Blood-Conservation Techniques in Craniofacial Surgery

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Abstract: Attempts at reducing exposure to allogeneic transfusions, using blood conservation techniques such as controlled hypotension and normovolemic hemodilution, have met with mixed results and are not always practical in small infants. Recombinant human erythropoietin (RHE), a hormone that stimulates RBC production, increases the hematocrit when administered to infants.

A retrospective chart review of all patients undergoing fronto-orbital advancement for craniosynostosis by the same plastic surgeon between January 2002 and December 2002 was conducted. A subgroup of patients (10/19) received RHE as a blood-conservation strategy.

Transfusion requirements were lower in the RHE group (5/10) versus the control group (9/9). Total volume of blood products transfused was statistically lower in the RHE group (154 mL RHE group versus 421 mL control) ($P < 0.03$).

RHE combined with blood-conservation techniques was associated with a decreased need for blood transfusion, thus exposing the patient to fewer risks associated with allogeneic transfusion.

Key Words: erythropoietin, craniofacial, craniosynostosis, blood conservation, fronto-orbital advancement, blood transfusion

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Fronto-orbital advancement (FOA), performed in infants and young children with craniosynostosis has evolved from simple suture excisions to extensive osteotomies with bony repositioning. The nature of these procedures leads to significant blood loss. Between 80% and 100% of patients undergoing FOA require blood transfusion.[1–3] Estimates of blood loss during FOA have ranged from 42% to 126% of blood volume.[2]

Options for blood replacement include allogeneic, autologous, and directed donor transfusion. Despite the ease of administration and relative low cost of allogeneic transfusion, there are notable risks, including acute hemolytic reactions, the development of autoantibodies, spread of infectious diseases, and immunosuppression that may lead to increased incidence of postoperative infection and prolonged hospitalization.[4] Over the last 20 years, it has become increasingly apparent that allogeneic blood transfusion has generalized effects on patients' immune functions.[5] These effects underlie the clinical observations that some transfused patients have more rapid or frequent return of malignancy, decreased allograft rejection, increases in severity of viral infection, and several-fold increases in postoperative bacterial infections.[6,7]

Autologous transfusion, although ideal in that theoretically it does not have the risks associated with allogeneic transfusion, is difficult to obtain from patients less than 30 kg due to insufficient blood volume. While many parents elect to donate blood for their child's operation, there is no evidence to support that blood from a directed donor decreases morbidity associated with allogeneic transfusion.[8]

Given the frequent need for blood transfusion in FOA, perioperative blood-conservation techniques have evolved. Intraoperative blood salvage presents inherent risks, including coagulopathy, hemolysis, bacterial contamination, and damage to platelets, and only recently has this technique been successfully used in craniofacial surgery.[9]

Controlled hypotension is one of the most common techniques used for FOA procedures. Concerns regarding cerebral hypoperfusion and diminished oxygen delivery in the presence of anemia limit the use of this technique without concomitant blood transfusion. Acute normovolemic hemodilution (ANH) involves the isovolemic exchange of whole blood with colloid or crystalloid solutions to reduce the red blood cell count while maintaining normovolemia.[1] ANH is a technique that requires specific expertise and additional hemodynamic monitoring. Specific agents to enhance coagulation or prevent fibrinolysis have been used anecdotally on plastic and neurosurgical procedures, and although they may

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have definitive mechanisms of action, their efficacy has not been systematically proven.

Recombinant human erythropoietin (RHE) is a hormone that stimulates the production of red blood cells. The administration of RHE to infants has been shown to increase hematocrit levels, thus increasing total red cell mass and the allowable blood loss.[1,10,11]

We conducted a retrospective chart review of patents undergoing FOA surgery over a 1-year period by the same plastic surgeon. A subset of patients received RHE, iron supplementation, and vitamin K preoperatively in an attempt to reduce transfusion requirements. A combination of intraoperative blood-conservation techniques (ANH, hypervolemic hemodilution, hypotensive anesthesia, and antifibrinolytic agents) was used based on the individual case.

