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REVIEW ARTICLE

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Blood conservation in orthopaedic surgery: the role of epoetin alfa

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Blood management in orthopaedic surgery

Major elective orthopaedic surgery is often associated with the necessity for allogeneic blood transfusion. Bierbaum et al. [2] collected data on blood management from a total of 9482 patients who underwent a total hip replacement or total knee replacement. Of the total patient population, almost half (46%) received a blood transfusion. Of the patients requiring transfusion, 34% received allogeneic blood. Compared with patients who did not receive a transfusion, patients who were transfused with allogeneic blood were more likely to develop infection ($P \leq 0.001$), fluid overload ($P \leq 0.001$), and increased duration of hospital stay ($P \leq 0.01$).

Because allogeneic transfusions carry risks of viral disease transmission, allergic reactions, and posttransfusion immunosuppression (Table 1), [12, 19, 29, 30, 37] orthopaedic surgeons have investigated various blood management strategies in orthopaedic surgery to reduce patient exposure to allogeneic blood [26].

Although innovations in surgical technique and autologous blood options reduce the risk from allogeneic blood transfusions, these techniques alone are unlikely to completely protect patients who are anaemic at the time of surgery. The stimulation of red blood cell (RBC) production by erythropoietin therapy is one means of treating this anemia preoperatively [20].

Perioperative epoetin alfa

Recombinant human erythropoietin (r-HuEPO, epoetin alfa, EPREX®, Janssen-Cilag, Bucks., UK; PROCRIT, Ortho Biotech Products, L.P., Raritan, N.J., USA) is a recombinant protein that is identical in amino acid sequence to and is functionally indistinguishable from endogenous human erythropoietin [36, 39]. Normal endogenous erythropoietin levels range from 4 to 30 IU/ml and support basal synthesis of new RBCs, but erythropoietin levels can increase dramatically after significant blood loss [14]. There may be a minimal increase in erythropoietin levels after preoperative autologous blood donation (PABD), but this increase in erythropoietin is often insufficient to produce a compensatory increase in RBC production. Therefore, PABD may actually produce preoperative anemia [28].

Epoetin alfa can be administered perioperatively as a primary blood management strategy to accelerate RBC production and increase hemoglobin (Hb) concentration

Table 1 Estimated risks of allogeneic blood transfusion per unit

Risk	Frequency of occurrence
Viral infection	
Human immunodeficiency virus	1:1,000,000
Hepatitis B virus	1:100,000
Hepatitis C virus	1:500 to 5,000
Human T-cell lymphotropic virus I and II	1:200,000
Cytomegalovirus	Varies; 1:2
Immunosuppression	
Infection	25% to 30% increase after surgery
Cancer	Shortened survival, shortened disease-free interval
Transfusion reaction	
Fatal hemolytic	<1:100,000
Nonfatal hemolytic	1:6,000
Fever or urticaria	1:100
Allergic reaction	
Graft-versus-host disease	Rare
Alloimmunization	Up to 50%

Adapted from Klein [29]. With permission from Excerpta Medica Inc. Data in part from Klein [30]

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Table 2 Epoetin alfa efficacy in major orthopaedic procedures

