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ORIGINAL ARTICLE

Minimizing transfusion in sagittal craniosynostosis surgery: the Children's Hospital of Minnesota Protocol

Paul J. Escher[1] · Albert Tu[2] · Susan Kearney[3] · Matthew Wheelwright[1] · Joseph Petronio[2] · Meysam Kebriaei[2] · Sivakumar Chinnadurai[4] · Robert J. Tibesar[4]

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Abstract

Purpose To assess the success of a protocol using preoperative erythropoietin (EPO) and iron with perioperative tranexamic acid (TXA) in reducing blood transfusion in sagittal craniosynostosis surgery.

Methods A retrospective chart review of all sagittal craniosynostosis patients undergoing open repair at our institution since 2010 was conducted. A novel protocol of preoperative EPO with iron and perioperative TXA, along with a shift away from automatic transfusion, was initiated in 2014. Perioperative hemoglobin levels, length of stay, and transfusion rates were compared between the historical control and the study group receiving the protocol.

Results A total of 36 patients met inclusion criteria. Twenty-eight patients were male and 8 were female. Twenty-two patients were in the control group receiving neither TXA nor EPO and automatically received a transfusion, while 14 were in the study group and received the full protocol. There were no significant demographic differences between groups. Within the control group, 100% of patients were transfused compared with 14.3% of the study group ($p < 0.0001$). The study group also had a shorter postoperative length of stay in the hospital (mean, 3.4 days; range, 3–6) than the control (mean, 4 days; range, 2–5.5, $p = 0.038$). The study group had a higher preoperative hemoglobin than the control (13.6 vs. 11.8 g/dL, $p = 0.0001$).

Conclusion Our protocol of preoperative EPO and iron with perioperative TXA increased the preoperative hemoglobin and was associated with a low transfusion rate without negatively impacting postoperative course.

Keywords Sagittal craniosynostosis · Erythropoietin · Tranexamic acid

Introduction

Craniosynostosis is a congenital disorder arising from premature fusion of the cranial sutures resulting in restricted skull volume and dimension. Craniosynostosis occurs in approximately 1 in 2000 to 1 in 2500 births, most commonly affecting the sagittal suture [7]. Treatment involves surgical removal of the affected suture(s) with or without cranial vault remodeling, typically occurring around 5–6 months of age. These surgeries can result in significant blood loss, and historically, most patients have required allogeneic packed red blood cell (pRBC) transfusion perioperatively [6, 17]. Because of the numerous risks of allogeneic transfusions such as infection, hemolytic reactions, allergic reactions, and transfusion-related acute lung injury (TRALI), strategies for reducing the need for transfusions in craniosynostosis patients are a subject of ongoing research [10, 21, 29]. The purpose of this study is to assess whether a protocol of preoperative erythropoietin (EPO) with iron supplementation and perioperative tranexamic acid (TXA) was effective in reducing transfusions among non-syndromic sagittal craniosynostosis patients at our institution.

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✉ Robert J. Tibesar
Robert.tibesar@childrensmn.org

[1] University of Minnesota Medical School, Minneapolis, MN, USA

[2] Children's Minnesota Department of Neurosurgery, Minneapolis, MN, USA

[3] Children's Minnesota Center for Bleeding and Clotting Disorders, Minneapolis, MN, USA

[4] Children's Minnesota ENT and Craniofacial Surgery, Minneapolis, MN, USA

Methods

After IRB approval was obtained, we performed a retrospective chart review of all cases of patients undergoing sagittal craniosynostosis repair from March of 2010 through June of 2018 at Children's Minnesota. Patient demographics, preoperative and perioperative medications, intraoperative fluids, perioperative transfusion, postoperative days in the PICU and on the floor, and perioperative hemoglobin (Hb) levels were collected.

Surgical procedure

All patients in this study underwent the same operative technique of open repair of sagittal craniosynostosis. The sagittal suture was removed in its entirety along with 1.5 cm of bone on either side of the suture. A posterior triangle wedge of bone was removed on each side near the lambdoid suture and additional middle and anterior barrel stave osteotomies were performed. These parietal bone segments were then out-fractured. Another partial thickness osteotomy was made in each parietal bone segment for further out-fracture. The scalp was then closed over a drain (see Fig. 1).