PATIENTS AND METHODS

Ethics approval was obtained from the institutional review board at Children's Hospital Los Angeles (CHLA) for a retrospective review of patients undergoing FOA procedures during the calendar year 2002 by a single craniofacial surgeon. Nineteen patients were identified. Ten (10/19) patients received preoperative RHE as part of a protocol used by the anesthesiology team at CHLA to reduce perioperative transfusion requirement. Nine (9/19) patients prior to the initiation of this protocol did not receive RHE.

Patients who received RHE preoperatively (RHE group) were given 600 U/kg in weekly subcutaneous doses. Hematocrit values were obtained weekly and on the day prior to surgery. Daily iron supplementation (5 mg/kg elemental Fe) and Vitamin K 2 mg PO on the night prior to surgery were administered in the RHE group. For all patients, a single craniofacial surgeon performed the surgery along with 1 of 2 neurosurgeons. There were multiple anesthesiologists and pediatric intensivists involved in the care of the patients. Criteria for intraoperative transfusion included hemodynamic instability, hematocrit $\leq$20, or low urine output (less than 0.5mL/kg/h).

Intraoperative blood-conservation strategies included ANH, hypervolemic hemodilution, and controlled hypotension.

ANH was accomplished by sterilely removing blood via a central venous catheter and collecting it into a blood-collection bag (eg, citrate phosphate dextrose with adenine Teruflex Blood Bags). During blood collection, the patient was administered crystalloid or colloid and the central venous pressure and arterial pressure were monitored and maintained in the normal range.

The ANH technique used is described in detail below and was used in 2 of the 9 RHE patients. After induction of anesthesia and endotracheal intubation, central venous access, arterial access, and additional peripheral intravenous access were obtained. Whole blood was then collected via the central line while infusing a colloidal solution containing Plasma-lyte (400 mL), 25% albumin (100 mL), mannitol (12 g), furosemide (20 mg), and calcium chloride (200 mg) through a peripheral line to maintain the central venous pressure within the normal range. Anesthesia was maintained with an infusion of ketamine (1–2 mg/kg/h), midazolam (0.05–0.1 mg/kg/h), sufentanil (0.5–1 μg/kg/h), and 100% oxygen. At the completion of hemodilution, all blood collected via CDPA bags was reinfused at 2 mL/h through the peripheral IV to maintain continuous circulation. Prior to skin incision, desmopressin acetate (DDAVP) (0.3 μg/kg IV), vitamin K (2–10 mg IM), and aprotinin (860,000 kallikrein inhibitor units (KIU)/m^2 over 30 minutes followed by a continuous infusion of 100,000 KIU/m^2/h) was administered. Activated coagulation factor VII (Novo-seven) (80 μg/kg IV every 90 minutes) was administered after observing clinical signs of nonsurgical bleeding and after obtaining approval for use by the hematologist. Mean blood pressure was maintained 10% to 20% below preoperative levels during critical periods of surgery associated with bleeding by infusions of nitroglycerin 2 to 20 μg/kg/min. Dopamine 2 to 10 μg/kg/min was titrated to maintain continued hemodynamic stability and enhance oxygen delivery. Metabolic acidosis requiring repeated correction was not encountered.

Hypervolemic hemodilution was instituted at the anesthesiologist's discretion by administering crystalloid or colloid 30 to 50 mL/kg in excess of maintenance fluid, blood loss, and urine output. Vasodilators and/or higher inhaled concentrations of general anesthetics were used to maintain blood pressure and central venous pressure in the normal range. This technique, when used reliably, decreased the starting hematocrit level (Hct) by 10%.

Controlled hypotension (the deliberate reduction of systolic and mean arterial blood pressure by greater than 20% of baseline age-appropriate values) was induced by a variety of techniques, depending upon the anesthesiologist. Vasodilators, volatile anesthetics, and narcotics were used alone or in combination.

