The development of indications for the preoperative use of recombinant erythropoietin

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Objective: To develop indications for the preoperative use of recombinant erythropoietin (rHuEPO) alone and in conjunction with preoperative autologous donation (PAD).

Design: A 2-round modified Delphi-consensus process.

Participants: Nine physicians representing multiple clinical specialties, practice environments and geographic locations.

Method: From evidence tables and a literature summary (MEDLINE database from January 1985 to August 1996) provided and using the RAND-UCLA appropriateness method, the physicians developed 264 indications for the preoperative use of rHuEPO by permuting 7 clinical factors (age, history of transfusion or antibody incompatibility, hemoglobin level, anemia of chronic disease, expected blood loss, presence of cardiovascular or cardiopulmonary disease and patient anxiety). These indications were rated on a 9-point appropriateness scale. Median scores and measures of agreement were determined.

Outcome measures: The significance of cost constraints or cost and blood supply constraints and the impact of each clinical factor on the ratings as judged by statistical analysis.

Results: Of the 264 indications, 54% were rated appropriate, 18% uncertain and 28% inappropriate. Expected blood loss had the greatest impact on the ratings (high expected blood loss had a 5.9 point more appropriate rating on the 9-point scale than low expected blood loss [$p < 0.0001$]). Preoperative hemoglobin level also significantly influenced the ratings ($p < 0.0001$). Compared with the clinical context, the ratings under the cost constraint were 1.0 less appropriate ($p < 0.0001$) for rHuEPO alone and 1.2 less appropriate for rHuEPO and PAD ($p < 0.0001$). The ratings for patients with moderate expected blood loss were significantly influenced by the cost constraint (less appropriate).

Conclusions: Expected blood loss and preoperative hemoglobin level were the best indicators of rHuEPO appropriateness. Different contexts modify the appropriateness ratings of an expensive drug like rHuEPO.

Objectif : Établir des indications relatives à l'utilisation préopératoire de l'érythropoïétine recombinée (rHuEPO) seule et conjuguée à un don autologue préopératoire (DAP).

Conception : Dégagement de consensus par la méthode Delphi modifiée en deux temps.

Participants : Neuf médecins représentant de multiples spécialités cliniques, contextes d'exercice de la profession et endroits géographiques.

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MÉTHODE : À partir de tableaux de données probantes et d'une recension des écrits (base de données MEDLINE de janvier 1985 à août 1996) qui leur ont été fournis et en se servant de la méthode de la pertinence RAND-UCLA, les médecins ont établi 264 indications portant sur l'utilisation préopératoire de la rHuEPO en permutant sept facteurs cliniques (âge, antécédents de transfusion ou incompatibilité d'anticorps, taux d'hémoglobine, anémie chronique, perte de sang prévue, présence d'une affection cardiovasculaire ou cardio-pulmonaire et anxiété du patient). Ces indications ont été cotées sur une échelle de pertinence de 9 points. On a établi des résultats médians et des mesures d'entente.

MESURES DE RÉSULTATS : L'importance des contraintes représentées par les coûts ou des contraintes représentées par les coûts et l'approvisionnement en sang, et l'impact de chaque facteur clinique sur les résultats jugés au moyen d'une analyse statistique.

RÉSULTATS : Sur les 264 indications, 54 % ont été jugés appropriées, 18 %, incertaines, et 28 %, inappropriées. La perte de sang prévue a eu le plus d'impact sur les évaluations (une perte de sang élevée prévue avait, sur l'échelle de 9 points, une cote de pertinence de 5,9 points de plus, qu'une perte de sang faible prévue [$p < 0{,}0001$]). Le taux d'hémoglobine préopératoire a aussi agi considérablement sur les cotes ($p < 0{,}0001$). Comparativement au contexte clinique, les évaluations liées à la contrainte coût présentaient une pertinence de 1,0 de moins ($p < 0{,}0001$) pour la rHuEPO seule et de 1,2 de moins pour la rHuEPO et le DAP ($p < 0{,}0001$). La contrainte coût (moins pertinente) a eu une incidence considérable sur les évaluations dans le cas des patients chez lesquels on prévoyait une perte de sang moyenne.

CONCLUSIONS : La perte de sang prévue et le taux d'hémoglobine avant l'intervention étaient les meilleurs indicateurs de la pertinence de la rHuEPO. Des contextes différents modifient les cotes de pertinence d'un médicament coûteux comme la rHuEPO.

Use of allogeneic red blood cell transfusions in Canada has been carefully scrutinized in recent years because of concerns about the safety of the blood supply. Several highly publicized incidents involving the transfusion of infected blood led to the re-examination of blood collection, storage and use.[1] The volume of packed red blood cells (PRBCs) used annually in Canada exceeds 720 000 units, approximately 60% of this being associated with surgery. Each year, approximately 198 000 patients undergo orthopedic surgical procedures and 48 000 patients undergo cardiovascular procedures.[1] Many of these patients receive blood transfusions. Although generally safe, transfused blood carries definable risks, including transfusion reactions (1% to 5%)[2] and viral infection (1:34 000)[3] (with specific risks of 1:493 000 for HIV transmission, 1:63 000 for hepatitis B and 1:103 000 for hepatitis C).

A synthetic erythropoietin that increases the production of red blood cells, recombinant erythropoietin (rHuEPO) (Eprex, Janssen-Ortho Inc., North York, Ont.) has recently been released for preoperative use. Several studies have shown the efficacy of rHuEPO in reducing the need for perioperative transfusions.[4,5] However, rHuEPO carries associated risks (exacerbation of hypertension, thrombotic vascular events) as well as substantial costs. At approximately $4000 per patient, widespread preoperative use could have important financial consequences for institutions, provincial drug benefit plans and ministries of health.

