Minimizing transfusion requirements for children undergoing craniosynostosis repair: the CHoR protocol

Clinical article

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Object. Children with craniosynostosis may require cranial vault remodeling to prevent or relieve elevated intracranial pressure and to correct the underlying craniofacial abnormalities. The procedure is typically associated with significant blood loss and high transfusion rates. The risks associated with transfusions are well documented and include transmission of infectious agents, bacterial contamination, acute hemolytic reactions, transfusion-related lung injury, and transfusion-related immune modulation. This study presents the Children's Hospital of Richmond (CHoR) protocol, which was developed to reduce the rate of blood transfusion in infants undergoing primary craniosynostosis repair.

Methods. A retrospective chart review of pediatric patients treated between January 2003 and February 2012 was performed. The CHoR protocol was instituted in November 2008, with the following 3 components; 1) the use of preoperative erythropoietin and iron therapy, 2) the use of an intraoperative blood recycling device, and 3) acceptance of a lower level of hemoglobin as a trigger for transfusion (≤7 g/dl). Patients who underwent surgery prior to the protocol implementation served as controls.

Results. A total of 60 children were included in the study, 32 of whom were treated with the CHoR protocol. The control (C) and protocol (P) groups were comparable with respect to patient age (7 vs 8.4 months, p = 0.145). Recombinant erythropoietin effectively raised the mean preoperative hemoglobin level in the P group (12 vs 9.7 g/dl, p < 0.001). Although adoption of more aggressive surgical vault remodeling in 2008 resulted in a higher estimated blood loss (212 vs 114.5 ml, p = 0.004) and length of surgery (4 vs 2.8 hours, p < 0.001), transfusion was performed in significantly fewer cases in the P group (56% vs 96%, p < 0.001). The mean length of stay in the hospital was shorter for the P group (2.6 vs 3.4 days, p < 0.001).

Conclusions. A protocol that includes preoperative administration of recombinant erythropoietin, intraoperative autologous blood recycling, and accepting a lower transfusion trigger significantly decreased transfusion utilization (p < 0.001). A decreased length of stay (p < 0.001) was seen, although the authors did not investigate whether composite transfusion complication reductions led to better outcomes.

Key Words • blood recycling • craniosynostosis • erythropoietin • transfusion • craniofacial surgery

Craniosynostosis is characterized by the premature fusion of 1 or more cranial sutures resulting in head shape abnormalities. The goal of surgical remodeling of the cranial vault is to prevent or relieve elevated intracranial pressure (ICP) and to correct physical abnormalities of the craniofacial skeleton. Corrective surgical repair of craniosynostosis may require extensive removal or dislocation of calvarial bones at an early age (usually 2–3 months). Substantial intraoperative blood loss may be encountered and may require transfusion to replace lost red cell mass. Blood loss is therefore a cause of morbidity after extensive craniofacial procedures. Transfusions have the known associated risk of transmission of infectious agents, bacterial contamination, acute hemolytic reactions, transfusion-related lung injury (TRALI), and universal transfusion-related immune modulation (TRIM). There have been a variety of approaches developed with the aim of reducing blood loss and transfusions during craniosynostosis surgery (autologous blood predonation, normovolemic hemodilution, controlled hypotension, intraoperative blood salvage). Recently, the ad-
ministration of recombinant human erythropoietin alpha (EPO) and iron in combination with these blood-saving techniques has yielded increased hematocrit concentrations before surgery and has led to an overall decrease in transfusion usage.3,0,20,26,38 Based on these findings, we instituted a protocol that consisted of lowering the acceptable transfusion trigger level of hemoglobin, initiating EPO/iron treatment prior to surgery to increase the preoperative hemoglobin level, and utilizing an intraoperative blood recycling device such as Cell Saver or OrthoPAT (Haemonetics Corporation) to minimize the overall rate of allogenic blood transfusion at our institution.

Methods

After institutional review board approval was obtained, we performed a retrospective chart review of cases involving infants who underwent primary cranial vault remodeling surgery at our institution between January 2003 and February 2012. A protocol to minimize the rate of transfusion was instituted in November 2008 with the following 3 components: 1) the use of EPO/iron therapy to increase preoperative hemoglobin levels, 2) the use of an intraoperative blood recycling device, and 3) acceptance of a hemoglobin level less than 7 g/dl as a trigger for transfusion. Consecutive patients prior to protocol implementation comprised the control group. Demographic data collected included age and weight of patients at surgery; type of craniosynostosis; preoperative, intraoperative, postoperative, and postoperative Day 1 hemoglobin levels; amount of autologous and allogenic blood transfusion; estimated surgical blood loss (EBL); type and length of procedure; and length of hospital stay. Exclusion criteria included age older than 18 months, prior surgery, and failure to complete the protocol, incomplete medical records. Patients with syndromic as well as nonsyndromic craniosynostosis were included.

