, the use of PABD is limited because it cannot be used in patients with anemia and sometimes causes wastage if the operation is postponed or all units harvested are not transfused.[36] Other strategies employed to decrease ABT include tourniquets, local injection of adrenaline, intraoperative cell salvage, reinfusion drains, platelet-rich plasmapheresis, acute normovolemic hemodilution, and pharmacological agents.[7,36]

Another important result of our analysis was the increased reticulocyte counts (or percentages) and hemoglobin levels after use of EPO. Hemoglobin levels of patients receiving EPO were higher than those of patients who did not receive EPO. Additionally, the growth pattern of hemoglobin and reticulocytes was noteworthy. Data from the included studies indicated that the count (or percentage) of reticulocytes rose within 7 days after the injection of EPO and reached a plateau after 2 to 4 weekly injections given before surgery. There was similar pattern with hemoglobin level, which was consistent with previous studies.[37,38] After joint arthroplasty, however, the hemoglobin levels of patients who did not receive PABD decreased constantly and reached a valley at 3 or 4 days post-surgery.[11,24] This may have been caused by hidden blood loss after the operation.[39,40] As such, it is rational to recommend that EPO be given at least 2 to 3 weeks before the day of the operation, to raise the hemoglobin to a relatively high level to compensate for acute blood loss during surgery and hidden blood loss after surgery.

For the purpose of maximizing the positive effect of EPO and avoiding any possible drawbacks, the indication, dose, administration frequencies, and course must be optimized. The latest guidelines from the National Institute for Health and Care Excellence in the UK suggest that EPO be given when the patient has anemia and meets the criteria for blood transfusion, but declines a blood transfusion because of religious beliefs or other reasons, or the appropriate blood type is not available because of the patient's red cell antibodies.[41] Our review finds that patients with a normal hemoglobin level may also benefit from preoperative use of EPO and provides evidence for the use of EPO in nonanemic patients. To clarify the indications and contraindications of EPO, more studies regarding this issue are necessary, especially in patients with normal hemoglobin levels.

The treatment regimen of EPO varied substantially among the included trials. The most frequently used protocol was 40,000 IU (approximately 600 IU/kg) injected subcutaneously weekly starting 3 or 4 weeks before surgery.[13,24,25,28,30,32,34,35] This was consistent with the pharmacokinetics and pharmacodynamics of EPO.[37,38] Additionally, during this process, patients may

