Increased hematocrit and decreased transfusion requirements in children given erythropoietin before undergoing craniofacial surgery

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Object. This study was undertaken to determine the efficacy of preoperative erythropoietin administration in infants scheduled for craniofacial surgery and, in so doing, to minimize problems associated with blood transfusions.

Methods. Families were offered the option of having their children receive erythropoietin injections before undergoing craniofacial surgery. The children whose families accepted this option received daily iron and 300 U/kg erythropoietin three times per week for 3 weeks preoperatively. Weekly complete blood counts with reticulocyte counts were measured and transfusion requirements were noted. Blood transfusions were administered depending on the clinical condition of the child. A case-matched control population was also evaluated to compare initial hematocrit levels and transfusion requirements. Thirty patients in the erythropoietin treatment group and 30 control patients were evaluated. The dose of erythropoietin administered was shown to increase hematocrit levels from 35.4 ± 0.9% to 43.3 ± 0.9% during the course of therapy. The resulting hematocrit levels in patients treated with erythropoietin at the time of surgery were higher compared with baseline hematocrit levels obtained in control patients at the time of surgery (34.2 ± 0.5%). Transfusion requirements also differed: all control patients received transfusions, whereas 64% (19 of 30) of erythropoietin-treated patients received transfusions.

Conclusions. The authors conclude that treatment with erythropoietin in otherwise healthy young children will increase hematocrit levels and modify transfusion requirements. Erythropoietin therapy for elective surgery in children of this age must be individualized according to the clinical situation, family and physician beliefs, and cost effectiveness, as evaluated at the individual center.

Key Words • craniofacial surgery • erythropoietin • transfusion • children

In healthy children, plasma erythropoietin levels fall in the 1st month of life, which is associated with a fall in hemoglobin and reticulocyte levels. In the 2nd month of life, plasma erythropoietin levels rise with a slow continuous increase in hemoglobin over subsequent months. When erythropoietin is administered to premature infants in neonatal intensive care units (ICUs), the hematocrit level rises and transfusion requirements diminish. In addition, when erythropoietin is administered to adults, erythropoiesis increases and preoperative blood collection is increased. It is not known whether otherwise healthy children would exhibit an increase in erythropoiesis in response to exogenous erythropoietin administration when they are at an age that is associated with a relatively high plasma erythropoietin level yet a relatively low hemoglobin level.

Understanding the response to exogenous erythropoietin administration in infants is clinically important, because erythropoietin could be administered to children before craniofacial surgery, a procedure that is associated with significant blood loss. By increasing the hematocrit level, the rare, but ever-present risks of transfusion would be avoided as would transfusions to patients who are Jehovah’s Witnesses and those religiously opposed to the procedure. In addition, there is growing evidence that perioperative anemia may contribute to increased morbidity and mortality rates.

Clinical Material and Methods

Patient Population

This study complied with the internal review board for clinical investigations at Johns Hopkins Medical Institutions. From 1992 to 1996, patients scheduled for craniofacial surgery were offered the option of receiving erythropoietin therapy. If the family consented, the patient’s pediatrician was contacted and administration and monitoring took place at that office.

Preoperative Erythropoietin Therapy

Subcutaneous erythropoietin (10,000 U/ml, Procrit, Epoetin alfa; Ortho Biotech Inc., Raritan, NJ) was administered at a dosage of 300 U/kg three times per week for a
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![Graph showing that preoperative administration of erythropoietin increases hematocrit level in patients receiving 300 U/kg three times per week for 3 weeks. Open circles connected by lines represent individual patients; closed circles and bars represent means ± SEMs. The hematocrit level 1 week before surgery and the hematocrit level on the day of surgery (0 weeks) are both greater than the baseline hematocrit level obtained 3 weeks before surgery. (p < 0.05).](image)

**Fig. 1.** Graph showing that preoperative administration of erythropoietin increases hematocrit level in patients receiving 300 U/kg three times per week for 3 weeks. Open circles connected by lines represent individual patients; closed circles and bars represent means ± SEMs. The hematocrit level 1 week before surgery and the hematocrit level on the day of surgery (0 weeks) are both greater than the baseline hematocrit level obtained 3 weeks before surgery. (p < 0.05).

