General Anesthesia

Erythropoietin is an effective clinical modality for reducing RBC transfusion in joint surgery

[Le traitement à l'érythropoïétine réduit efficacement les transfusions de culots globulaires en chirurgie orthopédique]

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Purpose: Efficacy trials of preoperative erythropoietin therapy (PET) recommend a dosing schedule that cannot always be adhered to in everyday clinical practice. Consequently, we instituted a flexible dosing schedule and routinely offered it to anemic patients [hemoglobin (Hb)] ≤ 130 $g \cdot L^{-1}$) undergoing total joint arthroplasty (TJA). The purpose of this observational, cohort study was to assess the effectiveness of this practice in reducing red blood cell (RBC) transfusion.

Methods: After obtaining Institutional Ethics Board approval, data were collected prospectively on all patients who underwent TJA at our institution from July 1999 to June 2003. Patients with baseline Hb ≤ 130 $g \cdot L^{-1}$ were offered PET as follows: one to three sc injections (20,000 IU for those ≤ 70 kg, and 40,000 IU for those > 70 kg) every three to seven days before surgery. Since treatment was not randomly assigned, multivariable logistic regression analysis and propensity score case-control matching were used to adjust for baseline differences in patient demographics and perioperative risk factors for RBC transfusion. The adjusted relationship between PET and RBC transfusion was then determined.

Results: Of the 1,782 patients that underwent TJA during the study period, 770 (47.9%) had a Hb < 130 $g \cdot L^{-1}$. Of these patients, 214 received PET and their RBC transfusion rate was 16.4%, whereas the transfusion rate was 56.1% in those who did not receive PET ($P < 0.0001$). The adjusted odds ratio of RBC transfusion with PET was 0.33 (95% confidence interval = 0.21–0.49).

Conclusion: PET, used as part of routine clinical practice, is an effective blood conservation modality.

Objectif : *Les études de l'efficacité du traitement préopératoire à l'érythropoïétine (TPE) recommandent un dosage programmé difficile à observer au quotidien. Nous avons donc institué un programme flexible et l'avons offert automatiquement aux patients anémiques [hémoglobine (Hb)] ≤ 130 $g \cdot L^{-1}$) devant subir une arthroplastie articulaire totale (AAT). Notre étude observationnelle d'une cohorte veut évaluer l'efficacité de cette pratique.*

Méthode : *Après avoir obtenu l'approbation du Comité d'éthique de l'institution, nous avons recueilli les données prospectives sur les patients qui ont subi une AAT entre juillet 1999 et juin 2003 à notre hôpital. Le TPE a été offert aux patients dont l'Hb de base était ≤ 130 $g \cdot L^{-1}$: de une à trois injections sc (20 000 UI pour un poids ≤ 70 kg et 40 000 UI pour un poids > 70 kg) tous les trois à sept jours avant l'opération. Le traitement n'étant pas assigné au hasard, une analyse de régression logistique multivariée et un appariement sujet-témoin du score de propension ont été utilisés pour ajuster les différences dans les caractéristiques des patients et les facteurs de risque périopératoires de transfusion de CG. La relation ajustée entre le TPE et la transfusion de CG a ensuite été déterminée.*

Résultats : *Des 1 782 patients qui ont subi une AAT pendant la période étudiée, 770 (47,9 %) avaient une Hb < 130 $g \cdot L^{-1}$. De ces patients, 214 ont reçu le TPE et leur taux de transfusion de CG a été de 16,4 %, tandis qu'il a été de 56,1 % chez ceux qui n'ont pas reçu de TPE ($P < 0,0001$). Le risque relatif ajusté de transfusion de CG avec le TPE était de 0,33 (intervalle de confiance de 95 % = 0,21–0,49).*

Conclusion : *Le TPE utilisé dans le cadre d'une pratique clinique courante est une modalité efficace de conservation du sang.*