Study	No. patients	Orthopaedic procedure	Treatment and dose	Key findings in epoetin alfa-treated patients
Beris 1993 [1]	101	Orthopaedic surgery (general)	Epoetin alfa 10,000 IU s.c. ×6 at week 4, 10,000 IU s.c. ×6 at week 2, or placebo; p.o. iron	Increased reticulocyte count Minimized decrease in Hb concentration
Canadian 1993 [4]	198	Hip arthroplasty	Epoetin alfa 300 IU/kg s.c. daily ×14 days, 10 days preoperative; placebo ×5 days, 10 days preoperative then epoetin alfa 300 IU/kg s.c. daily ×9 days, or placebo	Dose-dependent increase in reticulocyte count and Hb concentration in epoetin alfa-treated patients Exposure to allogeneic blood decreased in epoetin alfa-treated patients
Cazenave 1997 [5]	80	Orthopaedic or cardiovascular surgery	Epoetin alfa 600 or 300 IU/kg i.v., or placebo ×3 per week for 1 week, 18 to 21 days preoperative p.o. iron	Significantly increased predonation of ≥4 units blood Dose-related increase in RBC volume and production
de Andrade 1996 [7]	290	Hip or knee arthroplasty	Epoetin alfa 300 or 100 IU/kg s.c., or placebo, daily×15 days, 10 days preoperative p.o. iron	Dose-related increase in reticulocyte count, Hb, and Hct Reduction in risk of exposure to allogeneic blood
Faris 1996 [11]	185	Hip or knee arthroplasty	Epoetin alfa 300 or 100 IU/kg s.c., or placebo, daily×15 days, 10 days preoperative p.o. iron	Dose-related increases in reticulocyte count, Hb concentration, and Hct Reduction in risk of exposure to allogeneic blood
Goldberg 1996 [15]	140	Hip or knee arthroplasty	Epoetin alfa 600 IU/kg s.c.×4 weekly doses, 21 days preoperative or 300 IU/kg i.v. daily ×15 days, 10 days preoperative p.o. iron	Increased Hb concentration from baseline to presurgery Weekly s.c. regimen comparable to daily i.v. regimen in terms of transfusion needs
Goodnough 1989 [18]	47	Orthopaedic surgery	Epoetin alfa 600 IU/kg, or placebo, i.v.×2/week for 3 weeks; p.o. iron	Minimized Hct decrease from phlebotomy Increased RBC volume
Goodnough 1992 [17]	44	Orthopaedic surgery	Epoetin alfa 600 IU/kg or placebo, i.v., ×2 per week for 3 weeks; p.o. iron	Increased RBC production and donation
Goodnough 1994 [16]	116	Orthopaedic urgery	Epoetin alfa 600, 300, or 150 IU/kg, or placebo, i.v. ×2 per week for 3 weeks; p.o. iron	Increased reticulocyte count and RBC volume expansion
Graf 1990 [21]	10	Total hip arthroplasty	Epoetin alfa 150 to 200 IU/kg i.v.×3 per week for 2 to 6 weeks (6–18 doses)	Predonation of 4.4 units blood/patient Safety demonstrated
Hochreiter 1992 [22]	82	Total hip arthroplasty	Epoetin alfa 200 or 100 IU/kg, or placebo, i.v. ×2 per week for 3 weeks	Increased predonation of blood in mildly anaemic patients
Mercuriali, 1993 [33]	50	Total hip arthroplasty	Epoetin alfa 600 or 300 IU/kg, or placebo, i.v. ×2 per week for 3 weeks; p.o. and i.v. iron	Increased predonation of blood Reduced risk of exposure to allogeneic blood
Mercuriali, 1994 [32]	23	Total hip arthroplasty	Epoetin alfa 300 IU/kg, or placebo, i.v. ×2 per week for 3 weeks; i.v. iron	Increased predonation ≥2 units blood Reduced risk of exposure to allogeneic blood
Stowell 1999 [40]	490	Total joint arthroplasty	Epoetin alfa 600 IU/kg/week ×4 weekly doses, or participate in PABD	Hb significantly higher in epoetin alfa patients pre- and postoperatively, and at discharge versus PABD patients Overall transfusion rate reduced in epoetin alfa group versus PABD group
Tasaki 1992 [41]	25	Orthopaedic surgery	Epoetin alfa 9,000, 6,000 or 3,000 IU i.v. ×2 per week for 3 weeks; p.o. iron daily and i.v. iron ×2 per week	Dose-dependent increase in RBC volume
Tryba 1997 [42]	125	Orthopaedic surgery	Epoetin alfa 150, 100, or 50 IU/kg, i.v. or placebo ×2 per week for 3 weeks, 18–21 days preoperative i.v. iron	Increased reticulocyte count and predonation ≥4 units blood Reduction in mean volume of allogeneic blood transfused

Epoetin alfa=Recombinant human erythropoietin; Hb=haemoglobin; RBC= red blood cell; Hct=haematocrit; PABD=preoperative autologous blood donation. Adapted with permission from Keating [26]

prior to surgery and reduce the risk of allogeneic blood transfusion in anaemic patients scheduled for elective orthopaedic surgery.