The protocol

Prior to 2014, patients with sagittal craniosynostosis were scheduled for surgery and received no preoperative or perioperative hematopoietic medications or supplements. Blood transfusion was automatically given at the beginning of every case in anticipation of impending bleeding to prevent hemodynamic instability.

Starting in 2014, patients identified for sagittal craniosynostosis repair received the following protocol, developed collaboratively by our departments of hematology, neurosurgery, and otolaryngology. After initial consultation for surgery, a complete blood count and ferritin level were obtained. Elemental iron at 2 mg/kg/dose twice daily by mouth was initiated at least 1–2 months prior to surgery. A hematology consult was obtained to assess bleeding and thrombosis risk and to discuss the use of preoperative EPO as well as the use of TXA during surgery. EPO was only administered if the Hb was 13.5 g/dL or lower. Dosing of EPO was 600 units/kg subcutaneously once weekly for 2–4 weeks leading up to the surgery. A complete blood count (CBC) was checked weekly to determine whether EPO should be administered. TXA was given perioperatively using the following doses: 40 mg/kg IV push preoperatively and 10 units/kg/h intraoperatively followed postoperatively by 10 mg/kg/dose IV every 8 h for 3 doses. Intraoperatively, Hb measurements were assessed from an arterial line. If the Hb was 6 g/dL or less, an allogeneic RBC transfusion was administered. If the Hb dropped below 8 g/dL, the anesthesia team in conjunction with the surgeons would consider transfusion based on the patient's hemodynamic parameters. If the patient was stable and the cranial osteotomies were complete, transfusion was not administered. If the patient exhibited any degree of tachycardia or hypotension, or the surgeon anticipated further blood loss, then a Hb of less than 8 g/dL triggered the transfusion. Patients who only partially completed this protocol were excluded from analysis, as were patients with syndromic sagittal craniosynostosis.

Statistical analysis

Comparisons of means between groups were performed with Student's *t* test. Comparisons of ratios or percentages between groups were performed with Fisher's exact test. All statistical analysis was carried out with GraphPad Prism software (GraphPad Software Inc., La Jolla, CA).

Results

Thirty-six patients met the inclusion criteria. Twenty-two patients were treated before the institution of the perioperative protocol and 14 received the full protocol of EPO, iron, and TXA. There were no significant differences in age, sex, weight, duration of surgery, or volume of crystalloid received intraoperatively (Table 1).

The study group had a higher preoperative Hb than the control group (13.6 ± 0.4 g/dL vs. 11.8 ± 0.4 g/dL, $p < 0.0001$) and was transfused with pRBCs at a significantly lower rate than the control group (14.3% vs. 100%, $p < 0.0001$). The study group also had a significantly shorter hospital stay than the control group (3.4 ± 0.6 days vs. 4.0 ± 0.4 days, $p = 0.04$). Among those who were transfused, the study group received an average of $25.9 \pm 12.8\%$ of their estimated total blood volume, compared with $37.7 \pm 13.3\%$ in the control group. Multiple regression analysis showed no significant effect of patient weight ($p = 0.79$), operative time ($p = 0.52$), postoperative complication ($p = 0.66$), or receipt of transfusion ($p = 0.053$) on the length of stay. Estimated intraoperative blood loss was significantly lower for the study group (93.9 ± 40.6 mL vs. 168.1 ± 50.6 mL, $p = 0.038$). Estimated blood loss correlated with operative time ($R^2 = 0.429$, $p < 0.0001$; see Fig. 2). Five of 22 (22.7%) patients in the control group required additional postoperative transfusion of pRBCs while none of those in the study group did; however, this finding did not reach significance ($p = 0.13$). There was no significant difference between groups in lowest intraoperative Hb, days spent in the PICU, or Hb on postoperative day 1. These findings are summarized in Table 2. There were no adverse events related to the protocol medications in any patients.