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THE efficacy of preoperative erythropoietin (Epo) therapy (PET) for increasing patients' hemoglobin (Hb) concentration and reducing exposure to allogeneic red blood cell (RBC) transfusion in orthopedic surgery has been demonstrated by several double-blinded randomized clinical trials.[1–5] Feagan and his associates, in a multicentre trial in which 201 patients undergoing primary total hip arthroplasty (THA) who had a pre-treatment Hb concentration of less than 137 $g{\cdot}L^{-1}$ and did not predonate blood were randomized into three groups to receive four weekly doses of Epo (20,000 or 40,000 IU) or placebo, found that PET increased the preoperative Hb concentration by more than 15 $g{\cdot}L^{-1}$ and reduced the frequency of RBC transfusion by more than 50%.[1] Laupacis *et al.*[5] combined the results of three of the other trials (including a total of 684 patients)[2–4] and found that the overall odds ratio of RBC transfusion in patients who received PET was 0.36 [95% confidence interval (CI) 0.24–0.56].

Because of this clear efficacy, PET gained regulatory approval in 1996 for use in anemic patients (pre-treatment Hb concentration of > 100 $g{\cdot}L^{-1}$ to ≤ 130 $g{\cdot}L^{-1}$) undergoing major surgery to reduce allogeneic RBC transfusions. The use of Epo for this indication, however, remains quite limited. A multinational survey published in 1999 found that PET was used in fewer than 10% of hospitals in all surveyed countries except in Canada and Japan, where it was used in 13% and 51%, respectively.[6] The results of a survey sent to 1,000 hospitals in the United States in 1997 showed that PET was used routinely in only 2% of the hospitals.[7] A more recent practice review of Canadian hospitals (2001) found that PET was used in fewer than 2% of eligible patients undergoing total joint arthroplasty (TJA).[8]

One reason for this limited use of PET in clinical practice may be the impracticality of the dosing schedule as recommended by the efficacy trials, particularly the required lead-time of four weeks. Another reason may be the high-cost of the recommended dosage – the full recommended dose of four 40,000 IU injections of recombinant Epo costs about CAN $2,500.

Because of these limitations, starting in July 1999, we implemented a more practical PET dosing schedule for eligible anemic patients undergoing TJA at our institution. Instead of the recommended four injections of Epo, we treated patients with a maximum of three injections. Instead of using a dose of 600 $IU{\cdot}kg^{-1}$, we used a total of 20,000 IU for patients less than 70 kg and 40,000 IU for those more than 70 kg. In cases where the lead-time was less than three weeks, we reduced the number of injections (allowing one or two injections rather than three) or the frequency of injections (to as little as every three days apart as opposed to weekly), or both.

The objective of this observational study was to assess the effectiveness of this more practical dosing schedule for PET in reducing allogeneic RBC transfusion in patients undergoing TJA.

Methods

Patient population and management

Since July 1999, all patients who were scheduled for elective TJA (hip or knee) were assessed by our Perioperative Blood Conservation Program (PBCP) where, depending on their baseline Hb concentration (Hb_{base}), they were offered one of two blood conservation modalities as part of routine clinical care: preoperative autologous donation (PAD) if Hb_{base} was > 130 $g{\cdot}L^{-1}$, or PET if Hb_{base} was ≤ 130 $g{\cdot}L^{-1}$. The Hb_{base} cut-off was used as a general guideline: a few patients were offered PAD or PET outside the stated criteria, and in certain cases [such as revision THA or bilateral total knee arthroplasty (TKA)] both modalities were offered to patients. Patients were not offered PET if they had contraindications to Epo (allergy, severe coronary artery disease, recent thromboembolic events, uncontrolled hypertension, carotid artery disease (> 50% stenosis)), if they had active infection or inflammation, or if they had anemia other than anemia of chronic diseases. During the study period, the PBCP was supported by Ortho-Biotech, the Canadian supplier of Epo. This support consisted of 50% reimbursement for the costs of Epo (with the remaining 50% provided by University Health Network) to any patient who did not have full third-party insurance coverage (approximately 60% of eligible patients) and allowed us to offer patients a more organized approach to perioperative blood conservation. Ortho-Biotech was not involved in any other aspect of the study, including treatment algorithm design, data analysis, or manuscript preparation.

