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Preoperative Erythropoietin Alpha Reduces Postoperative Transfusions in THA and TKA but May Not Be Cost-effective

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Abstract

Background Preoperative erythropoietin alpha (EPO) has been shown to be effective at reducing postoperative blood transfusions in total hip arthroplasty (THA) and total knee arthroplasty (TKA); however, treatment with EPO is associated with additional costs, and it is not known whether these costs can be justified when weighed against the transfusion reductions achieved in patients who receive the drug.

Questions/purposes The purpose of this study is to investigate (1) efficacy of preoperative EPO in reducing postoperative transfusions in TKA and THA; (2) whether patients treated with EPO have reduced length of stay or a different discharge disposition; and (3) whether EPO use reduces overall blood management costs.

Methods Patients undergoing primary THA or TKA over a 10-month period with preoperative hemoglobin < 13 g/dL were recommended to be treated preoperatively with EPO. During that time, 80 of 286 (28%) patients met that inclusion criterion and the treating team recommended EPO to all of them; of that group, 24 (30%) opted to take EPO and 56 (70%) opted not to. Patients receiving at least one dose of EPO and those not receiving EPO were compared in terms of transfusion frequency, length of stay and discharge disposition, and overall blood management costs. Demographics, preoperative hemoglobin, and operative blood loss for both groups were similar ($p > 0.05$). No transfusion triggers were used; rather, patients with postoperative hemoglobin < 10 mg/dL and who were symptomatic despite fluid boluses were transfused. The clinician responsible for transfusing symptomatic patients was blinded to the patient's EPO treatment status. Costs were defined as direct costs paid or incurred by our institution for EPO, allogeneic blood, and variable costs associated with patient care after THA/TKA. A decision-tree cost analysis was performed using the collected clinical data and cost data collected from our institution; the analysis considered total associated blood management cost for an EPO and a non-EPO strategy with sensitivity analysis of key cost variables.

Results The proportion of patients receiving transfusions was lower in patients who received EPO than in patients who did not (0% [zero of 24] versus 41% [23 of 56]; $p < 0.001$). The mean length of inpatient hospital stay (EPO: 3.0 ± 0.4 versus control: 3.3 ± 0.8 days, $p = 0.77$) and discharge disposition also was not different between the groups. The cost analysis demonstrated that the EPO strategy was more costly compared with no EPO (USD

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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2632 versus USD 2284) and its cost would need to be less than USD 225/dose for this to change.

Conclusions EPO reduced the need for postoperative transfusions in high-risk patients undergoing THA and TKA; however, it was not found to be cost-effective in our model. Our model could not consider relatively rare complications of blood transfusions, including disease transmission, deep periprosthetic infections, and transfusion reactions, but if surgeons or patients value avoiding these potential but rare factors highly, this could reasonably influence the decision of whether to use EPO despite our findings that it was not cost-effective.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Perioperative blood product management for THA and TKA has been extensively studied and includes many interventions such as autologous blood donation and transfusion, allogeneic blood transfusion, blood reinfusion drainage systems, hypotensive anesthesia, blood dilution techniques, iron supplementation, erythropoietin alpha (EPO), tranexamic acid, and the combination of some or all of these modalities [3, 6, 15, 20, 28, 29, 33]. Although many of these strategies are effective in maintaining or reconstituting red blood cell volume perioperatively, each is associated with its own costs. Our choices need to balance clinical efficacy against costs to deliver cost-effective care.

Several authors have compared commonly used blood management protocols that include autologous blood donation and transfusion, allogeneic blood transfusions, and EPO [4, 16, 21, 23, 27]. In a cost-minimization study associated with a specific blood management strategy, Green et al. [12] concluded that the least costly strategy was a combination of autologous and allogeneic blood [12, 27]. However, other authors have called into question the use of autologous blood donation and transfusion as being costly and possibly more wasteful than other strategies [3, 15]. In fact, some medical centers, including ours, no longer offer this service.

The use of preoperative EPO is a well-studied approach to blood management in patients at high risk for transfusion after arthroplasty, particularly those with low preoperative hemoglobin levels [6, 14, 31, 35]. The use of this medication may help decrease the frequency of blood transfusions (both allogeneic and autologous) as well as transfusion-associated concerns of disease transmission, immunosuppression, and transfusion reactions; however, EPO is expensive. We do not know whether the observed reduction in transfusion frequency associated with EPO justifies its cost.