...total of 3 weeks before surgery. In addition, elemental iron (6 mg/kg/day divided into three portions per day) was orally administered for the entire treatment period. Monitoring included weekly complete blood counts with reticulocyte counts.

**Surgical Procedures and Monitoring**

Operative procedures included sagittal synostectomy, anterior cranial expansion and reconstruction, posterior cranial reconstruction and expansion, and full cranial expansion.

On the day of surgery, anesthesia was induced in the patient in a standard fashion, with premedication of 0.5 to 1 mg/kg of oral midazolam mixed with 10 to 15 mg/kg acataminophen followed by inhalational induction of anesthesia with halothane in nitrous oxide. Intubation was facilitated by administration of pancuronium (0.1 mg/kg), and the patients were ventilated to maintain peak inspiratory pressures less than 20 cm H₂O and end-tidal CO₂ levels between 30 and 40 mm Hg. All patients were monitored in a standard manner by using a central venous catheter, an arterial catheter, and the precordial Doppler technique to detect air embolism. Anesthesia was maintained with a combination of halothane, isoflurane, and fentanyl. Fluid and blood replacement management was not determined by protocol, but central venous pressures were maintained between 4 and 7 mm Hg, hematocrit levels were maintained above 22%, urine outputs remained above 0.5 ml/kg/hour, and blood pressures and heart rates were maintained within 20% of baseline levels. The decision to transfuse blood was left to the discretion of the attending physicians, depending on the clinical condition of the child. Patients were extubated at the conclusion of surgery and monitored in the pediatric ICU overnight. Fluid and blood replacement therapy continued as managed in the operating room. Because the patients exhibited elevated initial hematocrit levels, the surgeons, anesthesiologists, and intensive care personnel were not blinded to treatment group. Blood loss was approximated by measuring the contents of suction canisters and weighing surgical sponges.

In all cases, meticulous hemostasis was attempted and a dual suction system was used to capture all of the blood for the cell saver so that it might be returned to the patient. Bone wax was used liberally.

Parameters examined over the course of therapy consisted of weekly complete blood count components, including mean corpuscular volume, hematocrit level, reticulocyte count, platelet count, and white blood cell count.

**Control Group**

For purposes of comparison, a control group of patients was defined by matching each erythropoietin-treated patient with a patient scheduled for the same surgical procedure on the same day. Because craniofacial surgery is performed at a very specific age, there is little age difference between the control and treatment groups. The families of the patients in the control group had been approached about erythropoietin therapy but declined the option. This control cohort was assigned to the study by one of the authors (D.D.) who was unaware of the results of the erythropoietin-treated patients. Data for both groups were collected regarding patient age, operation performed, beginning hematocrit level (on the day of surgery), amount of blood or blood products administered, amount of fluid administered, anesthesia time (defined as the time of arrival in the operating room to the time patient care was transferred to pediatric ICU staff), and surgical time (defined as the time when patient care was transferred from the anesthesiologist to the surgeon to the time care was returned to the anesthesiologist).

**Statistical Analysis**

Data are presented as means ± standard error of the means (SEMs). Statistical analysis of the changes in complete blood count over time in the erythropoietin-treated patients was performed by one-way analysis of variance (ANOVA). Comparisons made between control and treatment groups were performed by one-way ANOVA. The percentage of patients receiving transfusions was compared between groups by using the Wilcoxon signed-rank test. Statistical significance was set at a probability level of 0.05 or less.

**Results**

The families of 31 patients gave consent for their children to receive erythropoietin therapy. Thirty-one patients were assigned to the control group. One patient in the erythropoietin group and one patient in the control group were excluded from the study before completion of surgery because both patients experienced wheezing and difficulty with ventilation. These two patients were also excluded from the analysis. There were no signs of peri-
operative hypertension or other adverse effects due to the administration of erythropoietin in any of the patients.