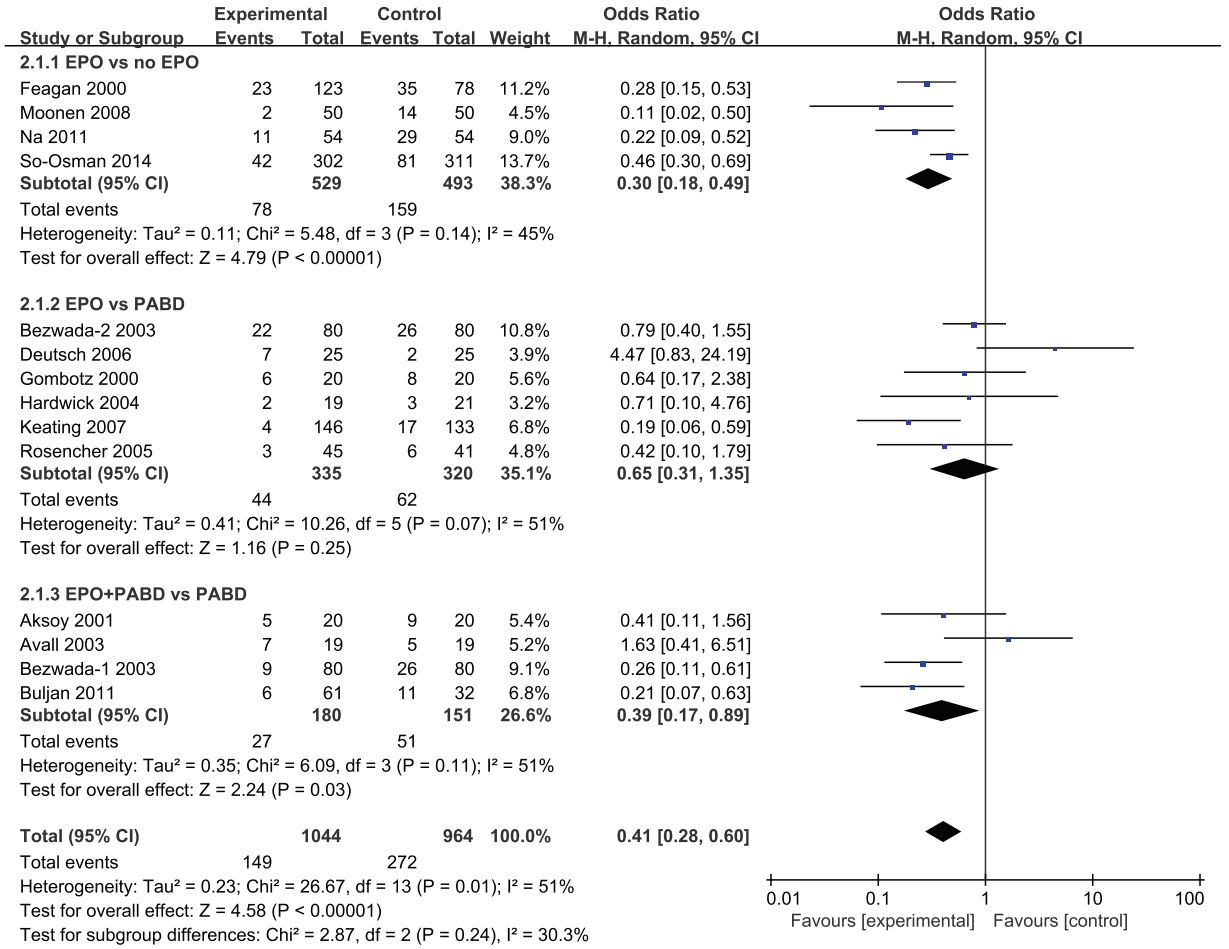

Figure 3. Forest plot of total number of patients who needed allogeneic transfusion.

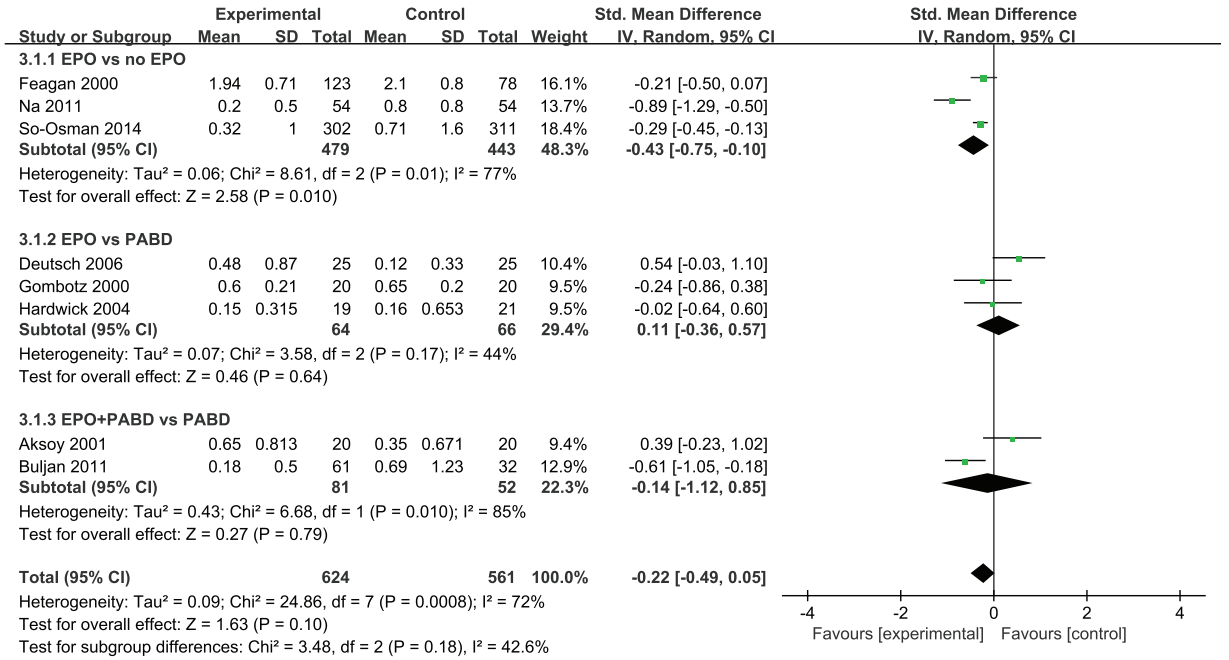

Figure 4. Forest plot of total volume of allogeneic blood needed.