The purpose of this study is to investigate (1) the efficacy of preoperative EPO in reducing postoperative transfusions in patients undergoing TKA and THA at high risk for transfusion; (2) whether patients treated with EPO have reduced length of stay or a different discharge disposition; and (3) whether EPO use reduces overall blood management costs.

Patients and Methods

All patients scheduled to undergo unilateral primary THA or TKA over a 10-month period were evaluated preoperatively with standard laboratory studies, including preoperative hemoglobin. Patients who were found to have a preoperative hemoglobin of < 13 g/dL were considered to be at high risk for postoperative blood transfusions and were recommended to be treated preoperatively with EPO. During that time, 80 of 286 patients (28%) met that inclusion criterion (45 THAs, 35 TKAs) and the treating team recommended EPO to all of them; of that group, 24 (30%) opted to take EPO, and 56 (70%) opted not to. No patients in this study predonated autologous blood. Patients with a preoperative hemoglobin of < 13 g/dL who received at least one dose (median, two doses; range, two to four) of EPO preoperatively (EPO group) were then compared with those patients with a preoperative hemoglobin of < 13 g/dL who did not receive EPO (control group) in terms of transfusion frequency, length of stay and discharge disposition, and overall blood management costs. Demographics, preoperative hemoglobin, operative blood loss, and anesthesia type for both groups (EPO, $n = 24$, versus control, $n = 56$) were similar ($p > 0.05$) (Table 1).

Table 1. Demographic data

Demographic	Control	EPO	p value
Age (years)	66.2 ± 1.6	60.8 ± 2.5	0.07
Sex (percent female)	78.6	83.3	0.63
ASA	1.98 ± 0.02	1.79 ± 0.09	0.0003
BMI (kg/m^2)	29.4 ± 1.3	26.3 ± 1.1	0.16
CCI	0.80 ± 0.2	0.33 ± 0.1	0.11
Preoperative Hgb (g/dL)	12.1 ± 0.7	12.3 ± 0.1	0.29
Preoperative doses of EPO	0	2.3 ± 0.1	
Percent THA	55.4	58.3	0.81
EBL (mL)	190 ± 21	220 ± 33	0.41
Anesthesia (general)	89%	83%	
Anesthesia (neuraxial)	11%	17%	0.48

Values are number or mean ± SD; EPO = erythropoietin alpha; ASA = American Society of Anesthesiologists; BMI = body mass index; CCI = Charlson Comorbidity Index; Hgb = hemoglobin.

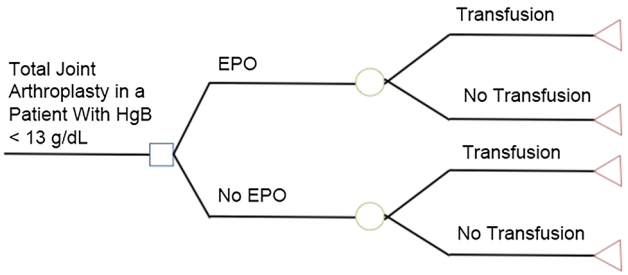

Fig. 1 Cost analysis decision tree graphically illustrates the model of a hypothetical clinical scenario with decision branch (square) and chance branches (circles) of potential outcomes based on clinical probabilities.

Table 2. Cost data

Parameter	Cost (2012, USD)	Sensitivity analysis range
Hospital stay (average daily variable cost, no transfusion)	581	
Hospital stay (average daily variable cost, transfusion)	684	
Single unit of EPO	380	100–500
Transfusion single unit of allogeneic blood	300	100–500

EPO = erythropoietin alpha.

Reasons patients who had a preoperative hemoglobin of < 13 g/dL did not receive EPO included patients who refused this treatment or those unable to pay for the treatment in cases in which the patient's health insurer refused to cover the cost. Demographic data and clinical data for these two groups, including American Society of Anesthesiologists, Charlson comorbidity index, procedure, estimated blood loss, daily postoperative hemoglobin levels, number of preoperative EPO doses, number of units of allogeneic blood transfused, inpatient hospital length of stay, and discharge disposition (home versus rehabilitation hospital), were retrospectively reviewed.

No specific transfusion triggers were used in any of these patients. Only patients with postoperative hemoglobin < 10 mg/dL who were also symptomatic (hypotension, tachycardia, dizziness, and/or an inability to participate in therapy) and whose symptoms were resistant to fluid boluses were transfused. The clinician responsible for transfusing symptomatic patients was blinded to the patient's EPO treatment status. The clinical data between groups were compared with independent sample t-tests for continuous variables and chi square tests for dichotomous variables (SAS Institute Inc, Cary, NC, USA).

