De-implementation of low-value care in hip and knee arthroplasty

Voorn, V.M.A.

Chapter 3

Erythropoietin to reduce allogeneic red blood cell transfusion in patients undergoing total hip or knee arthroplasty

Veronique MA Voorn, Anja van der Hout, Cynthia So-Osman, Thea PM Vliet Vlieland, Rob GHH Nelissen, M. Elske van den Akker-van Marle, Albert Dahan, Perla J Marang-van de Mheen, Leti van Bodegom-Vos

Vox Sang. 2016 Oct;111(3):219-225

Abstract

Background and Objectives: To determine the value of erythropoietin in reducing allogeneic transfusions, it is important to assess the effects, safety and costs for individual indications. Previous studies neither compared the effects of erythropoietin between total hip and total knee arthroplasty, nor evaluated the safety or costs. We performed a meta-analysis to assess the effects of erythropoietin in total hip and knee arthroplasty separately. Safety and costs were evaluated as secondary outcomes.

Materials and Methods: A systematic literature search was performed to identify randomized controlled trials evaluating the effect of erythropoietin in total hip and knee arthroplasty until April 2014. Study data were extracted using standardized forms and pooled using a random-effects model. Strength of the evidence was evaluated using Cochrane's Collaboration's tool for risk of bias assessment.

Results: Seven studies were included (2439 patients). Erythropoietin significantly reduced exposure to allogeneic transfusion in both hip (RR 0.45; 95%CI 0.33–0.61) and knee (RR 0.38; 95%CI 0.27–0.53) arthroplasty, without differences between indications ($P = 0.44$). Mean number of transfused red blood cell units was significantly decreased in erythropoietin-treated patients (mean difference −0.57; 95%CI −0.86 to −0.29)(unable to split). No differences in thromboembolic or adverse events were found. Only one study evaluated costs, so that no pooled cost-effectiveness estimates could be given.

Conclusion: Erythropoietin is effective in both hip and knee arthroplasty and can be considered as safe. However, the decision to use erythropoietin on a routine base should be balanced against its costs, which may be relatively high.

Introduction

Preoperative treatment with erythropoietin (EPO) is used in joint arthroplasty to correct preoperative anaemia, which is consequently a major risk factor for postoperative anaemia and allogeneic red blood cell (RBC) transfusion.[1] To determine the value of EPO in reducing allogeneic transfusions, it is important to assess the effects, safety and costs of EPO for individual indications. Previous reviews[1-3] and a recently published meta-analysis[4] showed that it is in general effective to use EPO to reduce allogeneic transfusion in orthopaedic procedures. However, neither of these studies compared the effect of EPO for individual indications such as total hip arthroplasty (THA) and total knee arthroplasty (TKA), nor evaluated the safety or cost involved in using EPO[4].

We hypothesized that the effects of preoperative EPO to reduce allogeneic transfusion might be larger in THA than in TKA due to a larger postoperative drop in haemoglobin (Hb) in THA than in TKA.[5] This hypothesis is supported by lower transfusion rates in TKA compared to THA,[6-9] with absolute differences up to 17%.[8] This might be due to differences in body mass index (BMI),[10,11] comorbidities,[10] anatomy of the surgical area and the extent of deep surgical dissection, leading to differences in blood loss.[10,12] These confounders necessitate a stratified analysis of patient blood management in TKA and THA, because a difference in the effect of EPO between TKA and THA could cause overtreatment.

In addition to the effects of EPO to reduce allogeneic transfusion, both the safety and costs of EPO need to be taken into account before implementation in daily practice. EPO increases the risk for thromboembolic and vascular adverse events and other non-thromboembolic adverse events.[3] On the other hand, treating patients with allogeneic transfusion might also be complicated by transfusion reactions.[13] Other concerns are the increased risks of wound or prosthesis infection after allogeneic transfusion, but the literature about this effect is ambiguous.[13-17]

Finally, also the costs of EPO treatment need to be considered. If EPO treatment is effective to reduce allogeneic transfusion, but the benefits of EPO do not outweigh the reduction in allogeneic transfusions which are relatively safe, there might be no advantage for routine use of EPO treatment in daily clinical practice.

Therefore, the aim of this meta-analysis was to assess the effect of EPO in reducing exposure to allogeneic transfusion and the mean number of RBC units transfused in both total hip and total knee arthroplasty. As secondary outcomes, the safety and costs of EPO were evaluated.