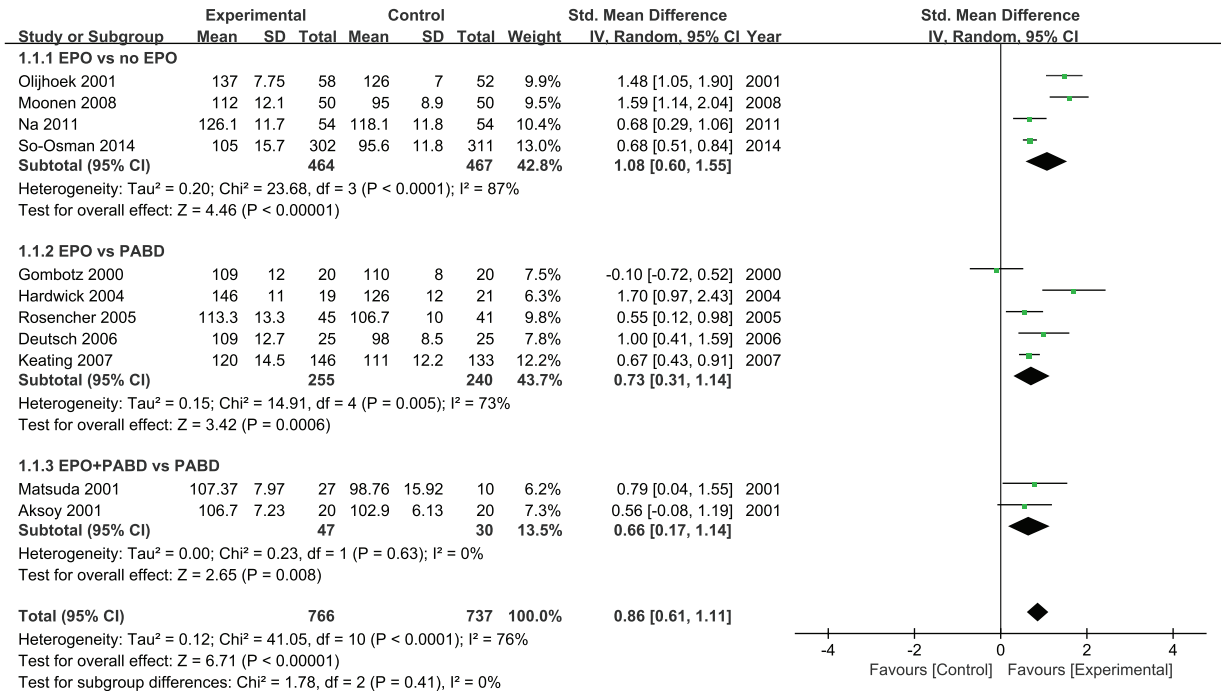

Figure 5. Forest plot of hemoglobin level at discharge.

receive EPO injections in clinic without being admitted, which may reduce the cost and the possibility of nosocomial infection.

Safety and cost-effectiveness must be considered as well. A major concern regarding the safety of EPO is venous thromboembolism (VTE), including DVT and PE. These were reported in 2 studies[24,32] and there were no significant differences of VTE occurrence between groups with EPO and without EPO. This result was contradictory to previous conclusions that EPO increased the risk of VTE after major orthopedic surgeries,[42] but the discrepancy might be explained by the use of prophylactic anticoagulation therapy in the 2 studies that showed no difference in the occurrence of VTE regardless of EPO use. Indeed, patients undergoing arthroplasty are at high risk of thrombosis, but use of updated guidelines regarding the use of prophylactic anticoagulation and risk stratification of patients will minimize the occurrence of thrombosis. We are confident that VTE will no longer be an obstacle to the use of EPO.[43,44]