Patients who met the Hb_{base} cut-off, had sufficient time before surgery for PET therapy, and opted for treatment received one to three injections of *sc* Epo (20,000 IU for those ≤ 70 kg, and 40,000 IU for those > 70 kg) every three to seven days before surgery, depending on the amount of time available to surgery. In addition, they received dietary iron supplementation (various formulations providing 100 mg elemental iron per day). These patients were considered as the treatment group for the purposes of this study. Patients who met the Hb_{base} cut-off but did not have sufficient time for PET therapy or opted against therapy were considered the control group. These patients were also

TABLE I Institutional red blood cell transfusion guidelines in effect during the study period*

Hemoglobin ($g \cdot L^{-1}$)	*Risk*	*Strategy*
> 100	Very low	Avoid
80–100	Low	Avoid; may occasionally require transfusion based on clinical evaluation†
60–80	Moderate	Try to avoid; base transfusion decision on clinical evaluation†
< 60	High	Usually requires transfusion

†Clinical evaluation: volume, respiratory, cardiac, and cerebrovascular status, duration of anemia, symptoms, ongoing blood loss, presence of coagulopathy

*Adapted with permission from: *Winslow RM.* A physiological basis for the transfusion trigger. *In:* Spiess BD, Counts RB, Gould SA (Eds). Perioperative Transfusion Medicine, 1st ed. Baltimore: Williams & Wilkins; 1997: 27–43.

TABLE II Procedure and transfusion breakdown in the total sample (n = 1,611)

Procedure	*n*	*% transfused*
THA, primary	653	28.8%
THA, revision	170	53.5%
TKA, primary	679	28.1%
TKA, revision	83	24.1%
TKA, bilateral	26	50.0%

THA = total hip arthroplasty; TKA = total knee arthroplasty.

advised to take dietary iron supplementation. Patients who did not meet the Hb_{base} cut-off or who opted for PAD were excluded from the study.

Other than the above interventions, patient care was not modified in any way. The personnel in the PBCP had no input regarding any other aspect of the patients' perioperative care, including blood product transfusion decisions. The clinical team, however, was aware of patients' preoperative therapy. The RBC transfusion guidelines in use at the hospital during this time period are presented in Table I.

Data collection

After obtaining Institutional Ethics Board approval, data were collected on all patients who underwent elective TJA at our institution from July 1999 to June 2003. The following information was collected: patient demographics; American Society of Anesthesiologists' (ASA) classification of medical status; baseline serum creatinine concentration; Hb concentration before PET (baseline), before surgery, nadir post surgery, and at the time of hospital discharge; duration of surgery; exposure to blood products; and postoperative length of hospital stay.

Data analysis

SAS™ version 8.2 (SAS Institute, Inc., Cary, NC, USA) was used for the statistical analyses. Categorical variables were summarized as frequencies and percentages, continuous variables as means and standard deviations if normally distributed and medians and 25th and 75th percentiles or range if not normally distributed. The one-way ANOVA with Duncan post hoc analysis was used to determine the relationship between the number of Epo injections and the increase in Hb concentration.

As noted above, only patients whose Hb_{base} was 130 $g \cdot L^{-1}$ or less and did not receive PAD were included in the analysis. The characteristics and outcomes of those who received PET were compared to those who did not receive PET using the t test or Wilcoxon rank sum test for continuous variables and the Chi-squared or Fisher's exact test for categorical variables.

Since PET was not randomly assigned, two statistical methods were used to adjust for baseline differences in patient demographics and perioperative risk factors for RBC transfusion. One method was the use of multiple logistic regression to adjust for any significant ($P \leq 0.3$; a standard criterion for selection of candidate variables to be used in multivariable analysis)[9] between-group differences.

A second method was the use of propensity analysis to match patients who received PET to similar patients who did not receive PET.[10] The propensity score derivation model was constructed using multivariable logistic regression to model for probability of RBC transfusion without inclusion of PET as a predictor variable. This model was then used to calculate the propensity score of RBC transfusion for each patient. Using a SAS macro,[A] patients receiving PET were individually matched to unique control patients based on their propensity score using a 5→1 greedy matching technique (cases were first matched to controls that had an identical propensity score to five digits. Those that did not match were then matched to controls on four digits of the propensity score. This continued down to a one-digit match on the propensity score for those that remained unmatched).[A]

A *Parsons LS.* Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Proceedings of the twenty-sixth annual SAS Users Group International conference, Cary, NC, USA, 2004.