Clinical rationale for perioperative epoetin alfa

The efficacy of epoetin alfa in patients undergoing major elective orthopaedic surgery has been demonstrated in numerous clinical studies (Table 2) [1, 4, 5, 7, 11, 15, 16, 17, 18, 21, 22, 26, 32, 33, 40, 41, 42]. These studies established the clinical rationale, the optimum dosage regimen, and identified orthopaedic patient populations that demonstrated significant benefits from epoetin alfa treatment [4, 7, 11, 15]. Three of these studies, in particular, demonstrated the efficacy and safety of epoetin alfa in elective orthopaedic surgery patients with baseline Hb>10 to ≤13 g/dl who were undergoing hip or knee arthroplasty [4, 7, 11]. These anaemic patients are known to be at increased risk of needing a transfusion [2]. In these studies, Hb, haematocrit (Hct), and reticulocytes were significantly higher in patients treated with a daily regimen of epoetin alfa (300 IU/kg administered subcutaneously [s.c.] for 14 days, beginning 10 days before surgery) compared with placebo-treated patients. In addition, epoetin alfa treatment significantly reduced the incidence of allogeneic blood transfusion compared with placebo.

A subsequent study [15] compared the efficacy of the daily epoetin alfa regimen with that of a weekly regimen (600 IU kg^{-1} $week^{-1}$ administered s.c. for 3 weeks; 4 doses starting 21 days before surgery) in patients with baseline Hb>10 to ≤13 g/dl who were scheduled to undergo hip or knee arthroplasty. Both the weekly and the daily regimens of epoetin alfa were effective in increasing the mean Hb, Hct, and reticulocyte values from baseline to presurgery; however, the mean increase in Hb was greater in the 600 IU kg^{-1} $week^{-1}$ epoetin alfa group, as could be expected by the prolonged time of presurgical erythropoietic stimulation (3 weeks), compared with only 10 days of stimulation in the daily regimen. In addition, both regimens were comparable with respect to reducing patient exposure to allogeneic blood transfusion (16% in the weekly regimen group compared with 20% in the daily regimen group). The weekly regimen, which provides a lower total dose and is therefore less expensive, is more convenient and, for these reasons, is preferred over the daily regimen.

The importance of concomitant iron administration

Efficient RBC production is dependent on the availability of adequate levels of vitamin B_{12}, folic acid, and iron. Most patients have adequate supplies of vitamin B_{12} and folic acid, but iron typically is less abundant and may require dietary supplementation [14]. Iron is a rate-limiting factor for erythropoiesis [3, 14, 33], and iron deficiency is likely to develop in anaemic patients receiving epoetin alfa treatment if adequate iron stores are not available. Therefore, epoetin alfa should be administered concomitantly with supplemental iron [33]. The efficacy of epoetin alfa is independent of the route of iron administration (i.e., oral [p.o.] or intravenous [i.v.]). However, because p.o. iron is more convenient than i.v. iron supplementation, p.o. iron supplementation is preferred for orthopaedic surgery patients without iron deficiency in whom treatment with epoetin alfa is considered.

Epoetin alfa as an alternative to PABD

Although PABD reduces the need for allogeneic blood in surgery, it also contributes to lowering preoperative Hct levels [28] and places the patient at greater risk for needing a transfusion [2, 38]. Kickler and Spivak [28] studied the effect of repeated phlebotomy on serum erythropoietin levels in 69 autologous blood donors. Anemia developed over the course of repeated blood donations in 71% of male and in 45% of female iron-replete patients; however, endogenous serum erythropoietin levels increased only minimally. Furthermore, the increase in endogenous erythropoietin induced by the repeated phlebotomy was insufficient to compensate for the RBC loss.

The erythropoietic response to repeated phlebotomy in PABD patients can be augmented in anaemic patients using epoetin alfa therapy [18]. Mercuriali demonstrated that allogeneic blood transfusions were reduced in anaemic (baseline Hct<0.40) patients treated with epoetin alfa plus PABD compared with PABD alone [33].