Materials and methods

Study selection

For this meta-analysis, Medline, Embase, Web of Science and the Cochrane library were systematically searched from inception through April 2014 without language restrictions (Appendix S1: Search strategy). Two reviewers independently performed the screening of titles, abstract and full-text articles. Consensus in the selection process was reached through discussion. If consensus was not reached, a third reviewer was consulted.

Articles were eligible for inclusion if they reported results of randomized controlled trials (RCT) that compared the effects of EPO and control in adult (age>18) patients undergoing elective THA or TKA. Studies had to report data on the number of patients exposed to allogeneic transfusion, or the mean number of allogeneic RBC units transfused. Administration of EPO should start prior to surgery. Excluded were studies in which the effect of EPO to augment preoperative autologous donation (PAD) was assessed. Studies with a combination of active comparisons were only included if both the intervention and control groups were equally exposed to the active treatment (active plus EPO compared to active only).

Data extraction

For each selected trial, the reviewers independently extracted study characteristics, primary (effect) and secondary (safety and cost) outcomes. When data could not be extracted separately for THA or TKA from the article, the authors of the study were contacted twice. When they did not respond, the article was excluded for the analyses. Study characteristics included type of surgery, description of the intervention (timing, dosage and frequency of EPO administration), description of the control group (placebo or no intervention), adjuvant usage of iron (oral or intravenous), usage of threshold for EPO eligibility, usage of threshold for allogeneic transfusion, concomitant interventions. Primary outcomes included the number of patients exposed to allogeneic transfusion and the mean number of RBC units transfused per patient. Secondary outcomes included the number of thromboembolic events, the number of adverse events and the costs per study arm (either EPO or control).

Statistical analysis

Data were analysed using Review Manager software (RevMan version 5.3 http://tech.cochrane.org/revman). Dichotomous and continuous data were pooled across trials using a random-effects model. For dichotomous data, a risk ratio was calculated using the Mantel–Haenszel method. For continuous data, a standardized mean

difference was calculated. If studies compared different EPO dosages or regimens with controls, these EPO arms were combined. Statistical heterogeneity was examined by the I^2 test. The I^2 test describes the percentage of the total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas values >50% indicate substantial heterogeneity[18].

The following *a priori* defined subgroup analyses with an explorative nature were performed to identify patient group(s) who might benefit from EPO use: 'Hb cut-off level for EPO treatment' including non-restricted use and restricted use; 'EPO dosage' including high dose (>1500 IU/kg bodyweight), low dose (<1500 IU/kg bodyweight) and fixed dose (fixed EPO dose irrespective to bodyweight); 'EPO timing' including short preoperative period (treatment starts 10–11 days preoperatively with daily injections) and long preoperative period (treatment starts 3–4 weeks preoperatively with a weekly injection regime); 'type of iron' including oral and intravenous; 'transfusion threshold' including restrictive (allogeneic transfusion if Hb </= 8.0 g/dl) and liberal (all others); and 'blinding' including blinded (placebo used in control group) and non-blinded (no placebo used). Differences were considered significant if the *P*-value was below 0.05.

Strength of the evidence

Included studies were assessed for methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias by two independent reviewers. Overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach using the GRADEpro guideline development tool. By assessing the quality of the evidence, the confidence in the effect estimates can be determined.

Results

The literature search strategy resulted in a total of 799 potentially relevant articles (Figure 1). Seventy articles were selected for full-text screening. Finally, seven articles describing a total of 2497 patients met the inclusion criteria and were used in the meta-analysis.[19-25] Of the seven identified studies, two only included THA patients, two studies included both THA and TKA, two studies included several types of orthopaedic surgery (e.g. THA, TKA, spine, upper extremity, ankle) and one study included orthopaedic as well as non-orthopaedic patients (THA, TKA, cardiac surgery and 'other'). Five of seven studies included both primary and revision surgery of the hip and/or knee,[19-21-23-24] one study excluded patients undergoing revision surgery,[22] and one study did not specify if

revision surgery was included.[25] (Appendix 2: Study characteristics). Only one study reported costs of EPO use.[24]