Given the clinical, economic and blood supply trade-offs outlined, decisions regarding the use of rHuEPO are complex. To assist decision-making by clinicians, patients and policy-makers, we convened an expert panel of Canadian physicians to develop indications for the appropriate use of this new agent. This article briefly summarizes the scientific evidence for the risks and benefits of rHuEPO, describes the indications development process, gives examples of selected indications and shows how the ratings varied based on a patient's clinical factors. It also shows how the ratings differed depending on whether the panel considered clinical factors alone or also incorporated cost and limitations in blood supply.

METHODS

Overview

To develop appropriateness measures for the use of rHuEPO given preoperatively, we (a) undertook a computer search of the literature to determine the indications for the use, risks and benefits of rHuEPO, (b) developed a list of indications or clinical scenarios where rHuEPO might be considered and (c) convened a consensus panel to review and rate each indication in 3 different contexts (clinical, cost constraint, and cost and blood supply constraint). We analysed the ratings to determine the clinical factors that influenced the ratings using the RAND-UCLA appropriateness method.[6,7]

Literature summary

The consensus panel was provided with a review of the literature describing the benefits and risks of perioperative anemia (as needed to assess whether any intervention is indicated) and the efficacy and risks of blood transfusion and rHuEPO therapy (as needed to evaluate whether rHuEPO

is an appropriate intervention). Information regarding the availability of blood and estimated costs of blood tranfusion and rHuEPO therapy were also provided. Articles were identified by searching the MEDLINE database for the period beginning in 1985 through August 1996. We identified further articles among the reference lists of papers located using MEDLINE and from the recommendations of clinicians with expertise in surgical blood loss.

Literature review results

We retrieved and evaluated 37 studies describing the benefits and risks of rHuEPO in surgical patients. We found many articles that assessed the clinical efficacy of rHuEPO in an ideal setting, such as a research study with strict selection criteria. Literature regarding the clinical effectiveness of rHuEPO (i.e., impact on outcomes under typical conditions in a community setting or in a less well-selected patient population) is currently lacking.

The studies of rHuEPO efficacy were "graded" by adapting a previously described scale.[8] We considered 11 randomized controlled trials to be large enough to be considered level I evidence and 17 smaller, randomized controlled trials to be level II evidence. In the review, we also included 3 nonrandomized (observational) controlled reports (level III evidence), 2 historically controlled reports (level IV evidence) and 4 case series (level V evidence). Three of the 37 studies potentially represent overlapping patients.

The need for intervention to treat perioperative anemia requires an understanding of the risks of anemia as well as the risks of intervention, such as blood transfusion. For detailed discussion regarding these topics, several review articles that discuss the pathophysiology of anemia in detail, and published recommendations and guidelines regarding red blood cell transfusion (including those recently issued by the Canadian Medical Association) are available.[2,9–19]

Efficacy of recombinant erythropoietin alone (without preoperative autologous donation [PAD])

The principle underlying the use of preoperative rHuEPO is to administer it in advance of surgery to stimulate a significant increase in red blood cell mass and a rapid regeneration of blood lost at the operation such that allogeneic transfusion is avoided or at least reduced. As outlined in Table I,[4,5,20–25] the majority of published studies of preoperative rHuEPO used alone involved elective orthopedic surgery. Less information was available regarding rHuEPO efficacy in cardiac surgery and other types of surgery, and for patients with a baseline hemoglobin level greater than 160 g/L or less than 100 g/L. The outcome measures most commonly used to evaluate rHuEPO efficacy were the impact on erythropoiesis, as measured by changes in hemoglobin, hematocrit or reticulocyte counts from baseline to the day of surgery, and the impact on perioperative transfusion requirements.

There was evidence that rHuEPO was effective in increasing red blood cell production between pretreatment and the day of surgery, but an increased hemoglobin level did not translate into a significant reduction in any exposure to allogeneic blood. rHuEPO appeared, however, to be effective in reducing the number of units of allogeneic blood transfused compared with placebo. From studies that stratified patients by baseline hemoglobin level, patients with a baseline hemoglobin level between 101 g/L and 130 g/L appeared to benefit the most from rHuEPO therapy, as assessed by decreased exposure to any allogeneic blood and a decreased number of allogeneic units transfused. The most studied effective regimen in decreasing exposure to allogeneic transfusion was rHuEPO 300 units/kg subcutaneously per day for at least 14 days, beginning 10 days before operation and continuing until the third or fourth day after. The evidence for lower doses or shorter duration was insufficient or conflicting, but it appeared that 100 units/kg dosing for at least 14 days or 600 units/kg subcutaneously weekly for 4 doses was effective in some patients.

Recombinant erythropoietin with PAD

The principle of using rHuEPO in combination with PAD is to enhance collection of autologous blood in advance of elective surgery by reversing existing anemia and attenuating phlebotomy-induced decreases in hemoglobin levels. The success of PAD is influenced by the patient's baseline hemoglobin level, the number of PAD units required and comorbid conditions. Nonanemic patients typically can donate 3 autologous units within a 3- to 4-week period before becoming anemic.[26] Patients who are anemic (hematocrit less than 39%) at first donation are more likely to be unsuccessful in donating the required number of units.[27,28] Information regarding the cost-effectiveness of PAD (including wastage of collected autologous blood) has been discussed elsewhere.[29–31]

The majority of published studies of rHuEPO with PAD involved elective orthopedic and cardiac patients (Table II[24,27,32–61]). These studies demonstrated that rHuEPO was effective in ameliorating PAD-induced anemia, thereby increasing the amount of autologous blood that could be donated preoperatively. All studies showed that rHuEPO

increases red blood cell production, as measured by increased reticulocyte, hematocrit or hemoglobin levels when compared with controls. rHuEPO significantly enhanced the success of reaching PAD targets of 4 or more units over placebo.