To determine the overall effect on blood management costs of preoperative EPO, a decision-tree cost analysis was performed (Fig. 1) using clinical data collected from this study and cost data collected from our institution in 2012 US dollars (TreeAge Pro, Williamstown, MA, USA).

The decision-tree analysis models a hypothetical patient of average comorbidity with a preoperative hemoglobin of < 13 g/dL undergoing hip or knee arthroplasty. Based on the probabilities of transfusion observed from patients in this study who did and those who did not receive preoperative EPO, the total dollar amount associated with the blood management component of this hypothetical patient's care is calculated based on the cost of EPO, allogeneic blood, increased resource use associated with transfusion administration, and length of stay.

The cost of a single dose of EPO used in this analysis is the dollar amount paid by our institution to the drug manufacturer as reported by our institution's pharmacy. The cost of a single unit of autologous blood is the dollar amount paid by our institution to obtain, transport, store, and match blood to the recipient. This value does not include the cost of administration, which is accounted for in the variable daily cost of patient care. The variable daily cost of patient care is based on a five-tiered structure of cost associated with different levels of care required by a patient on the orthopaedic unit at our institution. This tiered structure accounts for variable resource use based on medical need. Patients undergoing routine arthroplasty are, in general, at the third tier of cost, which is the value used for the variable cost of a single day. Patients requiring blood transfusions require increased resource use and will be elevated to the fourth cost tier for the day(s) during which the transfusion was administered (Table 2).

The model variables of cost of EPO and cost of allogeneic blood were subjected to a one-way sensitivity analysis to examine the effect that uncertainty in these key variables might have on the outcome of the model (Table 1). In a one-way sensitivity analysis, one variable in the model is varied through a plausible range, whereas the remaining variables in the model are held constant.

Results

Of the 24 patients who received EPO, none (0%) received postoperative blood transfusions (Fig. 2). Of the 56 patients who did not receive EPO, 23 (41%) required transfusions ($p < 0.001$ versus EPO group) with a mean of 1.6 units per patient transfused; no complications related to transfusion were reported. The postoperative hemoglobin levels were higher in the EPO group on postoperative Days 1 (10.5 ± 0.3 versus 9.4 ± 0.1; $p < 0.001$), 2 (10.2 ± 0.3 versus 9.2 ± 0.1; $p < 0.001$, and 3 (9.7 ± 0.3 versus 9.0 ± 0.1; $p < 0.001$) (Table 3).

The mean length of inpatient hospital stay was 3.0 ± 0.4 days for the EPO group and 3.3 ± 0.8 days for the control group ($p = 0.14$) The discharge disposition

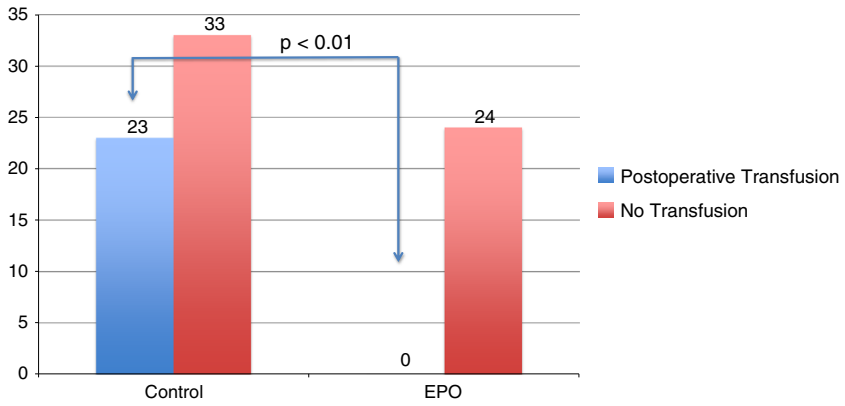

Fig. 2 Number of patients receiving postoperative allogeneic blood transfusions was significantly less in the EPO group.

Table 3. Postoperative data

Postoperative blood management measure	Control	EPO	p value
Transfused (%)	23 (41)	0 (0)	< 0.001
Units transfused*	0.41 ± 0.07	0	< 0.01
Postoperative Day 1 preoperative Hgb (g/dL)*	9 ± 0.1	10.5 ± 0.3	< 0.001
Postoperative Day 2 preoperative Hgb (g/dL)*	9 ± 0.1	10 ± 0.3	< 0.001
Postoperative Day 3 preoperative Hgb (g/dL)*	9 ± 0.1	10 ± 0.3	< 0.01
Length of stay (days)*	3 ± 0.1	3 ± 0.1	0.14
Percent discharged home	59	62.5	0.77

* Mean ± SD; EPO = erythropoietin alpha; Hgb = hemoglobin.