TABLE III Hemoglobin response to Epo

Number of doses of Epo	*n*	*Hb increase ($g \cdot L^{-1}$) (mean ± SD)**
0	1372	0.0
1	23	8.4 ± 6.5
2	93	14.3 ± 8.0
3	105	19.8 ± 10.0

Epo = preoperative erythropoietin; Hb = hemoglobin. *Difference in response significant ($P < 0.05$) between each group using two-way analysis of variance and Duncan's post hoc analysis.

Results

During the study period, 1,782 patients underwent elective TJA at our institution; 171 of them received PAD and were excluded from analysis. Of the remaining 1,611 patients, 503 (31.2%) received RBC transfusions (see Table II for breakdown according to procedure). Upon presentation to the blood conservation program, 770 (47.9%) were anemic ($Hb_{base} \leq 130$ $g \cdot L^{-1}$), 45.1% (347/770) of whom received RBC transfusions. In comparison, 18.3% (153/837) of non-anemic patients received RBC transfusions ($P < 0.0001$; four had missing Hb). Of the 770 anemic patients, 214 (27.8%) received PET. Of those who did not receive PET, 12 patients were excluded due to contraindications: eight who were considered at high-risk for thromboembolic events, and four for having an active inflammatory condition. The remaining patients who did not receive PET either were not assessed early enough before their surgery or opted against treatment. The number of doses given to patients and their Hb response is presented in Table III.

In the 770 anemic patients, the rate of RBC transfusion was 16.4% (35/214) in those who received PET compared with 56.1% (312/556) in those who did not ($P < 0.0001$; odds ratio = 0.15, 95% CI = 0.10–0.23). The number of RBC units transfused in the PET and no PET groups were: mean ± SD = 0.3 ± 0.8 and 1.5 ± 1.6; median (range) = 0 (0–4) and 2 (0–5), respectively; $P < 0.0001$. The characteristics of the two patient groups are presented in Table IV. The Hb concentration increased by 16.5 ± 9.6 $g \cdot L^{-1}$ in the PET group. The nadir and discharge Hb concentrations were also higher in the PET compared with the no PET group.

When multivariable logistic regression was used to adjust for potential confounders, the following variables remained in the model: ASA classification, age, weight, sex, renal dysfunction, baseline Hb concentration, PET, duration of surgery, surgeon, and procedure (categorized as primary THA, revision THA, primary TKA, and revision or bilateral TKA). The logistic regression model – which fitted the data well (Hosmer-Lemeshow Goodness-of-fit test = 4.6; $P = 0.8$) and was accurate (receiver operator characteristics area under the curve = 0.81) – showed that the adjusted odds ratio of RBC transfusion with PET was 0.33 (95% CI = 0.21–0.49; $P = 0.0002$).

Using propensity analysis, 198 of the patients who received PET were successfully matched to 198 control patients. The characteristics of the cases and controls are compared in Table V. Patient characteristics were similar in the two groups except for age: cases were younger than controls. The number of RBC units transfused in the cases and controls were: mean ± SD = 0.3 ± 0.8 and 1.1 ± 1.4; median (range) = 0 (0–4) and 0 (0–5), respectively; $P < 0.0001$. The rate of RBC transfusion was 15.7% (31/198) in the cases and 42.9% (85/198) in the controls ($P < 0.0001$; odds ratio = 0.24, 95% CI = 0.15–0.40).