The effectiveness of rHuEPO in increasing the volume of autologous blood collected preoperatively was dose-dependent. Treatment with 300 units/kg (1800 units/kg total) and 600 units/kg (3600 units/kg total) twice weekly for 3 weeks were both effective, as was 400 units/kg weekly for 4 weeks (1600 units/kg total). Both subcutaneous and intravenous administration of rHuEPO was effective.

rHuEPO risks (side effects)

Adverse effects were uncommon in the literature regarding short-term, preoperative use of rHuEPO. It should be noted that the randomized clinical trials for rHuEPO in the preoperative period may be too small to detect serious, but infrequent, adverse effects. The most extensive use of rHuEPO has been in patients with chronic renal failure. In these patients, hypertension (or worsening of existing hypertension) is seen frequently

Table I

Efficacy Studies of Perioperative Recombinant Erythropoietin (rHuEPO) Alone

Study	No. of patients	Evidence level	Design	rHuEPO intervention	Increase in hemoglobin or hematocrit	Decrease in allogeneic exposure	Decrease in allogeneic units used	Comment
Orthopedic surgery								
Canadian Orthopedic Preoperative Erythropoietin Study Group, 1993[4]	208	I	Multicentre, randomized, double blind	300 u/kg × 14 d (D–10–D+3)	S	S	S (Hgb 100–130 g/L)	
			Placebo	300 u/kg × 9 d (D–5–D+3)	S	NS	S (Hgb 100–130 g/L)	
de Andrade et al, 1996[20]	316	I	Multicentre, randomized, double blind	300 u/kg × 15 d (D–10–D+4)	S (Hgb 100–130 g/L)	S (Hgb 100–130 g/L)	S (Hgb 100–130 g/L)	S increase in DVT (by ultrasonography) in Hgb > 130 g/L
			Placebo	100 u/kg × 15 d (D–10–D+4)	S (Hgb 100–130 g/L)	NS	S (Hgb 100–130 g/L)	
Faris, Ritter and Abels,1996[21]	200	I	Multicentre, randomized, double blind	300 u/kg × 15 d (D–10–D+4)	NS (D–10–D0)	S (NS if Hgb > 130 g/mL	S	
			Placebo	100 u/kg × 15 d (D–10–D+4)	NS (D–10–D0)	S	S	
Goldberg et al, 1996[22]	145	I	Multicentre, randomized open label (dose finding)	600 u/kg × 4 doses (D–21,D–14,D–7, D0) 300 u/kg × 15 d (D–10–D+4)	NS between 2 dosing groups	NS between 2 dosing groups	NS between 2 dosing groups	
Cardiac studies								
D'Ambra et al, 1992[5]	41	II	Randomized, double blind	300 u/kg × 8 d (D–5–D+2)		S		
			Placebo	150 u/kg × 8 d (D–5–D+2)		S		
D'Ambra, 1996[23]	182	I	Randomized, double blind	300 u/kg × 8 d (D–5–D+2)		NS (S if pts with surgical complications are excluded)		7/126 receiving rHuEPO died v. 0/56 receiving placebo; 4/7 deaths were associated with vascular or thrombotic events
			Placebo	150 u/kg × 8 d (D–5–D+2)		NS		
Kyo et al,1992[24]	95*	II	Multicentre, randomized, controlled	3000 u 2–3 ×/wk × 4 wk	NS	NS		
				6000 u 2–3 ×/wk × 4 wk	NS	NS		
				9000 u 2–3 ×/wk × 4 wk	S	NS		
Other surgery								
Heiss et al, 1996[25] (colorectal surgery)	30	II	Randomized, double blind Placebo	150 u/kg q 2 d (D–10–D+2)	NS		NS	

S = significant, NS = not significant, u = units of rHuEPO, d = day, D = day no. (D0 is day of surgery, D– = preop day, D+ = postop day) DVT = deep vein thrombosis
*Subset of full study, includes only rHuEPO arm

Table II

Efficacy Studies of rHuEPO With Preoperative Autologous Donation (PAD)