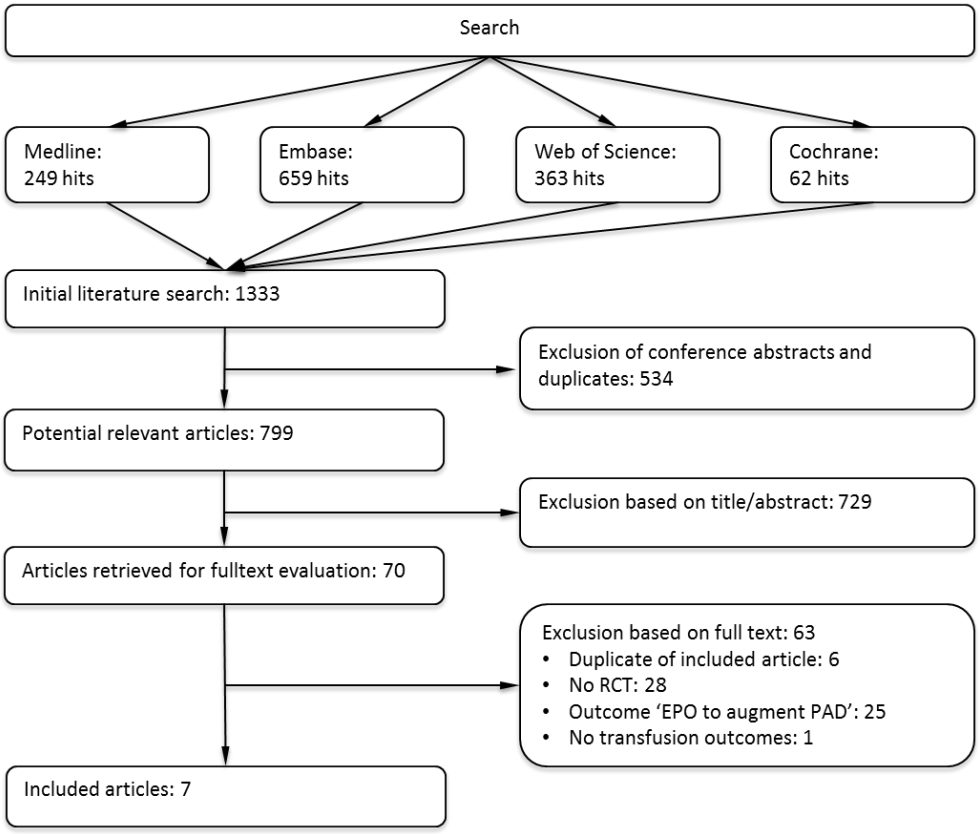

Figure 1: Flowchart

Effects of EPO

Overall EPO reduced the exposure rate by 54% compared with controls (RR 0.46; 95%CI 0.44–0.80) (Figure 2) in all included patients. However, various types of surgery were included in this analysis and the heterogeneity was substantial (I^2 = 71%). Subsequently, THA and TKA were analysed separately. In THA patients, EPO reduced the exposure rate by 55% (RR 0.45; 95%CI 0.33–0.61) (Figure 3). The heterogeneity between these studies was still substantial (I^2 = 67%). In TKA patients, EPO reduced the exposure rate by 62% (RR

0.38; 95%CI 0.27–0.53) (Figure 3), with no heterogeneity between studies (I^2 = 0%). There was no significant difference in the effect of EPO between THA and TKA (*P* = 0.44).

EPO significantly reduced the mean number of RBC units transfused (mean difference −0.57; 95%CI −0.86 to −0.29) (Figure 4), with substantial heterogeneity between the studies (I^2 = 84%). It was not possible to assess the effect of EPO on the mean number of RBC units transfused for THA and TKA separately.