The antifibrinolytics aprotinin (10,000 KIU/mL) (4 mL/kg) or amino-caproic acid (100 mg/kg) was used in selected patients.

Data collected included patient demographics, preoperative Hct, and intraoperative complications, and hemodynamic indices were recorded for each patient. In addition, each patient's postoperative course was recorded. A comparison between the erythropoietin and nonerythropoietin group was made of the recorded parameters. Specific parameters examined included perioperative transfusion, postoperative complications, and total length of hospital stay, and Hct on postoperative day 1 and on the day of discharge.

RESULTS

Age, weight, and duration of surgery were not statistically significantly different between the patients who received RHE and those that did not (Table 1). Initial Hct in

TABLE 1. Comparison of RHE Patients and Non-RHE Patients in Terms of Age and Weight

	Non-RHE Patients, Mean (Variance)	RHE Patients, Mean (Variance)	*P* Value
Age (mos)	13.1 (20.8)	11.0 (31.4)	0.393
Weight (kg)	10.1 (3.38)	10.5 (5.15)	0.724

RHE, recombinant human erythropoietin.

TABLE 2. Comparison of RHE Patients and Non-RHE Patients in Terms of Mean Perioperative Hematocrit Values and Mean Volume of Blood Transfused

	Non-RHE Patients, Mean	RHE Patients, Mean	*P* Value
Initial Hct (%)	36.2	34.9	0.288782
Preoperative Hct (%)	36.2	44.5	*0.000588*
Immediate Postoperative Hct (%)	35.3	30.3	.156
Day of discharge Hct (%)	33.5	33.3	.932
Volume of blood transfused (mL)	420	154	*.0274*

RHE, recombinant human erythropoietin; Hct, hematocrit level.

patients prior to receiving RHE was not statistically significantly different from those who did not receive RHE (Table 2). Patients who received RHE increased their red cell mass within 4 weeks by an average of 28% (Hct 34.9% to 44.5%). The incidence of transfusion was lower in the RHE group (5/10) versus the control group (9/9) ($P = 0.02167$) (Table 3). Total volume of blood products transfused was statistically lower in the RHE group (154 mL RHE group versus 421 mL control) ($P < 0.03$). Hematocrit on the day of discharge was not significantly different between the 2 groups (33.5 RHE versus 33.3 non-RHE) (Table 2). A hemodilution technique was used in 8 of 10 RHE patients and none of the controls. Controlled hypotension was used in 9 of 10 RHE and 6 of 9 control patients. Length of hospital stay was not significantly different between the groups. There were no intraoperative or postoperative complications.

DISCUSSION

Various anesthetic techniques aimed at minimizing blood loss can be beneficial in reducing the risk of allogeneic blood transfusion. ANH involves the sterile collection of whole blood from a well-flowing catheter into a blood-collection bag with anticoagulant and energy substrate (eg, CPDA). When ANH was used in combination with preoper-

TABLE 3. Description of Craniofacial Patients Who Underwent Fronto-Orbital Advancement (FOA) at Children's Hospital Los Angeles Between January 2002 and December 2002*

Patient	Diagnosis	Age (mos)	Erythropoietin Administered	Acute Normovolemic Hemodilution	Blood Transfusion (volume, mL)
1	Left coronal synostosis	18	Yes	Yes	No
2	Left coronal synostosis	10	Yes	Yes	285 mL
3	Right coronal synostosis	9	Yes	No	285 mL
4	Left coronal synostosis	22	Yes	No	500 mL
5	Left coronal synostosis	12	Yes	No	220 mL
6	Bicoronal synostosis	10	Yes	No	No
7	Right coronal synostosis	12	Yes	No	No
8	Apert syndrome	11	Yes	No	No
9	Left coronal synostosis	9	Yes	No	No
10	Metopic synostosis	18	Yes	No	250 mL
11	Left coronal synostosis	7	No	No	260 mL
12	Right coronal synostosis	11	No	No	585 mL
13	Right coronal synostosis	24	No	No	250 mL
14	Right coronal synostosis	10	No	No	500 mL
15	Pfeiffer syndrome	11	No	No	600 mL
16	Metopic synostosis	6	No	No	250 mL
17	Right coronal synostosis	11	No	No	250 mL
18	Brachyturricephaly secondary to shunted congenital hydrocephalus	2	No	No	1100 mL
19	Metopic synostosis	8	No	No	285 mL