Study	No. of patients	Evidence level	Design	rHuEPO intervention	Increase in preop Hgb or Hct	Increased PAD goal met	Decrease in allogeneic exposure	Decrease in allogeneic units used	Comment
Orthopedic surgery									
Baudoux, 1996[32]	103	I	Multicentre, randomized, placebo PAD goal = 4 units over 1–3 wk	300 u/kg × 3 over 2–3 wk 600 u/kg × 3 over 2–3 wk		S S	NS NS		59% of placebo pts were able to donate ≥ 4 units
Beris, Mermillod and Levy, 1993[33]	102	I	Multicentre, randomized, controlled PAD goal = 3 units over 3 wk	10 000 units 3 ×/wk at 2 and 4 wk preop	S	NS	NS		
Biesma et al, 1994[34]	60	III	Nonrandomized, dose-finding PAD goal = 2 units on days 21 and 17	500 u/kg 2 ×/wk × 3 wk 250 u/kg 2 ×/wk × 3 wk 125 u/kg 2 ×/wk × 3 wk	S S S				S increased PAD units collected at all dosages
Biesma et al, 1994[35]	105	I	Randomized, controlled PAD goal = 2 units over 1 wk	500 u/kg 2 ×/wk × 3 wk	NS	NS	S	S	
Biesma et al, 1994[36]	62	II	Randomized, controlled PAD goal = 2 units on days 21 and 17	500 u/kg 2 ×/wk × 3 wk	S	S			
Biesma et al, 1993[37]	40	II	Randomized, controlled PAD goal = 2 units on days 21 and 17	500 u/kg 2 ×/wk × 3 wk	S	NS	NS	NS	
Flecknoe-Brown, Ross and Fox, 1995[38]	40	V	Observation, no controlled PAD goal = 2 units/wk	300 u/kg 2 ×/wk					Average 3.7 units PAD collected
Goodnough et al, 1994[39]	116	I	Multicentre, randomized, placebo PAD goal = 6 units over 3 wk	150 u/kg 2 ×/wk × 3 wk 300 u/kg 2 ×/wk × 3 wk 600 u/kg 2 ×/wk × 3 wk	NS NS S	NS S S	NS NS NS	NS NS NS	S increased PAD units collected at all dosages
Goodnough et al, 1989[40]	54	II	Multicentre, rangomized, placebo PAD goal = 6 units over 3 wk	600 u/kg 2 ×/wk × 3 wk	S	S	NS	NS	S increased PAD units collected

Table II

Maeda Hitoma and Hirata, 1989[41] (colorectal surgery)	12	III	Controlled PAD goal = 3 units over 3 wk	6000 units 3 ×/wk	S		NS	NS	
Mercuriali et al, 1995[42]	38	II	Randomized, double blind, placebo PAD goal = 6 units over 3 wk	75 u/kg 2 ×/wk × 3 wk 150 u/kg 2 ×/wk × 3 wk 300 u/kg 2 ×/wk × 3 wk	NS S S	NS NS NS			S increased PAD units collected at 300 u/kg
Mercuriali et al, 1994[43]	11 with RA	III	Historical controls PAD goal = 1 unit	300 u/kg 2 ×/wk × 3 wk		S	NS	S	
Mercuriali, 1993,[27] 1994,[44] 1996[45]	50	II	Randomized, Controlled PAD goal = 6 units over 3 wk	300 u/kg 2 ×/wk × 3 wk 600 u/kg 2 ×/wk × 3 wk			NS	NS	S increased PAD units and RBC volume collected at both dosages
Price et al, 1996[46]	204	I	Multicentre, placebo PAD goal = 6 units over 3 wk	600 u/kg 2 ×/wk × 3 wk		S	NS (S if pts with > 6 units or Hct 33%–39% excluded		S increased PAD units collected
Saikawa et al, 1994[47]	22 (with RA)	V	Observation, open label PAD goal = 2–3 units	400 u/kg q wk 600 u/kg q wk					95% able to donate at least 1 unit
Schlaeppi, Gunter and Nydegger, 1994[48]	62	II	Randomized, placebo PAD goal = 4 units over 4 wk	100 u/kg q wk × 4 wk 200 u/kg q wk × 4 wk	S S		NS	NS	
Tasaki, Ohto and Motoki, 1995[49]	20	IV	Observation, historical control PAD goal = 3 units over 3 wk	12 000 u/wk × 4 wk	S	NS	NS		
Tryba, 1996[50]	125	II	Randomized, open label PAD goal = 6 units over 3 wk	50 u/kg 2 ×/wk × 3 wk 100 u/kg 2 ×/wk × 3 wk 150 u/kg 2 ×/wk × 3 wk	NS NS NS		NS NS NS		S increased RBC volume collected in men at 100 and 150 u/kg dosages
Cardiac studies									
Hayashi et al, 1994[51]	114	I	Multicentre, placebo PAD goal = 2 units over 2 wk	24 000 u/wk × 3 wk 12 000 u/wk × 3 wk	NS NS	S NS	S NS		
Hayashi et al, 1993[52]	26	II	Controlled PAD goal = 4 units over 2 wk	200 u/kg 3 ×/wk × 2 wk	S				S increased RBC mass donated
Konishi et al, 1993[53]	10	V	Observation	100 u/kg q d × 2–12 wk 600 u/kg q wk × 2–12 wk					All pts increased Hgb from < 100 g/L to 110–145 g/L