The erythropoietin-treated patients demonstrated a rise in hematocrit levels (Fig. 1) with values on the day of surgery as well as 1 week prior to surgery greater than the initial values obtained 3 weeks before surgery. In addition, there was a significant rise in the patients’ mean reticulocyte count over this period (1.7–6.9%) and a significant fall in the mean white blood cell count from 13.4 ± 1.8 × 10^3/mm^3 to 10.3 ± 0.8 × 10^3/mm^3. There was no change in the mean corpuscular volume from the baseline value (82.1 ± 0.9 fl) obtained 3 weeks before surgery.

A comparison of baseline complete blood count values obtained in erythropoietin-treated patients (3 weeks prior to surgery) with the initial complete blood count values obtained in the control patients just prior to surgery showed there were no differences in hematocrit and hemoglobin levels, mean corpuscular volume, platelet count, and white blood cell count.

The characteristics of the patients in the two groups are summarized in Table 1. Patients treated with erythropoietin had a lower estimated blood loss (227 ± 22 ml) compared with control patients (371 ± 45 ml). The mean hematocrit value on presentation to the operating room on the day of surgery was higher in erythropoietin-treated patients (43.3 ± 0.9%) than in control patients (34.2 ± 0.5%) (Fig. 2). The number of procedures performed in each group was identical (as designed by the cohort selection technique). Of the 30 patients in each group, three underwent a full cranial expansion, three anterior reconstruction, two sagittal synostectomy, and 22 posterior cranial reconstruction. This breakdown is not necessarily representative of the relative numbers of each of these procedures performed at the Johns Hopkins Hospital. Rather, these numbers reflect the fact that posterior expansions are generally considered to be the most elective type of procedures and, therefore, were the most amenable to study.

In the erythropoietin-treated group, 11 patients received no blood products (Fig. 3). Of these, two underwent a sagittal synostectomy, two anterior reconstruction, one a full cranial expansion, and six posterior reconstruction. This was different from the control group, in which all 30 patients received transfusions (p < 0.05). Of those patients who did receive blood products, patients treated with erythropoietin received fewer intraoperative packed red blood cells (60 ± 18 ml) compared with controls (241 ± 55 ml) (Table 1). Hemoglobin levels on discharge from the pediatric ICU were the same in the two groups (control group 10.4 ± 0.4 g/dl; erythropoietin-treated group 10.6 ± 0.5 g/dl).

![Fig. 2. Graph showing that at the time of surgery the hematocrit level is greater in patients receiving erythropoietin compared with control patients (p = 0.05). Open circles represent individual patients; closed circles represent means ± SEMs (error bars are small enough to be obscured by the symbol).](image1.png)

![Fig. 3. Bar graph showing that blood transfusions were more common in control patients (30 of 30) compared with patients receiving erythropoietin (19 of 30) (p = 0.05).](image2.png)
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Discussion

In this study we have demonstrated that preoperative administration of 300 U/kg erythropoietin three times per week will increase the hematocrit level over a 3-week period in otherwise healthy children beyond the neonatal period. Associated with this higher hematocrit level at the start of surgery is a decrease in transfusion requirements in children undergoing craniofacial reconstructive surgery.

Many studies have been performed in which the efficacy of administration of erythropoietin to neonates in ICUs has been demonstrated to avoid the need for transfusions. In studies in which a clear decrease in transfusion requirements is demonstrated, erythropoietin has been administered in the range of 400 U/kg three times per week to total weekly doses of 500 U/kg. These studies have been performed in premature infants who cannot mount a sufficient erythropoietic response to the blood loss associated with frequent lab tests. Erythropoietin production is triggered by low oxygen delivery, which in this age group is not solely a function of hemoglobin concentrations, but is also due to the left-shifted hemoglobin dissociation curves of fetal hemoglobin. This left shift stimulates erythropoietin production because oxygen delivery to the tissues is diminished. Importantly, when adult hemoglobin is transfused into the neonates, this decreases fetal hemoglobin concentrations and the stimulant to erythropoietin production is diminished. Therefore, it is rational that administration of exogenous erythropoietin raises hemoglobin concentrations and decreases transfusion requirements in this setting, as shown in this study.