In the protocol group, patients were given subcutaneous EPO injections at a dose of 600 units/kg weekly for 4 weeks prior to surgery. Elemental iron (15 mg per day) was administered orally during the same period. Informed consent was obtained from a legal guardian or parent of each patient prior to injections. A complete blood count was performed weekly, and the EPO injection was withheld if hemoglobin levels were at least 15 g/dL. Intraoperatively, autologous blood was recycled with an OrthoPAT (15–30 ml bowl) or Cell Saver device (Dideco Compact Advanced Cell Saver with a 55 ml bowl prior to April 2012 and Haemonetics VI Cell Saver with a 55 ml bowl after April 2012). The recycled blood cell washing and filtering was supervised by specialized perfusionists and blood was transfused in the operating room by the anesthesia team. The blood salvaging devices use a saline-heparin solution to wash cells followed by hemocentrification to hematocrit value of 66%. Allogenic blood transfusions were given if hemoglobin levels were 7 g/dl or less for the protocol group. Prior to the protocol implementation, the hemoglobin level triggering transfusion was not standardized. Estimated blood loss was based on Cell Saver quantity, suction canister contents, and laparotomy sponge counts. Drapes with plastic blood collection containers were used, and blood was suctioned from these into the suction canister.

In 2008, a change in surgical technique for posterior cranial vault remodeling, from in situ maneuvers, using a modification of the reverse pi procedure, to active remodelling, via bone flap transposition, was adopted in concert with protocol implementation. Pediatric anesthesiologists and pediatric intensivists were involved in the care of patients, but varied across the study period. Patients were transferred directly to the pediatric intensive care unit. Surgery procedures included posterior, anterior, and subtotal cranial vault remodeling.

In the protocol group, patients were given subcutaneous EPO injections at a dose of 600 units/kg weekly for 4 weeks prior to surgery. Elemental iron (15 mg per day) was administered orally during the same period. Informed consent was obtained from a legal guardian or parent of each patient prior to injections. A complete blood count was performed weekly, and the EPO injection was withheld if hemoglobin levels were at least 15 g/dL. Intraoperatively, autologous blood was recycled with an OrthoPAT (15–30 ml bowl) or Cell Saver device (Dideco Compact Advanced Cell Saver with a 55 ml bowl prior to April 2012 and Haemonetics VI Cell Saver with a 55 ml bowl after April 2012). The recycled blood cell washing and filtering was supervised by specialized perfusionists and blood was transfused in the operating room by the anesthesia team. The blood salvaging devices use a saline-heparin solution to wash cells followed by hemocentrification to hematocrit value of 66%. Allogenic blood transfusions were given if hemoglobin levels were 7 g/dl or less for the protocol group. Prior to the protocol implementation, the hemoglobin level triggering transfusion was not standardized. Estimated blood loss was based on Cell Saver quantity, suction canister contents, and laparotomy sponge counts. Drapes with plastic blood collection containers were used, and blood was suctioned from these into the suction canister.

As expected after EPO/iron therapy, the P group had a higher mean preoperative hemoglobin level (12.0 ± 1.4 g/dl vs 9.7 ± 1.2 g/dl for the C group, p < 0.001). Reflecting the more aggressive surgical technique, the mean operative blood loss in the P group was 212.0 ± 168.2 ml versus 114.5 ± 60.8 ml for the C group (p = 0.004). The mean length of surgery was longer for the P group (Table 2), 4.0 hours compared with 2.8 hours for the C group (p < 0.001). In the P group the type of craniosynostosis was sagittal in 18 cases, metopic in 7, coronal in 2, complex in 4, and lambdoid in 1. In the C group, the type was sagittal in 14 cases, coronal in 6, metopic in 5, and complex in 1.