Table II

Kulier et al, 1993[54]	24	II	Randomized, control PAD goal = 4 units over 4 wk	400 u/kg q wk × 4 wk	S	S	S	NS	S increased PAD units and RBC volume collected
Kyo et al, 1992[24]	137*	I	Multicentre, randomized, control PAD goal = 2–4 units	3000 units 2–3 ×/wk × 5 wk 6000 units 2–3 ×/wk × 5 wk 9000 units 2–3 ×/wk × 5 wk	S if dose 3 ×/wk S if dose 3 ×/wk S if dose 3 ×/wk		S S S		
Schmoeckel et al, 1993[55]	43	II	Randomized, placebo PAD goal = 1 unit	100 u/kg 2 ×/wk × 4 wk 200 u/kg 2 ×/wk × 4 wk 400 u/kg 2 ×/wk × 4 wk 800 u/kg 2 ×/wk × 4 wk	NS NS S S		NS NS NS NS		S increased RBC volume collected at 200–800 u/kg dosages
Walpoth et al, 1996[56]	31	II	Randomized, placebo PAD goal = 3 units over 3 wk	150 u/kg 2 ×/wk × 4 wk 300 u/kg 2 ×/wk × 4 wk	S S	NS NS	NS NS		Placebo also collected 3 units
Watanabe et al, 1992[57]	40	II	Randomized, placebo PAD goal = 2 units over 2 wk	100 u/kg q d × 14 d 600 u/kg q wk × 2 wk	S S		S S	NS NS	
Watanabe et al, 1991[58]	18	IV	Historical control PAD goal = 1 unit	100 u/kg q d × 3 wk (with Fe) 100 u/kg q d × 3 wk (without Fe)	S S				
Other surgery									
Braga et al, 1995[59]	22 GI cancer	II	Randomized, open label PAD goal = 2 units over 2 wk	300 u/kg × 1, then 100 u/kg × 3 doses			NS		S increase, able to donate at least 1 unit
Kajikawa et al, 1994[60]	42 hepatic cancer	II	Randomized, control PAD goal = 3 units over 2–3 wk	3000 u/d subcutaneously × 3 wk	S		S		
Yamawaki et al, 1994[61]	9 cervical cancer	V	Observation, historical control PAD goal = 3 units over 3 wk	6000 units qod		All pts donated 3 units	No pt exposed to allogeneic blood		

S = significant, NS = not significant, Hgb = hemoglobin, Hct = hematocrit, u = units of rHuEPO, d = day, RA = rheumatoid arthritis, RBC = red blood cell, GI = gastrointestinal
*Subset of full study, includes only rHuEPO with PAD arm

and may be related to the rate and extent of hematocrit increase.[62,63]

Deep vein thromboses, as detected by ultrasonography or surveillance venography, were higher in rHuEPO-treated patients than in those receiving placebo in 2 orthopedic studies.[20,22] Specifically, the risk was increased in patients on rHuEPO with baseline hemoglobin levels greater than 130 g/L. The occurrence of deep vein thrombosis in patients with a baseline hemoglobin level of 101 to 130 g/L was similar to that of patients receiving a placebo.[20] Patients who received doses of 600 units/kg weekly had a higher thrombotic vascular event rate (5%) than subjects administered 300 units/kg daily (0%), although the thrombotic events could not be attributed to rHuEPO.[22] Of greatest concern is a study in which rHuEPO was administered in the preoperative period to patients who underwent coronary artery bypass grafting (and not participating in PAD). Seven patients in the rHuEPO-treated group died (n = 126) versus none in the placebo-treated group (n = 56).[23] Four of the 7 deaths were associated with thrombotic or vascular events and a causative role of rHuEPO could not be excluded, although the death rate in the rHuEPO study group was comparable to that reported in the literature for coronary artery bypass grafting without rHuEPO treatment.

Resource considerations

The estimated procurement cost for rHuEPO in Canada is $134 per 10 000 units. For 14 doses of 300 units/kg for a patient weighing 70 kg (the labelled dose of rHuEPO use alone), the cost would be approximately $4000. Four doses of 600 units/kg for a patient weighing 70 kg (the labelled dose for rHuEPO with PAD) would cost approximately $2300. These figures do not include administration costs.

To put the relative costs of rHuEPO into perspective, we applied direct cost data to the results of 2 studies to estimate the rHuEPO costs per unit of avoided allogeneic blood transfusion. In the Canadian Orthopedic Perioperative Erythropoietin Study Group study, patients receiving rHuEPO and patients receiving placebo used a mean of 0.52 and 1.14 units of allogeneic blood, respectively.[4] Applying the direct costs for rHuEPO and allogeneic blood, the cost per rHuEPO patient was $4552 and for placebo patients, $240. Transfusions were reduced by an average of 0.62 units per patient by the use of rHuEPO. At an rHuEPO cost of $3940 per patient, the average cost per allogeneic unit of blood avoided was $6355. As a reference point, Goodnough, Bodner and Martin[28] estimated costs related to transfusion reactions and transmission of selected infectious agents (HIV, hepatitis B, hepatitis C and HTLV-I/II) to be US$21. A model of the net costs in quality-adjusted years of life for rHuEPO use would be similar to cost models for autologous blood donation (except for the costs associated with wasted units of autologous blood collected but not administered). In published models of autologous blood donation for surgical patients, the net costs in quality-adjusted years of life have ranged from US$235 000 to US$23 000 000.[29–31,64] These models were highly dependent on the estimates used for the incidence of post-transfusion hepatitis and the number of units of collected autologous blood.

Applying similar costs for rHuEPO, allogeneic blood and autologous blood to the results of a rHuEPO with PAD study,[39] we found that the direct costs associated with rHuEPO with PAD were between $2700 and $5400 per patient (depending on rHuEPO dose), compared with an average of $1600 per placebo (PAD without rHuEPO) patient.

Indications

We attempted to create a comprehensive list of all possible indications for the preoperative use of rHuEPO that might arise in clinical practice. The indications were divided into 2 clinical presentations; those pertaining to its use alone (192) and those pertaining to its use in conjunction with PAD, when it had *already* been decided to perform PAD (72). The panel did not consider or evaluate appropriate indications for PAD.