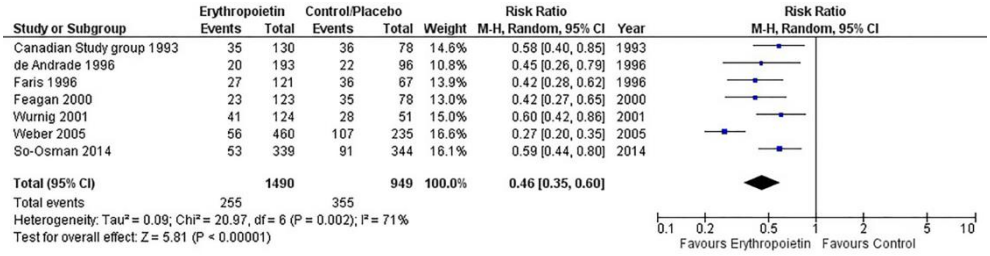

Figure 2: Patients exposed to allogeneic RBC transfusion

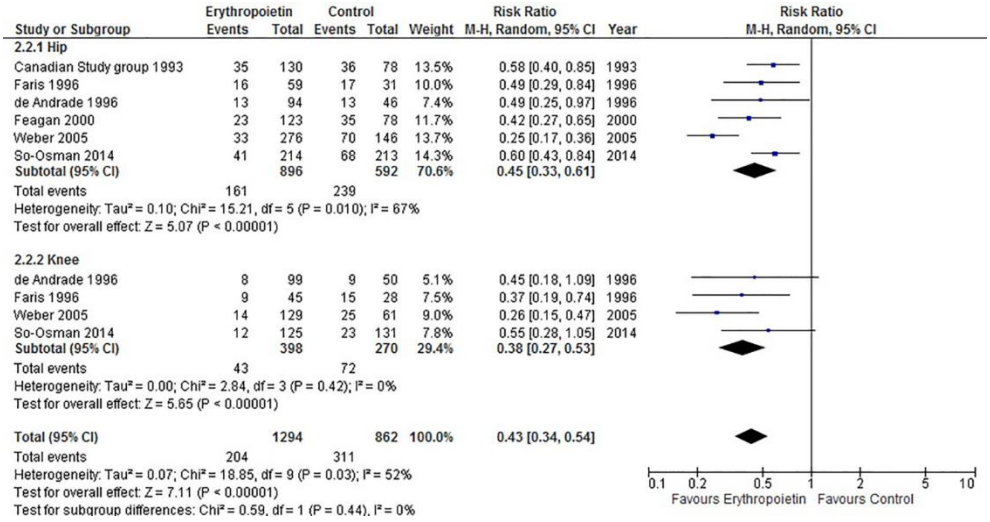

Figure 3: THA and TKA patients exposed to allogeneic RBC transfusion

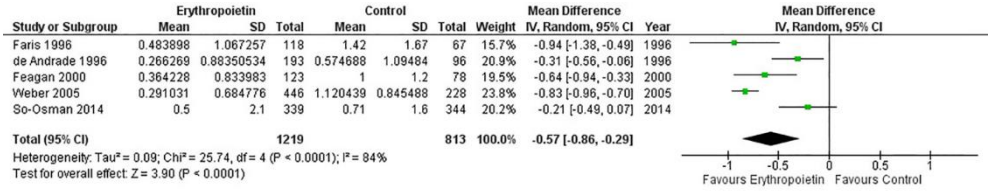

Figure 4: Mean number of RBC units transfused per patient

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Safety and costs of EPO

Thromboembolic events were reported in different ways. Three studies actively searched for the presence of deep venous thrombosis (DVT) by ultrasonography or venography[19,21,22] whereas two others only reported symptomatic DVTs,[24,25] and two did not report how they assessed DVT.[20,23] Four studies reported thromboembolic events,[19,21-23] whereas the three other studies reported a combination of thromboembolic and vascular events.[20,24,25] Reporting of other adverse events also varied severely between studies. One study reported adverse events in patients that underwent surgery (excluding patients with adverse events after receiving study medication).[22] Four other studies reported adverse events of all patients that received at least one dose of study medication[20,21,24,25] or only stated 'there were no differences'.[19,23] Analysis of the thromboembolic and vascular adverse events showed that the use of EPO did not lead to an increase of events (RR 1.14; 95%CI 0.71–1.84). Heterogeneity between studies was negligible (I^2 = 3%) (Appendix 3: Thromboembolic events and adverse events, figure 1). Analysis of the other adverse events showed no significant differences between EPO and control (RR 1.01; 95%CI 0.94–1.01), again without any heterogeneity between studies (I^2 = 0%) (Appendix 3: Thromboembolic events and adverse events, figure 2).

Only one study evaluated the costs of EPO use.[24] In that study, costs were estimated from a hospital perspective, with a 3-month horizon. The EPO strategy increased costs with €785 per patient in comparison with no intervention. With an absolute reduction in exposure to transfusion from 26.4% to 15.6% in this study, EPO avoided transfusion in every nine patients, translating the cost estimate to €7300 per avoided transfusion.[24]

Subgroup analyses

No subgroups could be identified in which the effect of EPO to reduce allogeneic transfusions differs from the overall effect (Appendix 4: Subgroup analyses).

Strength of the evidence

The overall strength of the evidence using the GRADE approach is 'high'. A detailed description of the strength of the evidence is shown in Appendix 5: Strength of the evidence.