*The incidence of transfusion was lower in the RHE group (5/10) versus the control group (9/9) ($P = 0.02167$).

ative erythropoietin, the allowable blood loss was doubled. This represented a major advantage of preoperative RHE administration. Due to the young age of many patients undergoing FOA surgery, this technique is not often used, and its use has historically been restricted to patients who refuse blood transfusion. The use of RHE may increase the indications for ANH as a technique in pediatric patients.

Hypervolemic hemodilution is a less technically challenging hemodilution technique to perform. Hypervolemic hemodilution is accomplished by rapidly expanding the intravascular blood volume with crystalloid or colloid 30 to 50 mL/kg in excess of maintenance fluid, blood loss, and urine output. Judicious use of vasodilators may also be helpful in facilitating this type of hemodilution while minimizing third spacing. Due to the elevated preoperative hematocrit in the RHE patients, this technique was most frequently used by our anesthesia group (6 patients), and transfusion was avoided in 4 of 6 patients in whom this technique was used. Since children undergoing FOA typically have starting hematocrit levels in the low 30s, reducing hematocrit levels into the low 20s via hemodilution is not routinely done in practice and was not done in any of the control patients in this series. Preoperative RHE administration allowed for the safe utilization of this technique in that the patients presented on the day of surgery with much higher Hct levels, thus allowing for safe hemodilution.

Controlled hypotension can be used successfully in pediatric patients, provided that proper monitoring and familiarity with the technique are ensured. Of all the hemodynamic variables, mean arterial pressure correlates best to the degree of blood-loss reduction. Concern for central nervous system injury is paramount in maintaining a safe level of hypotensive anesthesia. The practice of packing the orbits or significantly distracting the orbital contents should also be discouraged during these operations. It is also critical to avoid hyperventilation to an arterial carbon dioxide pressure below 35 mm Hg as hyperventilation below this level rarely improves surgical exposure and has been shown to worsen neurologic outcome in pediatric head-trauma patients.[11] In this study, moderate controlled hypotension was used in 9 out of 10 RHE patients and 6 out of 9 control patients.

In addition to RHE, other pharmacologic agents can also be used to decrease the frequency and volume of transfused blood products. Administration of DDAVP causes a 2- to 20-fold increase in plasma levels of factor VIII and stimulates the vascular endothelium to release larger multimers of vWF. A dose of 0.3 mg/kg achieves maximal increases in factor VIII and vWF in 30 to 60 minutes. Major side effects include flushing and hypotension as a result of prostacyclin release and the potential for free water retention and hyponatremia. Use of DDAVP may be of benefit during surgical procedures in which dilutional coagulopathy is possible. Recently a recombinant activated factor VII (NovoSeven) has been introduced for hemophiliac patients with inhibitors to factor VIII and IX. The factor binds to tissue factor and amplifies the activation of X and fibrinogen. Activated factor VII (factor VIIa) also binds to platelets, amplifying their effect at the site of tissue injury. Recent reports have found this factor to be effective in rapidly correcting dilutional coagulopathy during pediatric spine surgery and during massive transfusion.[12]

Aprotinin is a broad-spectrum serine protease inhibitor that amplifies primary hemostasis due to its action on platelet function, as well as inhibiting clot lysis. In a recent study involving craniofacial surgical patients, aprotinin decreased blood-transfusion requirements in pediatric patients undergoing craniofacial reconstruction, thereby reducing the risks associated with exposure to banked blood components.[13] Aprotinin was used in 3 RHE patients; 2 of 3 were not transfused.