Additionally, the cost of EPO must be considered while formulating treatment plans. No consensus has been reached on this issue. Hardwick et al[31] found that the cost of patients receiving EPO was higher than patients receiving PABD. Bedair et al and Coyle et al[14,45] concluded that use of EPO could reduce allogeneic transfusion, but that it was not cost-effective. In contrast, Green et al[46] conducted a cost minimization analysis and showed preoperative EPO would be significantly less costly than allogeneic blood transfusion and could save $800 per THA patient and $392 per TKA patient. However, a recent literature review found that most past economic evaluations were lacking depth and did not comply with common guidelines for pharmacoeconomic research. Consequently, a more differentiated approach is required to elucidate the cost-effectiveness of EPO in orthopedic surgeries.[47]

Compared to the previous meta-analysis conducted in 2013,[16] we performed a rigorous and complete review of the literature published in the past 2 decades. Apart from the safety of EPO, the need for ABT, and changes in hemoglobin levels, which were mentioned in the previous study, variation in trends of hemoglobin levels was also discussed in reference to the perioperative change. After analyzing the usage of EPO in all included studies and the pharmacokinetics and pharmacodynamics of EPO, a potential regimen of EPO treatment was proposed. Finally, the cost-effectiveness of EPO was summarized and analyzed to the best of our knowledge.

Our review has some limitations. First, despite the consistency of baseline hemoglobin levels, the heterogeneity of the included studies was still relatively high, but could be partially eliminated after subgroup analysis. The heterogeneity might be explained by the variance in patient demographics and treatment plans. Second, the studies included failed to provide sufficient data to analyze TKA and THA separately. A recent review claimed that patients benefited the most from EPO if they had lower preoperative hemoglobin levels and were undergoing TKA. This review demonstrated the need to differentiate between TKA and THA,[47] which is reasonable considering the difference between TKA and THA. Third, there were no adequate data to assess the impact of EPO on functional recovery after surgery and on length of hospitalization, which are important considerations for patients undergoing arthroplasty.

5. Conclusions

Preoperative use of EPO may reduce the requirement for allogeneic blood transfusion and increase the hemoglobin level after surgery, but its indication, treatment protocol, safety, and

Table 2

Occurrence of complications.

Author, year	Method	Number	PE		DVT		Myocardial infarction		Cerebrovascular accident		Cardiovascular complications other than MI		Urinary system		Gastrointestinal system		Wound/prosthesis-related complications		Others	
			EPO	Con	EPO	Con	EPO	Con	EPO	Con	EPO	Con	EPO	Con	EPO	Con	EPO	Con	EPO	Con
Feagan et al, 2000[24]	EPO vs. no EPO	201	0	1	7	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Aksoy and Tokgozoglu, 2001[26]	EPO+PABD vs. PABD	40	Examined but not reported	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Olijhoek et al, [28]2001	EPO vs. no EPO	110	No thrombotic and/or vascular events	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Bezwada et al, 2003[30]	EPO+VPABD vs. PABD	160	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Bezwada et al, 2003[30]	EPO vs. PABD	160	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Hardwick et al, 2004[31]	EPO vs. PABD	40	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rosencher et al, 2005[32]	EPO vs. PABD	86	No significant difference	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Deutsch et al, 2006[33]	EPO vs. PABD	50	—	—	—	—	—	—	0	1	1	3	1	0	—	—	—	—	2	6
Keating et al, 2007[34]	EPO vs. PABD	279	—	—	—	—	—	—	—	—	—	—	10	9	3	19	—	—	30	37
Moonen et al, 2008[35]	EPO vs. ABR	100	—	—	—	—	—	—	1	0	—	—	2	0	1	2	4	7	0	1
Buljan et al, 2011[12]	EPO+PABD vs. PABD	93	—	—	—	—	—	—	—	—	—	—	—	—	4	0	5	0	7	0
So-Osman et al, 2014[13]	EPO vs. no EPO	613	0	1	—	—	3	2	2	0	—	—	—	—	—	—	—	—	12	13

DVT = deep venous thrombosis, EPO = erythropoietin, MI = myocardial infarction, PABD = preoperative autologous blood donation, PE = pulmonary embolism.

cost-effectiveness need to be further investigated. Clinical practitioners may decide whether to use EPO before THA and TKA based on the potential benefit and risk in each case. Further studies and guidelines specific to blood management during the perioperative stage of TKA and THA are expected.

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