Discussion

This meta-analysis showed that the use of preoperative EPO reduces the exposure of patients to allogeneic transfusions in both THA and TKA, with no difference in its effect between THA and TKA. These results suggest that the differences between THA and TKA in the effect of EPO are either absent or too small to be detected given the number of studies and/or the number of patients. Furthermore, this meta-analysis shows that the use of EPO did not increase the number of thromboembolic events nor the number of other adverse events. Therefore, the use of EPO to prevent allogeneic transfusions in THA and TKA can be considered as safe. The costs of EPO treatment were derived from a single study and were estimated at an additional €785 per patient or €7300 per avoided allogeneic transfusion, but estimates may differ in other healthcare systems.

In addition to previous studies,[1-4] and the recently published meta-analysis on the effectiveness of EPO,[4] our study assessed the effects for hip and knee separately, and included safety and costs of erythropoietin. Furthermore, this meta-analysis included three more studies[21,24,25] and used more strict inclusion criteria as we believed that these more strict criteria increase the quality of the conclusion to whether or not to use EPO in hip and knee arthroplasty. The use of more strict inclusion criteria led to the exclusion of studies in which the effect of EPO to augment PAD was tested or in which the effect of EPO was compared with the effect of PAD,[4] a study that started EPO postoperatively[26] and a study in which the transfusion rate or mean number of RBC units was not reported[27] in comparison with the meta-analysis of Alsaleh *et al*.[4]

Some limitations of this meta-analysis should be mentioned. First, the studies included in this meta-analysis selectively reported their used methods for perioperative care (such as the use of venous thrombosis prophylaxis) and their outcomes. This made it impossible to analyse the mean number of transfused RBC units and safety outcomes for THA and TKA separately, to analyse postoperative Hb levels, and to compare the effect of EPO for primary or revision surgery separately. Despite several attempts, additional data could not be retrieved, except for the most recent study.[24]

A second limitation is that patient safety outcomes were not assessed nor reported in a uniform way in the included studies. Furthermore, studies may not be powered to find differences in safety as the adverse outcomes are more rare than allogeneic transfusions in the included studies. This heterogeneity in reporting and lack of power complicates the comparison between studies and limits the interpretability of the patient safety analyses for EPO. However, the non-uniform reporting of safety outcomes would be expected to result in heterogeneous estimates, which were not found so that we are confident that the results regarding the safety outcomes showing no effect are valid findings.

Third, the costs analysis of the use of EPO in both THA as well as TKA was only available in one study.[24] That study concluded that the EPO strategy costs were as high as €785 per patient or €7300 per avoided transfusion. Due to variation in dosage and frequency of administration of EPO and differences in costs of both EPO and allogeneic RBC units in countries,[28] the costs cannot be extrapolated to other studies or healthcare systems. However, the high costs of EPO treatment identified in this study[24] are confirmed by several non-randomized studies. Bedair *et al*. (2014) concluded that EPO was too expensive for routine use, especially because there are less expensive alternatives.[29] Coyle *et al*. (1999) concluded that the incremental costs of EPO compared with no intervention per life year gained were as high as $66 million.[30] This was substantiated further in a systematic review and economic model.[31] Only a single study concluded that EPO treatment was cost saving in orthopaedics, by assuming that in a population with a high-transfusion-rate EPO could prevent nearly all transfusions.[32] However, that assumption is not supported by our current findings.

In conclusion, this study shows that EPO reduces allogeneic transfusions in both hip and knee arthroplasty without any additional adverse outcomes. However, given that allogeneic transfusions are also relatively safe (Dutch data show that only 0.014% of the patients experience serious transfusion reactions[33]), in combination with the decreasing RBC use in THA and TKA (Figure 4) and the substantial costs for EPO treatment to avoid these allogeneic transfusions, it remains debatable whether routine use of EPO is justified in orthopaedic practice. Furthermore, less expensive alternatives can be considered as well. To decide on these issues, more well-designed studies, evaluating the costs relative to the effectiveness of individual elements in patient blood management, are needed. In addition, future research should be aimed at the identification of patients at risk for an allogeneic transfusion that benefit most from EPO treatment.

Acknowledgements

This study was funded by a grant from the Netherlands Organisation for Health Research and Development (ZonMw 171203001) and by a grant from Sanquin Blood Supply (PPOC13-010).