Erythropoietin was the principal pharmacologic agent and primary focus of this retrospective review. Erythropoietin-stimulated erythropoiesis is independent of age and gender.[14] Variability in response is due to iron-restricted erythropoiesis.[15] There is no evidence that surgery or erythropoietin therapy affects the endogenous erythropoietin response to anemia or to the erythropoietic response to erythropoietin.[16] Therefore, it is paramount that supplemental iron be administered to these patients. As a result of the successful use of RHE in multiple areas of surgery and 1 recent randomized trial of RHE use in craniofacial surgery, RHE was added to the clinical protocol at CHLA for patients whose parents preferred blood-conservation techniques in an attempt to reduce the likelihood of blood transfusion during FOA procedures.[10] In the present study, this did result in a statistically significant decrease in the volume of blood transfused, as well as a decrease in the number of patients requiring transfusion.

Cost is still an issue raised with the use of RHE. Fearon and Weinthal[19] found that at their institution, the approximate cost of using RHE in a 9 kg patient is US $250 per treatment. Two studies examining the cost of transfusing 2 units of red blood cells found the average combined indirect and direct cost per pediatric unit was between $548 and $569.[17,18] Fearon and Weinthal[19] conclude that, "If one takes into account the potential costs associated with the treatment of a transfusion reaction, transfusion-related lung disease, human immunodeficiency virus, or either acute or chronic hepatitis, the cost-to-benefit ratio might shift toward erythropoietin use."[10] At our institution, due to the cost of erythropoietin we were unable to show a direct cost savings. The cost to our hospital for erythropoietin is $109 per 10,000 units. The cost for preparation and storage of 1 donor-directed unit of blood is $180. Thus, 6000 U (600 U/kg times the average-weight child of 10 kg) administered weekly (total of 4 doses preoperatively) would cost $262, slightly more than a unit of

blood. Indirect cost savings incurred by a decrease in morbidity associated with allogeneic blood transfusion (namely, an increase in length of hospital stay) may have been seen with a larger sample size. Given that the cost estimates above are reasonably similar, ethical or patient/family preference issues may need to be considered regarding the use of RHE versus allogeneic or donor-directed blood transfusion.

One recent adverse reaction involving RHE is red cell aplasia. This rare reaction has occurred in 188 reported cases worldwide and has only occurred in patients with renal failure, and no cases have been reported in the pediatric population.[19]

The weaknesses in this study include the retrospective design and the lack of randomization of RHE usage. Additionally, multiple anesthetic techniques were used in both patient cohorts, thereby confounding the results. In spite of these weaknesses, this review represents a single surgeon experience using preoperative RHE combined with blood-conservation techniques and was associated with a statistically significant decreased need for blood transfusion both in terms of the volume transfused and the number of patients requiring transfusion, thus exposing the patient to fewer risks associated with allogeneic transfusion (Table 3). There were no complications in this series involving the use of RHE or the anesthetic techniques. In addition, RHE significantly increased red blood cell mass, allowing for the safer administration of blood-conservation techniques, including hypervolemic hemodilution, ANH, and controlled hypotension. It is also interesting to note that the patients who received RHE had lower postoperative Hct values but were discharged with statistically similar Hcts, which could have been the result of a more brisk bone marrow response resulting from the RHE. Since FOA is associated with significant postoperative bleeding, this may add an additional degree of protection against postoperative anemia leading to transfusion.

The results of this study indicate that it may be possible to significantly and safely reduce the incidence of blood transfusion in craniofacial surgery primarily using erythropoietin, possibly in combination with other pharmacologic agents and anesthetic hemodilution techniques; however, a randomized prospective trial using more stringent anesthetic plans is warranted.

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