There was a statistically significant difference in the rate of transfusion between groups, 96% in the C group and 56% in the P group (p < 0.001). The amount transfused was higher for the C group (mean 21.6 ± 12.9 ml/kg, median 18.6 ml/kg) than for the P group (mean 14.7 ± 16.6 ml/kg, median 12.6 ml/kg), but the difference was not statistically significant (p = 0.082) due to the large standard deviation. The size of the standard deviation may reflect the fact that patients who received transfusions tended to receive generous amounts of packed red blood cells. Of the patients who received intraoperative
autologous transfusion, the average amount transfused was 6.6 ± 5.5 ml/kg. Of the 26 patients in the C group, 3 did not receive autologous transfusion as it was deemed unnecessary by the anesthesiologist based on hemoglobin values and hemodynamics. Of the 18 of 32 patients in the P group who received transfusions, 10 were given transfusions intraoperatively and 8 postoperatively; none were given transfusions in both settings. Of the 25 of 26 patients in the C group who received transfusions, 15 were given transfusions intraoperatively and 13 postoperatively; 3 were given transfusions in both settings. There was no statistically significant difference in the amount of fluid resuscitation between groups (mean 80.5 ± 48.0 ml/kg for the P group vs 69.5 ± 31.6 ml/kg for the C group, p = 0.296). The P group had a significantly shorter mean length of stay in the hospital (2.6 days vs 3.4 days in the C group p < 0.001). No side effects of EPO were noted. No stroke or abnormal clotting was reported for either group.

A subanalysis of the P group revealed that 70% of children younger than 6 months of age received transfusions, whereas 50% of children older than 6 months received transfusions (p = 0.446). Also, during the first 18 months after initiating the CHoR protocol, 70% of the patients received transfusions, but the percentage fell to 40% in the last 18 months (p = 0.165), suggesting an institutional learning curve. The study, however, was underpowered in both instances to determine statistical significance.

### TABLE 1: Patient characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>CHoR Protocol Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>26</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>mean age (mos)</td>
<td>7.0 ± 3.9</td>
<td>8.4 ± 3.4</td>
<td>0.145</td>
</tr>
<tr>
<td>mean weight (kg)</td>
<td>8.0 ± 1.7</td>
<td>9.0 ± 1.5</td>
<td>0.019</td>
</tr>
<tr>
<td>procedure type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>posterior vault remodeling</td>
<td>14</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>anterior vault remodeling</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>total vault remodeling</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>EPO no</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>autologous blood recycling no</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values represent numbers of patients unless otherwise indicated. Means are presented with SDs.

### TABLE 2: Control and CHoR protocol group data*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group</th>
<th>Protocol Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>preop hemoglobin (g/dl)</td>
<td>9.7 ± 1.2</td>
<td>12.0 ± 1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>lowest intraop hemoglobin (g/dl)</td>
<td>7.6 ± 1.0</td>
<td>8.4 ± 1.2</td>
<td>0.016</td>
</tr>
<tr>
<td>postop hemoglobin (g/dl)</td>
<td>9.7 ± 2.6</td>
<td>9.8 ± 2.1</td>
<td>0.778</td>
</tr>
<tr>
<td>EBL (ml)</td>
<td>114 ± 60.8</td>
<td>212.0 ± 168.2</td>
<td>0.004</td>
</tr>
<tr>
<td>length of surgery (hrs)</td>
<td>2.8 ± 0.9</td>
<td>4.0 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>percentage receiving transfusions</td>
<td>96%</td>
<td>56%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>amount transfused (ml/kg)</td>
<td>21.6 ± 12.9</td>
<td>14.7 ± 16.6</td>
<td>0.082</td>
</tr>
<tr>
<td>total intraop IV fluid (ml)</td>
<td>69.5 ± 31.6</td>
<td>80.5 ± 48.0</td>
<td>0.296</td>
</tr>
<tr>
<td>length of stay (days)</td>
<td>3.4 ± 0.7</td>
<td>2.6 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* With the exception of the percentage of patients receiving transfusions, all values are means ± SD. IV = intravenous.

