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

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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.

Key words: allogeneic red blood cell transfusion, erythropoietin, hip arthroplasty, knee arthroplasty, meta-analysis, patient blood management.

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, comanminant 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 \( \leq \) 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 (Fig. 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 S2: Study characteristics). Only one study reported costs of EPO use [24].

Effects of EPO

Overall EPO reduced the exposure rate by 54% compared with controls (RR 0.46; 95%CI 0.44–0.80) (Fig. 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) (Fig. 3). The heterogeneity between these studies was still substantial (I² = 67%). In TKA patients, EPO reduced the exposure rate by 62% (RR 0.38; 95%CI 0.27–0.53) (Fig. 3), with no heterogeneity between studies (I² = 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) (Fig. 4), with substantial heterogeneity between the studies (I² = 84%). It was not possible to assess the effect of EPO on the mean number of RBC units transfused for THA and TKA separately.

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 (I² = 3%) (Appendix S3: Thromboembolic events and adverse events, Fig. 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 (I² = 0%) (Appendix S3: Thromboembolic events and adverse events, Fig. 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 S4: 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 S5: 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 2016 The Authors. Vox Sanguinis published by John Wiley & Sons Ltd on behalf of International Society of Blood Transfusion Vox Sanguinis (2016) 111, 219–225

| Study or Subgroup | Erythropoietin | Control/Placebo | Risk Ratio | Risk Ratio |
|-------------------|----------------|----------------|------------|------------|
|                    | Events         | Total          | Weight     | M-H, Random, 95% CI | Year |
| Canadian Study group 1993 | 35 | 130 | 36 | 78 | 14.6% | 0.58 [0.40, 0.85] | 1993 |
| de Andrade 1996 | 20 | 193 | 22 | 96 | 10.6% | 0.45 [0.26, 0.79] | 1996 |
| Fars 1996 | 27 | 121 | 36 | 67 | 13.9% | 0.42 [0.28, 0.62] | 1996 |
| Feagan 2000 | 23 | 123 | 35 | 78 | 13.0% | 0.42 [0.27, 0.65] | 2000 |
| Wurnig 2001 | 41 | 124 | 28 | 51 | 15.0% | 0.60 [0.42, 0.88] | 2001 |
| Weber 2005 | 56 | 460 | 107 | 235 | 16.6% | 0.27 [0.20, 0.35] | 2005 |
| So-Danen 2014 | 53 | 338 | 91 | 344 | 16.1% | 0.59 [0.44, 0.80] | 2014 |
| **Total (95% CI)** | **1490** | **949** | **100.0%** | **0.46 [0.35, 0.60]** | **2016** |

Total events: 255
Heterogeneity: Tau² = 0.09; Chi² = 20.97, df = 6 (P = 0.002); I² = 71%
Test for overall effect: Z = 5.81 (P < 0.0001)
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 were 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 (Fig. 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.

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Author contributions
The study was designed by VV, CS, TV, RN, PM and LB. Selection of studies and data extraction were executed by VV, AH, LV. Interpretation and analysis of data were performed by VV, AH, CS, RN, MA, AD, PM and LB. VV drafted the manuscript. All authors critically revised the manuscript and approved the final version.

Conflict of interests
The authors declare no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1 Search strategy performed on 2–4–2014
Appendix S2 Study characteristics
Appendix S3 Thromboembolic events and adverse events
Appendix S4 Subgroup analyses
Appendix S5 Strength of the evidence