Discussion

In this observational cohort study, we found that PET was highly effective in reducing perioperative RBC transfusions when it was used in anemic (Hb ≤ 130 $g \cdot L^{-1}$) patients undergoing elective TJA as part of routine practice that employed a more flexible dosing regimen than those used in randomized clinical trials. The most recent clinical trials used four weekly *sc* injections of 600 $IU \cdot kg^{-1}$ (or approximately 40,000 IU) of Epo starting three to four weeks before surgery.[1,5] In our study, however, patients received one to three *sc* injections of 20,000 IU or 40,000 IU of Epo given every three to seven days. Despite this lower, more flexible dosing regimen, our results were comparable to those of the randomized clinical trials. In our study, PET was associated with a 16.5 ± 9.6 $g \cdot L^{-1}$ increase in the average Hb concentration and was associated with a 40% reduction in the absolute risk of RBC exposure. After adjustment for potential confounders, the odds ratio for RBC transfusion with PET was 0.33 (95% CI = 0.21–0.49). These findings were similar to those of randomized controlled trials, which found that PET increased the preoperative Hb concentration by approximately 15 $g \cdot L^{-1}$ and reduced the frequency of RBC transfusion by approximately 50%,[1] and that the odds ratio of RBC transfusion with PET was 0.36 (95% CI 0.24–0.56).[5]

Since this was an observational study, the validity of our results depends on the appropriateness of our management of important sources of bias. One important bias is susceptibility bias, which occurs if variables that are associated with a better outcome occur more

TABLE IV Comparison of patients based on preoperative Epo therapy

*Variable**	*Class*	*Epo†* *(n = 214)*	*No Epo†* *(n = 556)*	*P value*
Pre-treatment Hb ($g \cdot L^{-1}$)		119.2 ± 7.9	118.8 ± 10.1	= 0.6
Preoperative Hb ($g \cdot L^{-1}$)		135.6 ± 12.0	118.8 ± 10.1	< 0.0001
Nadir Hb ($g \cdot L^{-1}$)		95.2 ± 13.7	83.1 ± 11.4	< 0.0001
Discharge Hb ($g \cdot L^{-1}$)		100.0 ± 10.3	96.5 ± 10.6	< 0.0001
Procedure	THA: primary	39.7%	38.0%	= 0.4‡
	THA: revision	8.4%	12.9%	
	TKA: primary	44.9%	43.8%	
	TKA: revision or bilateral	7.0%	5.4%	
ASA	III or IV	26.5%	36.5%	= 0.01
Gender	Female	86.0%	76.4%	= 0.004
Renal dysfunction	Yes	8.9%	15.1%	= 0.02
Age (yr)		64.4 ± 11.9	70.2 ± 11.9	< 0.0001
Height (cm)		159 ± 13	161 ± 10	= 0.1
Weight (kg)		75.4 ± 18.1	76.3 ± 18.3	= 0.5
Duration of surgery (min)		131 ± 31	137 ± 40	= 0.1
Length of stay (days)		7 (6,8)	7 (6,9)	= 0.03

*See text for definitions. †Mean (± SD) if normal distribution; median (25^{th}, 75^{th} percentile) if not normal distribution; percent if categorical. ‡Primary THA or TKA *vs* other. Epo = preoperative erythropoietin; Hb = hemoglobin; THA = total hip arthroplasty; TKA = total knee arthroplasty.

TABLE V Comparison of propensity matched cases and controls

*Variable**	*Class*	*EPO†* *(n = 198)*	*No EPO†* *(n = 198)*	*P value*
Pre-treatment Hb ($g \cdot L^{-1}$)		119.6 ± 7.4	121.5 ± 8.0	= 0.01
Preoperative Hb ($g \cdot L^{-1}$)		135.9 ± 11.8	121.6 ± 8.1	< 0.0001
Nadir Hb ($g \cdot L^{-1}$)		95.4 ± 13.6	85.9 ± 11.1	< 0.0001
Discharge Hb ($g \cdot L^{-1}$)		100.0 ± 10.4	96.5 ± 10.3	= 0.001
Procedure	THA: primary	39.4%	45.0%	= 0.5‡
	THA: revision	8.6%	5.6%	
	TKA: primary	45.0%	41.9%	
	TKA: revision or bilateral	7.1%	7.6%	
ASA	III or IV	24.6%	26.9%	= 0.6
Gender	Female	84.9%	79.8%	= 0.2
Renal dysfunction	Yes	8.1%	5.6%	= 0.3
Age (yr)		64.5 ± 11.9	69.2 ± 10.8	< 0.0001
Height (cm)		159 ± 13	161 ± 10	= 0.1
Weight (kg)		75.5 ± 18.4	77.2 ± 17.5	= 0.4
Duration of surgery (min)		131 ± 32	135 ± 36	= 0.3
Length of stay (days)		7 (6,8)	7 (6,9)	= 0.2