(home versus rehabilitation hospital) also was not statistically different between the EPO group (15 of 24 [63%] discharged home) and the control group (33 of 56 [59%] discharged home; p = 0.77).

The decision-tree cost analysis, using the clinical information reported and the cost data collected from our hospital (Table 1), demonstrated that the EPO strategy was more costly (USD 2632) than the non-EPO strategy (USD 2284). The sensitivity analysis demonstrated that the cost per unit of EPO would need to be less than USD 225 for the preoperative EPO strategy to be less costly (Fig. 3).

Discussion

Perioperative protocols for blood management for THA and TKA are a critical element of the arthroplasty episode of care. Although multiple protocols have demonstrated efficacy in terms of reducing the need for allogeneic blood [2, 8, 22, 35, 37], considered by many to be the least desirable option as a result of fear of transfusion reactions and disease transmission, there are few data accounting for the cost of these strategies [7, 12, 23]. Our study demonstrated that using preoperative EPO was an effective strategy for reducing transfusions in patients at high risk preoperatively, but overall EPO represented a more costly blood management strategy.

The limitations of this study are that this is not a randomized study. Patients entered their respective groups based only on their desire to receive EPO preoperatively and/or their insurer's (or personal) willingness to cover this expense; moreover, only a small minority of those screened were eligible for EPO using our selection criteria, and only a small minority of those patients were willing to consider taking it. This may introduce a selection bias, particularly because it concerns social and/or religious beliefs, type of insurance, and socioeconomic status. This concern may be somewhat mitigated by the absence of observed differences between the groups in terms of age, preoperative hemoglobin levels, or medical comorbidities. In addition, this study included a relatively small number of patients. However, as a result of the large effect size of EPO on postoperative transfusion rates, and in light of the sensitivity analysis, which showed the main finding to be relatively robust, our sample size may be relevant to any subgroup analyses, but future studies may need to confirm this. No transfusion triggers were used in this study, a practice that has been called into question [5, 13, 34]. Transfusion criteria used in this study are consistent with those outlined by the American Society of

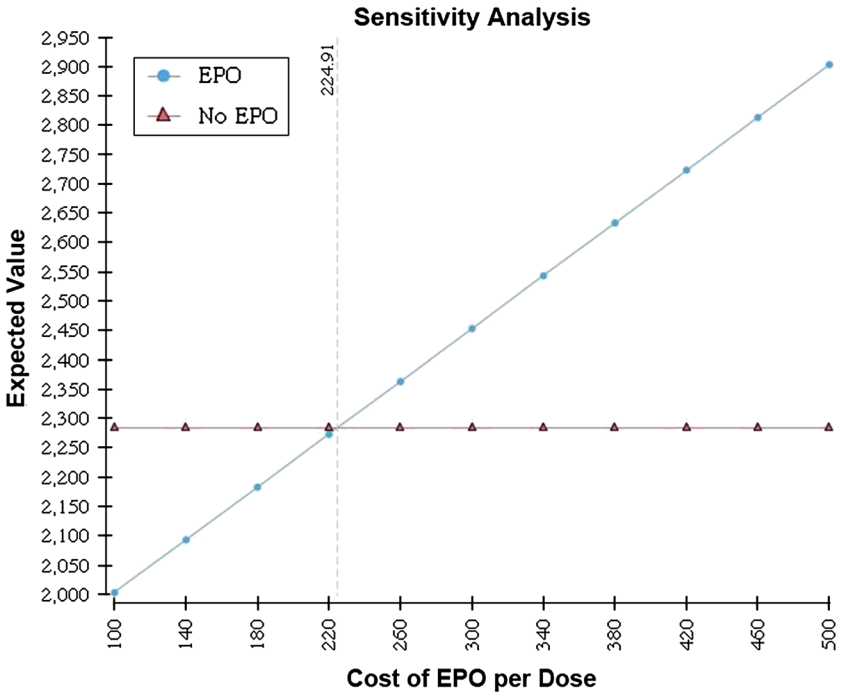

Fig. 3 One-way sensitivity analysis demonstrates that the cost of a single dose of EPO would need to cost less than USD 225 for this to be a less costly strategy.