Patients were categorized according to hypothetical situations or indications based on permutations of the following factors: age (18 to 70 years, older than 70 years), history of transfusion or antibody incompatibility, preoperative hemoglobin level (more than 130 to 150 g/L, 101 to 130 g/L, 80 to 100 g/L) expected blood loss (0, 1 to 2, 3 or more units PRBCs) (or use of PAD: 1 to 2, 3 to 4, 5 or more expected units), anemia of chronic disease (present versus absent), significant stable cardiovascular or cardiopulmonary disease (present versus absent), and patient anxiety about receiving an allogeneic blood transfusion (present versus absent). Examples of indications are listed in Table III.

Consensus panel

We convened a panel of 9 Canadian physicians representing a diversity of specialties (cardiac surgery, orthopedic surgery, urologic surgery, anesthesiology, critical care medicine, transfusion medicine), practice settings (university and community) and geographic sites. The panelists received the literature review and an ini-

tial set of indications by mail, which they rated. The first round ratings were summarized and presented to the panel. During the meeting, the panelists revised the indications structure, modified the definitions of key terms, discussed reasons for the degree of agreement or disagreement in ratings from the first round and confidentially "re-rated" all indications. Each indication was rated on a 9-point scale of appropriateness (9 = extremely appropriate, 5 = uncertain and 1 = extremely inappropriate).

The panel rated each of the 264 indications under 3 separate contexts: clinical, cost constraint, and cost and blood supply constraint. In the *clinical context*, the panel based their rating of the appropriateness on a comparison of expected clinical benefits to the patient for the use of rHuEPO (e.g., fewer transfusions, improved quality of life), with its clinical risks (e.g., morbidity, toxicity). Next, the panel rated the indications considering the risks and benefits — to both the patient and the health care system. Under the context of *cost constraint*, the panel considered a health care environment needing to decrease overall costs by 10%. Lastly, the panel rated the indications under the context of both *cost and blood supply constraint* — a health care environment needing to decrease overall costs by 10% and in which 5% or more of hospital blood orders cannot be met.

The final appropriateness rating was the median rating of the 9 panelists. The consensus method did not force agreement. We considered that indications were appropriate for median ratings between 7 and 9 (without disagreement), inappropriate for median ratings between 1 and 3 (without disagreement) and uncertain for median ratings between 4 and 6 or if panelists disagreed. We defined disagreement as occurring when at least 2 panelists rated the indication appropriate and at least 2 rated the indication inappropriate regardless of the median rating.

Statistical methods

Influence of clinical factors on median ratings

We used categoric variables to represent the levels of the clinical factors that define indications and did analysis of variance of median ratings on the categoric variables. To judge the

Table III

Selected Indications and Ratings*

Indication	Context		
	Clinical	Cost constraint	Cost and blood supply constraint
Erythropoietin alone			
Hgb 131–150 g/L, no/mild patient anxiety and			
1–2 units expected PRBC loss	Inappropriate	Inappropriate	Inappropriate
≥ 3 units expected PRBC loss	Uncertain	Uncertain	Uncertain
Hgb 101–130 g/L and anemia of chronic disease, 1–2 units expected PRBC loss, and			
No/mild patient anxiety	Uncertain	Inappropriate	Uncertain
Moderate/severe patient anxiety	Appropriate	Inappropriate	Uncertain
Erythropoietin with preoperative autologous donation (PAD)			
Hgb 131–150 g/L, no/mild patient anxiety, and			
1–2 units expected use of PAD	Inappropriate	Inappropriate	Inappropriate
3–4 units expected use of PAD	Uncertain	Uncertain	Uncertain
Hgb 110–130 g/L and anemia of chronic disease, no/mild patient anxiety, and			
1–2 units expected use of PAD	Appropriate	Uncertain	Appropriate
3–4 units expected use of PAD	Appropriate	Appropriate	Appropriate

PRBC = packed red blood cell
*In all scenarios: patients were aged 18 to 70 yr, there was no history of transfusions or antibody incompatibility, and there was no significant cardiopulmonary or cardiovascular disease.
Appropriate = median of 9 panelists ratings was 7–9 without disagreement, inappropriate = median of 9 panelists ratings was 1–3 without disagreement, uncertain = median of 9 panelists ratings was 5–7 or disagreement occurred (see text)

significance of each clinical factor, we used the p value for the corresponding categoric variable in the analysis of variance. To illustrate the effect of the clinical factors, we compared mean median ratings for extreme levels of each clinical factor (e.g., high versus low expected blood loss).

Influence of context on median ratings

To judge the significance of cost constraints, or cost and blood supply constraints, we used paired comparison t-tests for equality of ratings in each of the constrained versus clinical contexts. To illustrate the effect of the constraints, we calculated mean median ratings in each of the 3 contexts.

Influence of expected blood loss on differences in median ratings by context

To check for systematic variations across indications in the influence of context on median ratings, we did an analysis of variance with constrained minus clinical median rating as the dependent variable and categoric variables for the clinical factors that define indications as independent variables. Expected blood loss was the only highly significant characteristic (for cost constraints: $p < 0.0001$ versus $p = 0.18$ to 0.94 for the other characteristics; for cost and blood supply constraints: $p < 0.0001$ versus $p = 0.04$ to 1.0). Consequently, we examined the influence of context on median ratings separately for each of the 3 categories of expected blood loss (low, medium and high), using the same methods described in the preceding paragraph.

All calculations were done using Stata version 5.0. (Stata Statistical Software: Release 5.0; Stata Corp., College Station, Tex.)