The role of erythropoietin in the modulation of hemoglobin concentrations beyond the neonatal period has been evaluated previously. In one study, premature infants who never received transfusions displayed a decrease in erythropoietin levels during the second postnatal month of life to levels equivalent to those in adults, despite lower hemoglobin levels. The authors of this study concluded that the failure to mount a greater erythropoietic response may be responsible for the physiological anemia seen in premature infants. In a similar manner, healthy infants have been studied during the period associated with physiological anemia, which occurs between 4 and 8 weeks of age. Erythropoietin levels are lowest in the first and highest in the second postnatal months; this was negatively correlated with hemoglobin concentrations. In premature children who develop bronchopulmonary dysplasia, erythropoietin administration is associated with higher hematocrit levels and fewer blood transfusions.

Recent interest in the use of erythropoietin in adults is focused on increasing erythropoiesis before surgery to enhance preoperative autologous blood collection and to avoid exposure to homologous blood products. Increased erythropoiesis has been demonstrated in open heart surgery, elective orthopedic surgery, mediastinal surgery, and colorectal surgery in cancer patients suffering from anemia. This approach has been demonstrated to be safe and does not alter the postoperative response to erythropoietin.

Preoperative autologous blood collection is difficult and impractical in children because they cannot donate a single blood unit. Because of this, children undergoing operations associated with a high blood loss have not enjoyed the benefits of autologous blood donation. However, there have been certain circumstances in which erythropoietin has been administered to raise the preoperative hematocrit level, so that pediatric patients can afford a significant blood loss before requiring a transfusion. This approach has been taken in children who are Jehovah’s Witnesses undergoing scoliosis surgery, as well as in skull based surgery and craniofacial surgery. The present study is the first study to use this approach in otherwise healthy children.

The advantages of selecting preoperative erythropoietin treatment over more conventional homologous blood transfusions are mostly theoretical but are of real concern. Because the relationship between acquired immunodeficiency syndrome and exposure to blood products was not understood until years after exposure, concern has been expressed in the lay as well as the medical press about blood transfusions. In fact the known risks of transmitting viral infections from transfused blood is between 1 in 493,000 for human immunodeficiency virus to 1 in 63,000 for hepatitis B. This small risk is likely to grow smaller as better and faster screening tests for banked blood become available. Other complications of transfused blood, such as febrile nonhemolytic transfusion reactions, may be more common but less severe; these complications may also become less common as new practices are instituted to rid banked blood of more white blood cells. The benefits of a higher hematocrit level are likely also theoretical. There are no clear indicators to dictate initiation of a blood transfusion; that decision is individualized for the particular clinical scenario. Of interest is the fact that the estimated blood loss in the erythropoietin-treated group was less than that of the control group (with a lower hematocrit level). The estimated blood loss in a small child is a very inexact measure; however, it is conceivable that the higher hematocrit level, associated with a higher viscosity, may be associated with diminished surgical bleeding. The cost effectiveness of this therapy is dependent on the costs of blood transfusion and erythropoietin administration. At the present time, cost evaluation does not support the widespread use of erythropoietin, especially because 64% of the patients who did receive erythropoietin also received a blood transfusion. If costs and availabilities change, however, this therapy may become more cost effective.

Treatment with erythropoietin in otherwise healthy young children will increase hematocrit levels and modify transfusion requirements. This treatment warrants examination for other indications. As risks and costs change, administration of erythropoietin may become a safe, cost-effective adjuvant to allogeneic blood transfusion. The institution of erythropoietin therapy for elective surgery in this age group must be individualized depending on the clinical situation, family and physician beliefs, and cost effectiveness, as evaluated at the individual center.

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