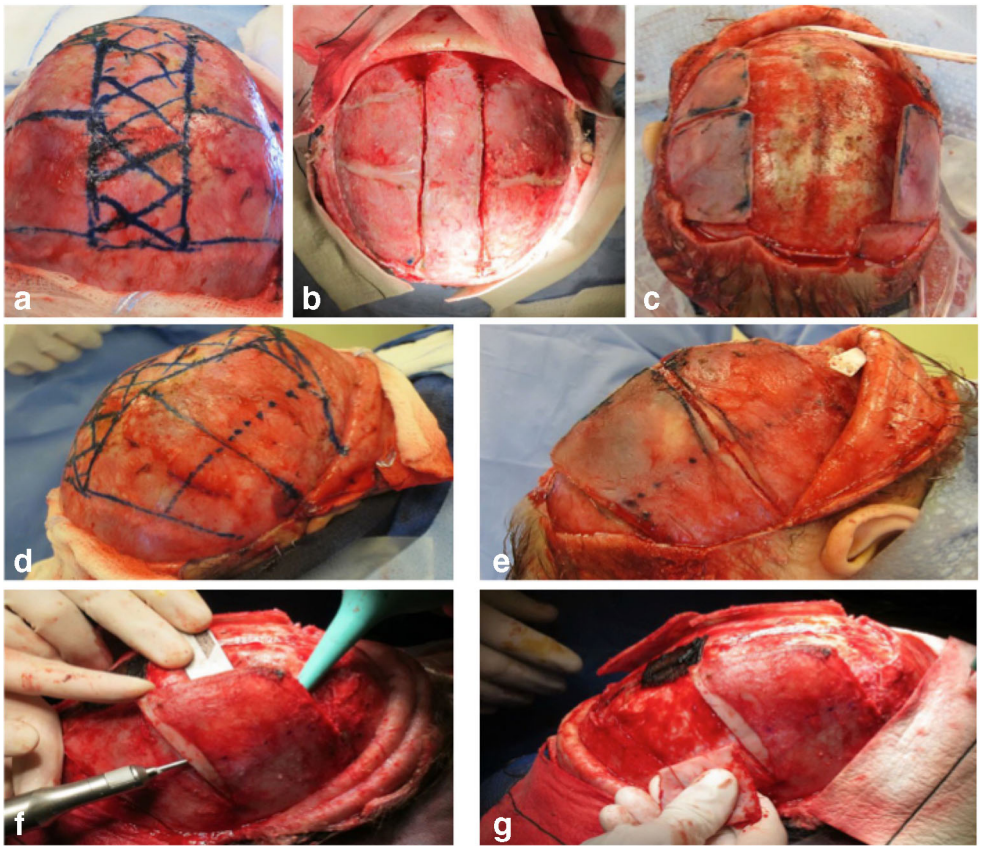

Fig. 1 **a** Anterior view, 3-cm strip of bone to be excised over the sagittal suture. **b** Strip of bone cut, lambdoid suture osteotomies visible at the top. **c** Cranial vault immediately before closure; parietal bones are fractured and loose allowing for lateral expansion with drain visible posteriorly. **d** Anterolateral view showing planned parietal bone osteotomies and lambdoid wedge. **e** Lateral view after osteotomies. **f** Greenstick osteotomy made in the parietal bone. **g** Greenstick fracture in parietal bone

Discussion

Major cranial vault remodeling surgery is a significant physiologic stressor. There is a normal decrease in red blood cell production in term infants after birth as a result of improved oxygenation and a natural adaptation to extra-uterine life. The concentration of Hb typically decreases over the first 2 to 3 months of life and then slowly rises between 4 and 6 months of age in response to increased endogenous EPO, stabilizing to about 12–13 g/dL between 5 and 7 months of age. This "physiologic nadir" is generally well tolerated in healthy infants; however, surgery during this period requires special attention to the patient's hematologic needs [4]. This is especially true for craniosynostosis repair given the well-established high volumes of surgical blood loss, which can amount to 40–60% of a child's total circulating blood volume [8, 17]. The timing of surgery to correct craniosynostosis is controversial, with some favoring later repair so that patients can tolerate greater intraoperative blood loss, and some favoring earlier repair to avoid intracranial hypertension and allow for cranial growth [3, 19, 20]. The practice at our institution has typically been to repair sagittal craniosynostosis at 5–6 months of age.