Results

Panelists rated each of the 264 indications under the 3 contexts for a total of 792 indications. Table III shows selected indications and ratings (chosen to show the full range of ratings and the influence of the clinical factors and context). Overall, 54% of the indications (428 of 792) were rated appropriate, 18% uncertain (143 of 792) and 28% inappropriate (221 of 792). Although the structure of the indications differed, in general the ratings for the use of rHuEPO alone were lower than the ratings for the use of rHuEPO with PAD (clinical context — 5.7 versus 7.3, cost constraint — 4.7 versus 6.1, cost and blood supply constraint — 5.6 versus 7.0). According to our definition, the panel disagreed for 13% of the final indications (from 20% on the first round).

To determine which clinical factors influenced the panel's median rating for the use of rHuEPO alone, we carried out an analysis of variance (Table IV). Expected blood loss had the greatest impact; high blood loss indications were rated significantly more appropriate (5.9 points higher for rHuEPO alone, 3.6 points higher for rHuEPO with PAD) than indications with low expected blood loss ($p < 0.0001$). Preoperative hemoglobin levels also significantly influenced the ratings: a low preoperative hemoglobin level was associated with greater appropriateness than a high preoperative hemoglobin level (4.4 points higher for rHuEPO alone, 3.0 points higher for rHuEPO with PAD, $p < 0.0001$).

The context had a substantial impact (Table V). Ratings were less appropriate under the cost constraint context

Table IV

Influence of Clinical Factors Alone on the Ratings

Clinical factor	Mean score*	Difference†	p value
Erythropoietin alone‡			
Expected blood loss,§ high/low	8.3/2.4	5.9	< 0.0001
Hemoglobin,¶ low/high	7.9/3.5	4.4	< 0.0001
History of transfusion incompatibility, yes/no	5.9/5.5	0.4	0.03
Patient anxiety, severe/mild or none	5.9/5.5	0.4	0.045
Cardiovascular/cardiopulmonary disease, present/absent	5.8/5.6	0.2	0.21
Age, > 70/18–70 yr	5.8/5.5	0.3	0.14
Erythropoietin and PAD‡			
Expected blood loss,§ high/low	8.8/5.2	3.6	< 0.0001
Hemoglobin,¶ low/high	8.4/5.4	3.0	< 0.0001
Patient anxiety, severe/mild or none	7.4/7.0	0.4	0.15
Cardiovascular/cardiopulmonary disease, present/absent	7.4/7.1	0.3	0.29
Age, > 70/18–70 yr	7.27/7.22	0.05	0.86

*The numbers in this column represent the mean of all ratings for the indications with that value (e.g., the mean of all ratings for high expected blood loss was 8.3).
†A positive number means that the panel rated the first scenario more appropriate than the second (e.g., high expected blood loss was more appropriate than low expected blood loss by 5.9 points on a 9-point scale).
‡Overall mean rating was 5.7.
§Erythropoietin alone: 3+ units expected packed red blood cell loss v. 0 units; erythropoietin and PAD: 5+ units expected PAD v. 1–2 units
¶Erythropoietin alone: 80–100 g/L v. > 130 g/L; erythropoietin and PAD 110–130 g/L v. > 130 g/L

than the clinical context (1.0 decrease for rHuEPO alone, $p < 0.0001$; 1.2 decrease for rHuEPO with PAD, $p < 0.0001$). Under the combined cost and blood supply constraint, the ratings differed only slightly from the clinical context (0.1 decrease for rHuEPO alone, $p = 0.04$; 0.3 decrease for rHuEPO with PAD, $p < 0.0001$).

Only 1 clinical factor (expected blood loss) had a significant influence on the variation in ratings across contexts (Table VI). The cost constraint and the combined cost and blood supply constraint had little effect on the ratings for patients with *no* expected blood loss or high expected blood loss. However, indications for patients with *intermediate* (1 to 2 units of PRBCs) expected blood loss were significantly affected by a cost constraint with ratings 2 points less appropriate than under the clinical context ($p < 0.0001$).

Discussion

We used expert panel consensus methodology to develop indications for the preoperative use of rHuEPO. Expected blood loss and preoperative hemoglobin level had the greatest impact on the ratings. The panel also evaluated use under 3 different contexts; considering clinical issues alone, adding a cost constraint, and cost in conjunction with a limited blood supply. These indications are timely owing to the recent approval of rHuEPO for general use, concerns about the safety and quantity of the blood supply and ongoing efforts to constrain health care expenditures.

Panelists received a literature summary but also rated indications and considered clinical factors where evidence was lacking. This guideline development method has been shown to have both reliability (e.g., panelists rating are stable over time) and validity (e.g., it correlates with published evidence and has internal consistency).[65] The resulting guidelines are enlightened by the evidence but use quantitative consensus judgement to evaluate the individual indications.

The rating structure had substantial clinical detail. This richness allowed the panelists to quantitatively express their viewpoints. In an effort to understand which clinical factors had the greatest impact, we performed an analysis of variance. Expected blood loss had the highest influence of the clinical factors (Table IV). On average, the panel rated indications for rHuEPO alone with *high* expected blood loss 5.9 points higher (more appropriate) on a 9-point scale than indications with *low* expected blood

Table V

Influence of Context on the Ratings

	Context		
Indication	Clinical	Cost constraint	Cost and blood supply constraint
Erythropoietin alone, $n = 192$			
Mean score*	5.7	4.7	5.6
Variation from the clinical scenario†	NA	–1.0 ($p < 0.0001$)	–0.1 ($p = 0.04$)
Erythropoietin and PAD, $n = 72$			
Mean score*	7.3	6.1	7.0
Variation from the clinical scenario†	NA	–1.2 ($p < 0.0001$)	–0.3 ($p < 0.0001$)