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Appendix 1: Search strategy performed on 2-4-2014

Pubmed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?otool=leiden

("Arthroplasty, Replacement, Hip"[Mesh] OR "Hip Prosthesis"[Mesh] OR "THA"[all fields] OR " hip Arthroplasty"[all fields] OR " hip prosthesis"[all fields] OR " hip replacement"[all fields] OR "Arthroplasty, Replacement, Knee"[Mesh] OR "Knee Prosthesis"[Mesh] OR "TKA"[all fields] OR "knee Arthroplasty"[all fields] OR " knee prosthesis"[all fields] OR "knee replacement"[all fields] OR "Orthopedics"[Mesh] OR "elective orthopedic surgery"[all fields] OR "elective orthopaedic surgery"[all fields] OR "elective orthopedic surgical"[all fields] OR "elective orthopaedic surgical"[all fields] OR ((“hip”[all fields] OR “knee”[all fields]) AND (“arthroplasty”[all fields] OR “prosthesis”[all fields] OR “replacement”[all fields] OR “total”[all fields]))) AND ("Erythropoietin"[Mesh] OR "erythropoietin"[all fields] OR "EPO protein, human" [Supplementary Concept] OR "epoetin alfa" [Supplementary Concept] OR "Heberitro"[all fields] OR "HX575"[all fields] OR "Epogen"[all fields] OR "Eprex"[all fields] OR "epoetin"[all fields] OR "absaemed"[all fields] OR "binocrit"[all fields] OR "Procrit"[all fields] OR "darbepoetin"[all fields] OR "epocept"[all fields] OR "nanokine"[all fields] OR "epofit"[all fields] OR "epogin"[all fields] OR "neorecormon"[all fields] OR "recormon"[all fields] OR "mircera"[all fields] OR "erythropoiesis stimulating"[all fields] OR "erythropoiesis-stimulating"[all fields] OR "ESA"[all fields] OR "hematinic"[all fields] OR "EPO"[all fields] OR "KRN 321"[all fields] OR "KRN321"[all fields] OR "KRN-321"[all fields] OR "Aranesp"[all fields] OR "Aranest"[all fields] OR "KRN 5702"[all fields] OR "KRN5702"[all fields] OR "KRN-5702"[all fields] OR "NESP"[all fields] OR "NESPO"[all fields] OR "darbopoetin"[all fields] OR "darbepoietin"[all fields] OR "TYB5220"[all fields] OR "TYB 5220"[all fields] OR "TYB-5220"[all fields] OR "SNB5001"[all fields] OR "SNB 5001"[all fields] OR "SNB-5001"[all fields] OR "Marogen"[all fields] OR "Hemax"[all fields] OR "Globuren"[all fields] OR "ESPO"[all fields] OR "ERYPO"[all fields] OR "Erantin"[all fields] OR "Epoxitin"[all fields] OR "Epoconn"[all fields] OR "Epoch"[all fields] OR "Dynepo"[all fields] OR "hemopoietin"[all fields] OR "hematopoietin"[all fields] OR "erythropoietic"[all fields] OR "recormone"[all fields])

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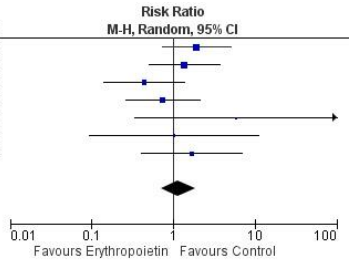
Appendix 2: Study characteristics