*See text for definitions. †Mean (± SD) if normal distribution; median (25^{th}, 75^{th} percentile) if not normal distribution; percent if categorical. ‡Primary THA or TKA *vs* other. Epo = preoperative erythropoietin; Hb = hemoglobin; THA = total hip arthroplasty; TKA = total knee arthroplasty.

frequently in the treatment group.[11] To control for this bias, we used multivariable modelling and propensity case-control matching to adjust for potential confounders previously shown to be related to RBC transfusion in patients undergoing TJA as well as other surgical procedures.[12–20] This does not, however, correct for the effects of unmeasured confounders on the observed association. An example of a potential confounder is coronary artery disease, the presence of which may lead to a higher RBC transfusion trigger. Although we adjusted for patients' ASA classification, which is a general measure of medical status, we did not correct for presence of coronary artery disease.

Another type of bias is proficiency bias, which occurs if the treatment being studied is supplemented by concomitant additional therapy.[11] Additional ther-

apy in this study would be the use of additional blood conservation modalities in the PET group. Our protocol for iron therapy may have introduced such a bias. Preoperative oral iron therapy has been shown to improve preoperative anemia independently of PET.[21] In this study, it is possible that the likelihood of iron therapy was higher in patients who received PET compared to those who did not receive PET since the former were prescribed iron therapy whereas the latter were only advised to take iron. This difference, if it exists, could account for some of the observed treatment effect.

Proficiency bias would also result if those making transfusion decisions, who were aware of patients' preoperative therapy, used lower RBC transfusion triggers in patients who received PET. This, however, is unlikely given that the nadir and discharge Hb concentrations were higher in the PET group.

A third form of bias is detection bias, which occurs if the outcome of interest is more frequently diagnosed or detected in the treatment group due to differences in patient monitoring and follow-up.[11] Detection issues were not a concern in this study because perioperative RBC transfusion is an objective outcome, and we used the most accurate data source – the transfusion laboratory database – to identify the patients who received RBC transfusions.

Having excluded or managed important sources of bias, we can therefore conclude that PET is effective in routine clinical practice. But does this mean that PET should be used as part of routine clinical care? The answer to this question depends to a large extent on the cost-effectiveness of PET. In the one study that has formally examined the cost-effectiveness of PET, the estimated cost of PET per quality adjusted life year gained was about 50 million US dollars,[22] a value that clearly does not favour the routine use of PET. This analysis, however, did not properly model for all the direct and indirect health-effects of RBC transfusion and its avoidance.[23] For example, a review of the economic analyses of PAD shows that the cost-effectiveness estimates for PAD are also clearly unfavourable when these health-effects are not included in the analysis,[24–26] but once they are included, the estimates become favourable.[27–29] In addition, PET, by increasing Hb concentration throughout the hospital stay, may improve functional recovery as has been demonstrated in patients undergoing surgery for hip fracture.[30,31]

Moreover, the economic analysis of PET also did not account for the substantial cost-effectiveness improvements that can be achieved by modifying the dosing schedule or by improving patient selection criteria such that PET is offered only to those patients who are at high-risk of requiring RBC transfusion. For example, our patients received an average of about 76,000 IU of Epo, which is more than 40% lower than the dose used in the economic analysis of Epo.[22] Despite this reduced dose, the treatment effect was similar to those of previous studies, the results of which were used in the economic analysis.[22] This dose reduction alone, therefore, translates to a 40% improvement in the cost-effectiveness of PET. Further improvements in cost-effectiveness can be achieved if the third injection of Epo is eliminated for patients in whom the Hb concentration exceeds 130 $g \cdot L^{-1}$ after two injections.

Thus, even though the 'true' cost-effectiveness of PET is yet to be determined, because of its excellent safety profile,[32] and this study's finding that it is effective when used in routine clinical practice, PET may be the preferred method of blood conservation for anemic patients undergoing TJA.

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