*Mean of all ratings for the listed context
†The negative value means that the panel rated the scenario *less* appropriate than the clinical scenario.
NA = not applicable

Table VI

Influence of Expected Blood Loss and Context on the Ratings for Erythropoietin Alone

	Context		
Expected blood loss	Clinical	Cost constraint	Cost and blood supply constraint
None, $n = 64$			
Mean score*	2.4	1.7	2.2
Variation from the clinical scenario†	NA	–0.7 ($p = 0.0001$)	–0.2 ($p = 0.02$)
1–2 units of PRBCs, $n = 64$			
Mean score*	6.3	4.3	5.9
Variation from the clinical scenario†	NA	–2.0 ($p < 0.0001$)	–0.4 ($p < 0.0001$)
3 or more units of PRBCs, $n = 64$			
Mean score*	8.3	8.0	8.6
Variation from the clinical scenario†	NA	–0.3 ($p = 0.01$)	0.3 ($p = 0.002$)

*Mean of all ratings for the listed context
†The negative value means that the panel rated the scenario *less* appropriate than the clinical scenario.
NA = not applicable

loss. Similarly, preoperative hemoglobin level had a substantial impact on appropriateness, with ratings 4.4 points higher (more appropriate) when the hemoglobin level was 80 to 100 g/L than when it was more than 130 g/L. Although statistically significant, a history of transfusion incompatibility and patient anxiety had only minimal impact on the ratings. Age and the presence of cardiovascular/cardiopulmonary disease had no impact.

The importance of expected blood loss and preoperative hemoglobin to the ratings is not surprising. The literature clearly shows that the need for allogeneic blood increases when patients present for surgery in an anemic state or lose substantial amounts of blood during the procedure. Retrospective reviews of surgical cases have found that the combination of low hemoglobin levels and high intraoperative red blood cell loss correlates with mortality.[14,66] It was unexpected that patient anxiety about allogeneic blood transfusion did not have more of an impact on the median ratings. This factor did influence certain panelists in specific indications but did not greatly shift the overall ratings. This factor has not been addressed in the literature and the ratings reflect the clinical judgement of the panelists.

On the surface, the lack of significance for the presence of cardiovascular disease seems to contradict the literature about the risks of rHuEPO. Several series have shown higher rates of thrombosis in patients receiving rHuEPO, with the greatest frequency in patients with pre-existing cardiovascular disease.[23] Why then, did the panel seemingly discount this clinical factor? During the panel discussion, a competing issue surfaced. Although rHuEPO has its greatest potential risk in patients with significant cardiovascular disease, it is in these same patients that rHuEPO has its greatest potential benefit. Acute blood loss can lead to ischemic events in patients who have cardiovascular compromise. rHuEPO can raise the preoperative hemoglobin level and potentially give the patient a greater ability to sustain that blood loss. Thus, the panel ratings reflect not an oversight of the literature but rather a balancing of risks and benefits.

To have utility, indications for rHuEPO must reflect the realities of current practice and not just model an ideal circumstance. Physicians feel most comfortable focussing on just the clinical factors. However, policymakers must consider that rHuEPO use is expensive, and widespread use would greatly impact hospitals' and provinces' ability to offer other services. Finally, the blood supply is also a constrained resource. Hospitals periodically do not have adequate supplies of blood for elective surgery. It was for these reasons that the panel evaluated rHuEPO use under the 3 separate contexts; clinical, cost constraint, and cost and blood supply constraints.

As expected, the ratings for rHuEPO use were highest (most appropriate) under the clinical context when cost was not considered (Table V). The addition of cost shifted the ratings 1 point less appropriate. The panel felt less willing to use rHuEPO when cost was a consideration. However, use of rHuEPO reduces the need for blood transfusion. In the context of constraints in cost and blood supply, the panel ratings generally resembled those of clinical issues alone. In essence, cost tended to make rHuEPO use *less* appropriate, whereas a constrained blood supply tended to make use *more* appropriate (bringing the ratings close to the original clinical context).

The impact of the context had differing importance for patients depending on the expected blood loss. When the patient had no expected blood loss, the panel felt that rHuEPO use was not warranted. Cost and blood supply constraint had minimal impact, since the panel rated each context inappropriate. In contrast, the panel rated most indications with 3 or more units of expected PRBC loss very appropriate (median rating 8.3). When the panel considered the cost constraint, the ratings only shifted a small amount (0.3), since the panel felt that in this circumstance the benefits of rHuEPO were substantial and cost did not greatly alter their judgement. With constrained blood supply, the panel ratings were even more appropriate than the clinical context, since rHuEPO use could reduce demands on this scarce resource.

The panel showed substantial cost sensitivity for indications with moderate (1 to 2 units of PRBCs) expected blood loss. It is in these patients that the panel felt that the clinical risks and benefits were about equal. The cost constraints shifted the ratings 2 points more inappropriate.

Our study evaluated the hypothetical indications for rHuEPO but did not examine actual use. To determine the appropriateness of current patterns of use requires an epidemiologic sampling of cases and determination of each clinical factor. Further research could answer this question.

In summary, we developed a detailed set of indications for the use of rHuEPO alone and its use in conjunction with PAD. By evaluating each indication under 3 separate contexts, providers and payers can tailor use, selecting the context that best reflects their environment. We identified that expected blood loss and preoperative hemoglobin level had the greatest impact on the determination of appropriateness, factors supported by the scientific literature. With this informa-

tion, clinicians can focus carefully on the selected issues that matter in a continuing effort to make best use of resources.

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