Author	No. of patients and mean age	Mean follow up-time	Type of surgery	Hb range to be eligible	Interventions	EPO dosage (total dosage)	Transfusion threshold
Canadian study group 1993	N=208 63 (SD 13)	3 weeks	THA	11-16 g/dl	Arm 1: EPO 14 days (started 11 days preoperative) + oral iron Arm 2: EPO 9 days, placebo 5 days (EPO started 11 days preoperative) + oral iron Arm 3: Placebo 14 days (started 11 days preoperative) + oral iron	14* 300IU/kg (4200 IU/kg) 9* 300 IU/kg (2700 IU/kg) -	Hb <9.0 g/dl
De Andrade 1996	N=316 67 (SD 12)	6 weeks	THA and TKA	≤15 g/dL	Arm 1: EPO 15 days (started 10 days preoperative) + oral iron Arm 2: EPO 15 days (started 10 days preoperative) + oral iron Arm 3: Placebo + oral iron	15* 300 IU/kg (4500 IU/kg) 15* 100 IU/kg (1500 IU/kg) -	Hb <9.0 g/dl
Faris 1996	N=200 66 (SD 13)	Until discharge	THA, TKA, spine, other orthopedic	not restricted	Arm 1: EPO 15 days (started 10 days preoperative) + oral iron Arm 2: EPO 15 days (started 10 days preoperative) + oral iron Arm 3: Placebo + oral iron	15* 300 IU/kg (4500 IU/kg) 15* 100 IU/kg (1500 IU/kg) -	Hb <9.0 g/dl
Feagan 2000	N=201 68 (SD 11)	Until discharge (at least 5 days)	THA	9.8-13.7 g/dl	Arm 1: EPO weekly (4 weeks preoperative) + oral iron Arm 2: EPO weekly (4 weeks preoperative) + oral iron Arm 3: Placebo + oral iron	4*40.000 U (160,000 U) 4*20.000U (80,000 U) -	None
Wurnig 2001	N=194 62-66 (SD N/A)	At least 6 days	Elective surgery (mainly orthopedic and cardiac)	10-14 g/dl	Arm 1: EPO weekly (3-4 weeks preoperative) + oral iron Arm 2: EPO weekly (3-4 weeks preoperative) + oral iron Arm 3: oral iron only	3-4*125 IU/kg (375-500 IU/kg) 3-4* 250 IU/kg (750-1000 IU/kg) -	Hb <8.5 g/dl
Weber 2005	N=695 67 (SD 11)	4-6 weeks	THA, TKA and spine	10-13 g/dl	Arm 1: EPO weekly (3 weeks preoperative) + oral iron Arm 2: 'usual care' (oral iron, IV iron or no iron)	4*40.000 U (160,000 U) -	Hb <8.0 g/dl
So-Osman 2014	N=683 71 (SD 12)	3 months	THA and TKA	10-13 g/dl	Arm 1: EPO weekly (3 weeks preoperative) + oral iron Arm 2: nothing	4*40.000 U (160,000 U) -	variable, Hb < 6.4 or 8.1 or 9.7 g/dl

Appendix 3: Thromboembolic events and adverse events

Study or Subgroup	Erythropoietin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Canadian Study group 1993	16	130	5	78	23.5%	1.92 [0.73, 5.04]	1993
de Andrade 1996	14	213	5	103	22.2%	1.35 [0.50, 3.66]	1996
Faris 1996	5	131	6	69	16.7%	0.44 [0.14, 1.39]	1996
Feagan 2000	7	123	6	78	19.8%	0.74 [0.26, 2.12]	2000
Wurnig 2001	6	134	0	60	2.8%	5.87 [0.34, 102.62]	2001
Weber 2005	2	460	1	235	4.0%	1.02 [0.09, 11.21]	2005
So-Osman 2014	5	339	3	344	11.1%	1.69 [0.41, 7.02]	2014
Total (95% CI)		**1530**		**967**	**100.0%**	**1.14 [0.71, 1.84]**	
Total events	55		26				

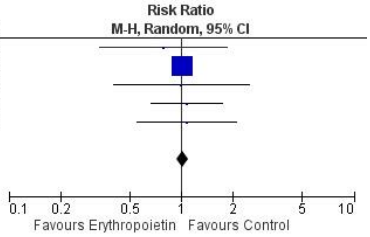
Heterogeneity: Tau² = 0.01; Chi² = 6.17, df = 6 (P = 0.40); I² = 3%
Test for overall effect: Z = 0.54 (P = 0.59)



Appendix 3 Figure 1: Thromboembolic events

Study or Subgroup	Erythropoietin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
de Andrade 1996	13	213	8	103	0.8%	0.79 [0.34, 1.84]	1996
Faris 1996	123	131	64	69	94.5%	1.01 [0.94, 1.10]	1996
Feagan 2000	11	123	7	78	0.7%	1.00 [0.40, 2.46]	2000
Wurnig 2001	41	134	17	60	2.6%	1.08 [0.67, 1.74]	2001
So-Osman 2014	17	339	16	344	1.3%	1.08 [0.55, 2.10]	2014
Total (95% CI)		**940**		**654**	**100.0%**	**1.01 [0.94, 1.09]**	
Total events	205		112				

Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 4 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)