Anesthesiologists Task Force [1]. Although this may introduce transfusion selection bias, these criteria were used across all patient groups, minimizing any potential bias. Moreover, despite not having been transfused, postoperative hemoglobin levels were higher in the EPO group than in those who were transfused. True costs are notoriously difficult to ascertain as a result of a general lack of transparency in the healthcare system. We feel that by directly obtaining best estimates of cost data from departments directly involved with blood management, we were able to obtain a best estimate of true cost for these scenarios. The cost modeling does not take into account the costs associated with complications related to allogeneic blood transfusions because these complications are rare and tremendously variable in their cost of care (eg, the cost of treating a transfusion fever is minimal compared with the cost of treating lifelong sequelae of an infectious disease).

EPO is human erythropoietin produced through a recombinant DNA process. It is highly effective at stimulating erythropoiesis. Many studies, including those specific to hip and knee arthroplasty, have demonstrated findings similar to ours in terms of reduction of transfusions after surgery [14, 31, 36]. Patients treated with EPO in our study, all of whom had anemia at baseline, avoided postoperative blood transfusions and had higher postoperative hematocrit levels on each of the first 3 postoperative days. In a similar fashion to our observations on the effect of EPO on this patient population, there have been many studies investigating various other approaches to improving blood management for THA and TKA including techniques such as hemodilution [11, 26], antifibrinolytics [36, 38], topical hemostatics [25], and reinfusion drain systems [24]. Although a singular, optimal strategy has not been established, many recent studies have shown tranexamic acid (an antifibrinolytic) to be extremely effective in large numbers of patients and certainly holds promise as a potential candidate strategy for best practice [39].

The use of EPO, however, did not reduce the length of inpatient hospital stay nor did it appear to influence postdischarge disposition (to home versus skilled nursing facilities). Husted et al. [17] observed in a large cohort of THA and TKA in Denmark that preoperative hemoglobin, postoperative hemoglobin, and the need for transfusion were strong predictors of length of stay. Similarly, in a cohort of over 700 patients undergoing THA and TKA in the United Kingdom, Kotze et al. [21] observed that improved blood management protocols reduced hospital length of stay. It is likely that many factors beyond the patient's hematologic status such as patient expectations, cultural norms, and insurance considerations contribute to length of stay and discharge disposition and that relatively smaller numbers of patients in this study may contribute to the lack of an observed difference.

The impressive clinical effect in terms of reduction of the frequency of blood transfusions after arthroplasty,

unfortunately, comes with a substantial monetary cost. EPO has become the single greatest drug expenditure for Medicare, topping USD 2 billion in 2010 alone [18]. The average cost of a single dose of EPO for the patients in this study was USD 380; when accounting for the fact that nearly all patients received either two or three doses preoperatively, the importance of this expense becomes obvious. Our sensitivity analysis found that the strategy could become cost-effective relative to a non-EPO strategy if the cost of a single dose of EPO were less than USD 225. Similar to the findings of this study, Etchason et al. [9] observed that preoperative autologous blood donation may not be a cost-effective strategy and called into question its use. Moreover, Rizzi et al. [30] questioned the high cost associated with postoperative blood salvage techniques and its utility for routine use. Tranexamic acid is an effective and relatively inexpensive approach to blood management in THA and TKA and several authors have observed a favorable cost-effect ratio for this medication in routine arthroplasty that may justify its routine use [10, 19, 32]. We are not aware of any head-to-head cost-effectiveness studies between EPO and tranexamic acid, but based on cost-effectives analyses of tranexamic acid, these types of studies may not be necessary. It is worth noting that there are a number of complications that, owing to their rarity, could not be considered in a direct cost-effectiveness model such as ours. These mainly are the complications of blood transfusions, including disease transmission, deep periprosthetic infections, transfusion reactions (including allergy and fever), transfusion-related acute lung injury, and hemolytic reactions, some of which are potentially life-threatening. It is possible that a more complex decision analysis, investigating not just costs but longer term outcomes, could consider these rare complications.

Blood management strategies for patients undergoing THA and TKA are a critical element in the episode of care. Although one approach may be highly effective, like EPO, the high costs of this treatment may not be cost-effective, particularly when other approaches exist that may be of comparable clinical efficacy but lower cost such as tranexamic acid. The results of this study demonstrate that although EPO was effective at minimizing allogeneic blood transfusions in patients at high risk for transfusion, its high cost may make it too expensive for routine use.

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