**Discussion**

Craniosynostosis occurs in the population at a rate of 1/2000–1/4000. Craniosynostosis corrections are elective procedures associated with a range of complications, including massive intraoperative hemorrhage, postoperative hemorrhage, air embolism, infections, hydrocephalus, and brain trauma. The high EBL is associated with large amounts of transfusions. In addition, fetal hemoglobin is replaced over the first 6–7 months of life; this timing often overlaps with the timing of cranial vault remodeling procedures, making these children particularly sensitive to blood loss as they are relatively anemic through the changeover in hemoglobin. The high transfusion rate exposes these patients to risks, which increases morbidity and mortality as well as hospital and intensive care unit time. Serious or fatal transfusion-related reactions occur in 3/10,000 units given. Although blood products are routinely tested for infectious agents, there is still a risk of transmission of blood-borne infections such as HIV (1/200,000) and hepatitis B and C (1/30,000 for each virus). Risks also include bacterial contamination, acute hemolytic reactions (1/250,000), TRALI (1/5000), and TRIM. Studies have reported EBL as high as 60%–100% of estimated blood volume (EBV) with almost all patients undergoing a blood transfusion during or immediately after the surgery. Our results were consistent with the high EBL presented in previous studies, with a
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15 ml/kg average EBL (18% EBV) for the C group and 23.5 ml/kg (29% EBV) for the protocol group.

Techniques for surgical repair of craniosynostosis have the goal of achieving a long-term normocephaly while minimizing risk, including the need for transfusion. Historically, these procedures carried a high risk for significant blood loss, and the majority of infants who underwent craniosynostosis surgery required transfusions. Several techniques have been described in the literature, including strip craniectomy, in which brain growth assists in the remodeling of the skull shape (passive remodeling); extensive reconstructive craniotomies including bony repositioning and fixation to immediately correct the skull contour; and more recently, endoscopic approaches followed by postoperative hemi-coring. For the purposes of this study, only patients treated with an open approach were included. Our study was not designed to evaluate or comment on specific surgical technique, but to evaluate a strategy to minimize transfusion requirements. Interestingly, a significant decrease in length of stay was noted in the protocol group despite the expected increase in length of surgery and operative blood loss.

Several techniques have been developed to decrease perioperative transfusion in craniosynostosis corrections. Preoperatively, autologous donations, EPO administration, new upper age limits for surgical correction, and surgical patient screening have been attempted. Changes in anesthetic management have also been attempted to decrease perioperative transfusion rates, including acute normovolemic hemodilution (ANH), acceptance of lower hemoglobin levels, the use of autologous blood cell recycling, induced hypotension, infusion of antifibrinolytic agents (aminocrinexamic acid, aprotonin), and factor administration (activated factor VIIa, prothrombin complex concentrate [PCC]).

Administration of EPO has been described by several authors. This is a recombinant human protein that functions by augmenting erythropoietin levels, ultimately yielding an increased red blood cell mass or hematocrit level. In the first clinical experience, Velardi and colleagues developed a protocol to minimize autologous blood transfusion that included treating patients preoperatively with EPO, ANH, and intraoperative blood cell salvage. Hemoglobin concentrations were increased in patients treated with EPO for at least 2 weeks. Krajewski and colleagues administered EPO 3 weeks, 2 weeks, and 1 week preoperatively and used Cell Saver intraoperatively; there was a marked increase in preoperative hematocrit and lower transfusion rates. Fearon and Weinfeld administered EPO weekly for 3 weeks preoperatively and found an increased hemoglobin level and reduced blood transfusion. Meneghini et al. performed acute preoperative normovolemic hemodilution in addition to administering EPO for 3 weeks before surgery and found a decreased transfusion rate. In our protocol, patients were given EPO weekly for 4 weeks preoperatively, and we found higher mean preoperative hemoglobin levels of 12 g/dl versus 9.7 g/dl for the control group, consistent with prior studies. Our patients treated with EPO also had a decrease in perioperative allogeneic transfusion rates and amounts.

Preoperative administration of erythropoietin-stimulating agents to surgical patients is thought to have few adverse side effects. This partly stems from the fact that the course of treatment is short term and the patient population typically has a low incidence of comorbidities. Specific adverse events cited in the literature commonly include thrombocytosis, hypertension, and death. Due to the low incidence of such events in these studies, no clear correlation with EPO treatment could be made. A concern for EPO use is the development of thrombotic complications associated with the higher hematocrit resulting from EPO therapy. The occurrence of thrombotic events in children receiving EPO is very low (0.07–0.14 per 10,000 children in the general population). Recently, Naran and coauthors from 3 major centers looked at the safety of preoperative erythropoietin in calvarial remodeling with respect to increased risk of thrombotic events in 569 patients. Their results yielded no postoperative thrombotic events, and no other major complications were seen (no death or blindness). Hypertension is another adverse effect of EPO therapy, more commonly encountered in patients with chronic renal failure. There seems to be a low risk of precipitating hypertension during short-course preoperative EPO therapy. Overall, the safety of EPO therapy in patients undergoing elective surgery has been demonstrated in more than 1000 patients in placebo-controlled trials. In our study, we did not observe any side effects of EPO therapy, which is in accordance with the data available in the literature.