Recently, Stowell et al. [40] compared the efficacy of PABD with that of epoetin alfa. In that study, 490 patients with Hb ≥11 to ≤13 g/dl prior to study enrollment were randomized to participate in PABD (n=249) or to receive epoetin alfa (n=241) 600 IU/kg weekly by s.c. injection on days –21, –14, –7, and on the day of surgery [40]. At baseline, mean Hb concentrations were similar in both cohorts (12.3 g/dl), but the mean preoperative Hb values increased in the epoetin alfa group (13.8 g/dl) and decreased in the PABD group (11.1 g/dl; P<0.0001). These data not only demonstrated that epoetin alfa improves hematologic status prior to surgery, but they also confirmed the observation of Kickler and Spivak [28] that the repeated phlebotomy of autologous donation can elicit a suboptimal erythropoietic response and suboptimal Hb recovery. Throughout the remainder of the study, mean Hb concentrations remained higher in the epoetin alfa group than in the PABD group both postoperatively (epoetin alfa = 11.0 g/dl, PABD=9.2 g/dl; P<0.0001) and at hospital discharge (epoetin alfa = 10.5 g/dl, PABD= 9.5 g/dl; P<0.0001). The overall transfusion rate (autologous and/or allogeneic blood) was substantially lower in the epoetin alfa group compared with the PABD group (12.9% of epoetin alfa patients transfused with 54 units of blood, compared with 74.4% of PABD patients transfused with 325 units of blood). The allogeneic transfusion rate was also lower in the epoetin alfa group (epoetin alfa=12.9%, PABD=19.2%), although the difference

between groups did not reach significance (P=0.078). These data suggest that in patients with moderate anemia perioperative epoetin alfa is an effective alternative to PABD as a blood management modality for reducing exposure to blood transfusion.

Surgical outcomes with epoetin alfa

Patient outcomes, such as time to rehabilitation and ambulation, postoperative vigor, length of hospital stay, cost of treatment, and rates of complications and mortality, have become important measures for evaluating the quality of healthcare and treatment outcomes. Improving patient outcomes can hasten recovery and reduce medical care costs. Consequently, the need for clinical studies to measure patient outcomes is growing along with the demand for reliable tools that can accurately assess subjective outcomes such as postoperative vigor.

An instrument for assessing postoperative vigor in total joint arthroplasty patients was recently developed by Keating et al. [27]. The "Vigor Instrument" (i.e., a questionnaire to be completed by the patient before and after surgery) was derived in part from the Vitality Subscale of the Short Form-36 and Activities of Daily Living from the Western Ontario and McMaster University Osteoarthritis Index. Two objective functional tests were also included: muscle strength and Hct. A hand-held dynamometer was used to measure muscle strength. Three novel scales were created for the instrument: 'Well-Being', 'Ready to Resume Activities', and 'ready to leave the hospital'. Statistically significant correlations were observed between muscle strength and Hct, suggesting that these objective measures may be relevant surrogates for vigor. Correlations were also noted between muscle strength, Hct, and subjective scales of Well-Being and Ready to Resume Activities. The fact that epoetin alfa increases preoperative and postoperative Hct values compared with placebo suggests that epoetin alfa may also increase postoperative vigor. Therefore, the Vigor Instrument may be a useful tool for assessing the effect of epoetin alfa treatment on postoperative vigor. Current clinical research is underway to prospectively test this hypothesis.

Recent studies in anaemic cancer patients have demonstrated the positive effect of epoetin alfa treatment on quality-of-life (QOL) parameters. For example, Glaspy et al. [13] evaluated the effect of epoetin alfa treatment on QOL in 2342 cancer patients undergoing cytotoxic chemotherapy. Significant increases in QOL parameters such as energy, activity, and overall QOL were observed as measured with the linear analogue scale assessment. In a comparable study, Demetri et al. [10] evaluated the effect of epoetin alfa treatment on QOL in 2370 patients with nonmyeloid malignancies who were undergoing chemotherapy. Marked improvements in QOL parameters were seen regardless of tumor response to chemotherapeutic agents and were associated with increases in Hb in patients treated 3 times a week with epoetin alfa at doses between 10,000 and 20,000 IU s.c. These results were corroborated in a similar study using epoetin alfa once weekly at 40,000 to 60,000 IU (Gabrilove et al., in press, J Clin Oncol, 2001).