Appendix 3 Figure 2: Adverse events

Appendix 4: Subgroup analyses

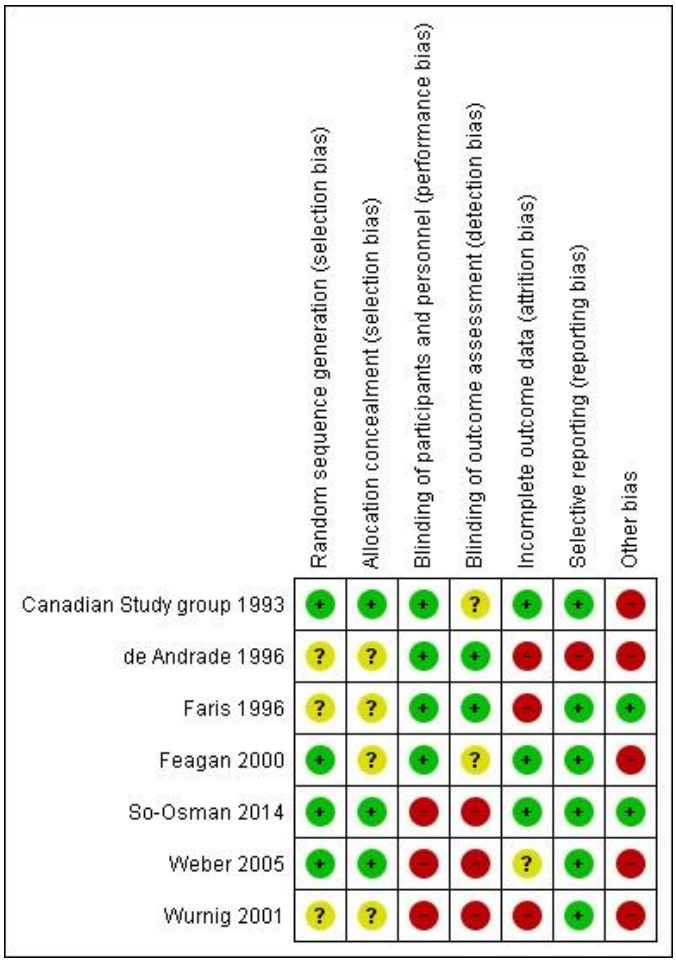
Two subgroup analyses, Hb cut-off level and type of iron used, could not be performed due to lack of variation between the studies on these variables

EPO was effective to reduce the percentage of patients exposed to allogeneic transfusion in all performed subgroups (EPO dosage, EPO timing, used transfusion threshold, and blinding). No differences in the effect of EPO between subgroups could be identified, with an I^2=0% in all subgroup analyses.

The effect of EPO to reduce the mean number of transfused RBC units varied between the subgroups. For this outcome only five out of seven studies could be used due to a lack in the availability of data on the mean number of transfused RBC units. In the subgroups 'high EPO dosage', 'short preoperative period', 'restrictive transfusion threshold' and 'non-blinded' EPO did not significantly reduce the mean number of transfused RBC units. All these subgroups included 2 studies. In all other subgroups EPO did reduce the mean number of RBC units transfused. There were no subgroup differences, with I^2=0 in all subgroup analyses.

Appendix 5: Strength of the evidence

Figure 1 describes the author's judgments about the risk of bias for each included study. All studies had a high or unclear risk of bias on at least one domain. The highest risk of bias was found on the 'other bias' domain. All included studies were sponsored or supported by a pharmaceutical company. However, two studies reported that, although being sponsored, the funding did not have any influence in the design, data-collection, analysis or reporting of the study results and were therefore judged to have a low risk of 'other bias'. The other five studies were judged to have a high risk of bias. The overall strength of the evidence using the GRADE approach is 'high' (figure 2)



Appendix 5 Figure 1: Risk of bias assessment

EPO compared to control in total hip and knee arthroplasty

Patient or population: total hip and knee arthroplasty
Intervention: EPO
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (Studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	**Risk with EPO**				
Patients exposed to allogeneic transfusion	**Study population**		**RR 0.46** (0.35 to 0.6)	2439 (7 RCTs)	⨁⨁⨁⨁ HIGH[1,2,3]	
	374 per 1000	**172 per 1000 (131 to 224)**				
	Moderate					
	455 per 1000	**209 per 1000 (159 to 273)**				
Mean number transfused	The mean mean number transfused in the control group was **0**	The mean mean number transfused in the intervention group was 0.57 lower (0.86 lower to 0.29 lower)	-	(5 RCTs)	⨁⨁⨁⨁ HIGH[1,2,3]	

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

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

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

1. No explanation was provided
2. All studies have a high or unclear risk of bias on at least one domain
3. There was substantial heterogeneity among studies

Appendix 5 Figure 2: Summary of findings