Previously in our institution, the transfusion trigger was not standardized, and transfusion was often performed to maintain a hemoglobin level of 10 g/dl. In our protocol, a transfusion trigger was defined as a hemoglobin level below 7 g/dl. Di Rocco previously stated that the cornerstone to reducing transfusions is accepting a lower hemoglobin level. According to the practice guidelines from the American Society of Anesthesiologists, in healthy, normovolemic individuals, tissue oxygenation is maintained and anemia tolerated at hematocrits of 18%–25% and the heart begins producing lactate at hematocrits of 15%–25%. One study found no changes in anaerobic metabolism as measured by mixed venous saturations and oxygen delivery index with hematocrits as low as 17%, while another study found stable lactate levels at hematocrits of 9%.

Autologous blood cell recycling systems have been evaluated in both neurosurgical and orthopedic procedures. Two studies found decreased allogeneic transfusion requirements in hip replacements and one study in hip revisions. Jimenez and Barone found a decrease in the amount of transfusion in craniosynostosis corrections and no associated transfusion reactions, infectious complications, or coagulopathies. The transfusion-minimizing protocol reported by Velardi and colleagues included Cell Saver use. Dahmani and coauthors found a significant decrease in the amount of homologous blood transfused in the continuous autotransfusion group. Fearon described a series of patients who received autologous recycled blood and found a rate of allogeneic transfusion of only 18% with no complications associated with the use of cell salvage. As previously mentioned, Krajewski
et al. found significantly reduced transfusion rates with the use of EPO and Cell-Saver. In our study, all but 3 infants in the protocol group and none in the control group received recycled autologous blood. The protocol group had a significantly lower transfusion rate, consistent with previous studies.

Acute normovolemic hemodilution involves exchanging whole blood for colloid or crystalloid while maintaining normovolemia, then reinfusing the removed blood at the end of the procedure. Two studies, as previously mentioned, found a decreased transfusion rate when ANH was combined with erythropoietin therapy. One study had a transfusion rate of 36% after ANH during craniosynostosis corrections. One study found no reduction in transfusion rates or amounts with ANH. Aly Hassan found that ANH was well tolerated in the pediatric population without measurable signs of anaerobic metabolism. As mentioned above, children with profound hemodilution and hematocrits as low as 9% were found to have stable lactate levels. While we did not choose to make ANH a part of our protocol, the infants in the protocol group had significantly lower transfusion rates but higher crystalloid and colloidal requirement (80 ml/kg vs 69 ml/kg for the control group).

Our study was limited in several ways. It is a retrospective chart review; prospective randomized data may be more valuable. Surgical techniques changed over time. After protocol implementation, the rate of transfusion was noted to fall as time elapsed, perhaps reflective of the time required for dissemination and multispecialty adoption of a novel protocol. As the decision for discharge in the protocol group versus the control group was made by different physicians, an inherent bias may exist based on individual physician philosophy. The children in the protocol group were on average 1 kg heavier than those in the control group and thus had a higher estimated blood volume (EBV). The estimated difference in EBV is about 100 ml, but the estimated difference in allowable blood loss (ABL) is only about 30 ml—a small amount compared with our average blood loss.

Conclusions

We describe our experience after implementation of a protocol designed to minimize transfusion requirements during craniosynostosis surgery. Our protocol, which includes preoperative administration of recombinant EPO and iron supplementation, intraoperative autologous blood recycling, and accepting a lower transfusion trigger, was shown to be effective in significantly decreasing the rate of autologous blood transfusion in cranial vault remodeling surgery. The concomitant decrease in transfusion-related complications may lead to better outcomes. One must also take into account that the introduction of a novel multimodal protocol may be associated with an institutional “learning curve.”

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Rhodes. Acquisition of data: Vega, Lyon, Rhodes. Analysis and interpretation of data: all authors. Drafting of the article: Vega, Lyon, Rhodes. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Vega. Statistical analysis: Vega, Lyon, Rhodes. Administrative/technical/material support: Rhodes. Study supervision: Rhodes.

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