Length of hospital stay

Increasing postoperative vigor is presumed to increase functional ability following surgery and, as a consequence, may allow patients to be more prepared for hospital discharge. In contrast, allogeneic transfusions are associated with increased length of hospitalization [2]. Bierbaum et al. [2] reported that in 9482 orthopaedic surgery patients the mean length of hospital stay was approximately 1 day longer for patients who had received allogeneic blood transfusions (6.6 days) than for patients who had received autologous blood (5.6 days) or no transfusion (5.4 days). This provides an additional reason to reduce the need for allogeneic blood transfusions.

Safety of epoetin alfa

Epoetin alfa is generally well tolerated for all indications. It has been used clinically for over 10 years, with over 3 million patients treated up to now. Adverse events related to the drug have been described mostly in patients with chronic renal failure and include development of hypertension and seizures [6]. Contraindications for the use of epoetin alfa include uncontrolled hypertension and known hypersensitivity to mammalian cell-derived products or human albumin. No evidence of interaction of epoetin alfa with other drugs was observed in clinical trials. Numerous studies using epoetin alfa in anaemic (i.e., Hb>10 to ≤13 g/dl) orthopaedic surgery patients demonstrated that epoetin alfa is safe and well tolerated [11, 16, 18, 33, 42]. The overall incidence of common adverse events, such as pyrexia, skin reaction at the injection site, and nausea were similar between the epoetin alfa and placebo groups [11]. Patients undergoing major elective orthopaedic surgery are at increased risk of developing thrombotic and/or vascular complications. This risk of thromboembolism is relatively high in patients undergoing hip or knee arthroplasty or suffering from multiple injuries [23, 34]. In these patients, the rate of proximal deep vein thrombosis (DVT) ranges from 3% to 37% [24, 34] and is highly dependent on the thromboprophylaxis regimen and the detection methods used. An integrated analysis of thromboembolism in patients enrolled in four large epoetin alfa trials [4, 7, 11, 15] demonstrated that there was no correlation between epoetin alfa therapy and the occurrence of thromboembolism [8]. All the patients received pharmacologic prophylaxis for DVT and had baseline Hb levels of >10 to ≤13 g/dl. Statistical analysis identified age, cardiac history, cardiac medications, and hypertension, but not epoetin alfa, as risk factors for thrombotic/vascular events. Furthermore, the analysis demonstrated that the incidence of throm-

botic events was not influenced by the maximum Hct obtained or the rate of rise in Hct prior to surgery.

Conclusions and future directions

The advent of epoetin alfa as a blood management option for patients with anemia undergoing procedures with risk of high blood loss, such as major orthopaedic surgery, has produced substantial increases in the margin of safety for perioperative blood loss. For patients with preoperative Hb>10 to ≤13 g/dl, epoetin alfa therapy increases perioperative Hb levels, reduces patient exposure to allogeneic blood, and may improve postoperative recovery. An instrument has recently been developed for patient- and caregiver-based assessment of postoperative vigor in patients undergoing total joint arthroplasty [27]. Results of this vigor validation study showed a direct positive relationship between postoperative Hct and muscle strength as well as readiness to resume activities. This study suggests that higher postoperative Hb and Hct levels may allow patients to recover better from total joint surgery. Furthermore, the well-documented safety, efficacy, and utility of epoetin alfa in patients undergoing elective total joint arthroplasty have provided the foundation for its use in other orthopaedic procedures, such as spinal surgery [9, 35], orthopaedic oncology [25], and orthopaedic trauma [31] where perioperative anemia is also of concern.

Orthopaedic surgical blood management continues to evolve and new advances in surgical techniques and pharmacologic agents, particularly epoetin alfa, are greatly reducing the risk of allogeneic blood exposure. Moreover, the impact of anemia on surgical outcome and QOL in orthopaedic surgery patients is now better understood and has increased the importance of managing perioperative Hb to reduce the need for transfusions and improve patient outcomes.

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