Efforts to raise patients' baseline Hb or decrease blood loss in craniosynostosis surgery to reduce the need for allogeneic transfusions and their associated complications are common, and many unique approaches have been examined in the recent years. Among those previously studied are iron supplementation, administration of EPO alone, cell saver (CS) devices, acute normovolemic hemodilution (ANH), preoperative autologous blood donation, TXA alone, and EPO with TXA [26, 27, 29].

Preoperative EPO has been studied in great detail in craniosynostosis patients. In a randomized controlled trial of patients with involvement of various sutures, Fearon and Weinthal observed a 57% rate of transfusion in children treated with preoperative EPO and iron compared with 93% in the control group receiving iron alone [9]. In a case-control study by Helfaer et al., children undergoing craniosynostosis correction who were treated with EPO preoperatively showed a higher preoperative hematocrit and a 64% transfusion rate compared with a control group with a 100% transfusion rate [13]. Aljaaly et al.'s meta-analysis found that EPO increased preoperative hematocrit in craniosynostosis patients, but did not demonstrate a reduction in transfusion rate [1]. While studies of CS and ANH used as the sole means of attempting to avoid transfusion have largely shown mixed efficacy, combination of these methods with EPO has shown greater promise. A study by Velardi et al. of 13 patients of mixed sutural involvement combined EPO with CS, ANH, and preoperative autologous donation, observing a 15% autologous transfusion rate and no adverse events related to their protocol [26, 29].

Table 1 Summary of patient demographics and operative parameters. Values are mean ± SD unless otherwise indicated

	Control group ($n = 22$)	Study group ($n = 14$)	p value
Male/female (%)	81.8/18.2	71.4/28.6	0.68
Weight (kg)	7.8 ± 1.6	7.5 ± 1.5	0.66
Age (months)	5.9 ± 1.3	7.0 ± 3.34	0.45
Operative time	136.1 ± 30.4	131.8 ± 34.5	0.85
Volume of crystalloid (mL)	329.4 ± 70.8	313.5 ± 91.6	0.78

Surgical patients tolerate brief preoperative EPO therapy well. Adverse events associated with EPO administration include thrombosis, thrombocytosis, hypertension, and death. However, many of these risks are associated with long-term use and in chronically ill and older patients [12, 18, 25].

The antifibrinolytic TXA has also been studied extensively in craniosynostosis patients. Although its effect on blood loss is controversial, multiple studies have found that perioperative TXA reduces the need for blood transfusions in craniosynostosis patients [23]. Martin et al. demonstrated a reduction in the transfusion volume of pRBCs needed in a cohort of sagittal craniosynostosis patients who received TXA compared with a control group [16]. Goobie et al. reported a randomized controlled trial showing that TXA reduces both blood loss and transfusion volume requirements [11]. TXA is associated with increased thrombotic risk in adults, but this potential risk is felt to be attenuated in pediatric populations who have a lower baseline risk for thrombosis [2, 14].

Of particular interest to our analysis was the randomized controlled trial of Dadure et al., which combined EPO with iron and TXA. In their study, all children were given 600 U/kg of EPO up to three times, with the treatment group receiving perioperative TXA. They found that 37% of the group receiving both agents required perioperative transfusion, compared with 70% of the group receiving EPO alone. This study was conducted on a mixed group of children with different sutures involved, with the majority having isolated sagittal craniosynostosis [6].

We are not aware of any studies that examined the combined use of EPO, iron, and TXA in a cohort composed solely of sagittal craniosynostosis patients. We chose to focus exclusively on patients undergoing non-syndromic sagittal craniosynostosis repair via cranial vault remodeling, as this patient group is very homogenous in terms of pathology, and their simpler defect and less demanding surgical approach mark them as a unique subgroup among craniosynostosis patients.

The lack of thrombotic events or any other complications typically associated with EPO and TXA use points to the safety of this protocol. These findings concur with the findings of studies cited prior examining EPO or TXA monotherapy, as well as those of Dadure et al. examining combination therapy [6, 9, 11, 13, 16]. The study group's postoperative course relative to the control group also provides evidence of the safety of this protocol. The lack of significant differences in Hb levels on postoperative day 1 suggests that the patients were hemodynamically similar postoperatively despite their different intraoperative management. PICU stays between the groups were also not significantly different, further suggesting a lack of any instability induced by our altered transfusion practices. The statistically significant reduction in the total length of stay for the study group requires further interpretation. Given our sample size and that length of stay could only be measured retrospectively to the nearest half day, we feel that the difference in means of 0.6 days is likely not clinically meaningful, especially considering the chronology of our intervention and the possibility of improvements in

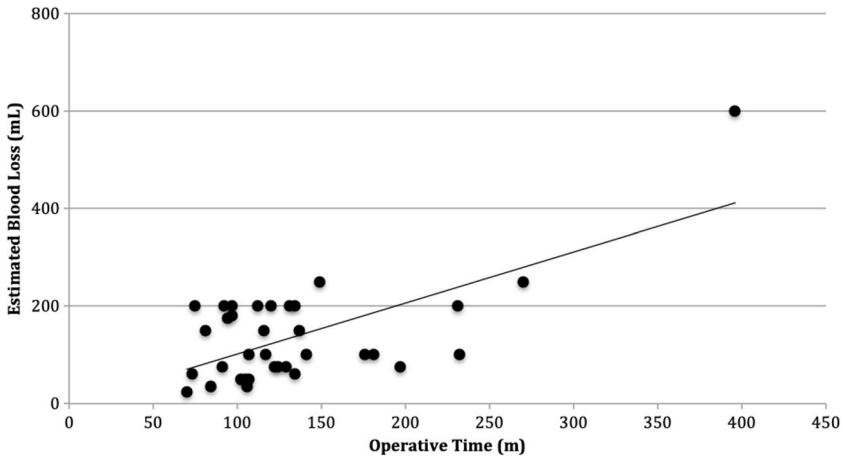

Fig. 2 Scatter plot of estimated blood loss vs. operative time with trend line

Table 2 Perioperative details by treatment group. Values are mean ± standard deviation unless otherwise indicated

	Control group ($n = 22$)	Study group ($n = 14$)	p value
Preoperative Hb (g/dL)	11.8 ± 0.4	13.6 ± 0.4	< 0.0001
Estimated blood loss (mL)	168.1 ± 50.6	93.9 ± 40.6	0.038
Fraction transfused	22/22 (100%)	2/14 (14.2%)	< 0.0001
Lowest intraoperative Hb (g/dL)	8.9 ± 0.5	9.2 ± 0.5	0.35
Days in PICU	1.6 ± 0.3	1.4 ± 0.6	0.51
Length of hospital stay (days)	4.0 ± 0.6	3.4 ± 0.6	0.04
Postoperative day 1 Hb (g/dL)	9.6 ± 0.6	9.1 ± 1.0	0.38
Fraction transfused postoperatively	5/22 (22.7%)	0/14 (0%)	0.13

postoperative care as our intensivists and hospitalists became more familiar with managing these patients. However, even if the length of stay remained constant between the two groups, it would seem to provide further evidence that our interventions were safe and that patients suffered no ill effects postoperatively as a result.

The stark reduction we observed in transfusion rate for this subset of patients is further evidence that agrees with the findings of Dadure et al. on the effectiveness of EPO with iron and TXA and shows that sagittal craniosynostosis patients can usually be brought safely through open surgery without the need for transfusion. In the context of Dadure's findings, which rigorously showed a benefit of combination therapy over EPO monotherapy in a mixed patient population and given the lack of studies examining transfusion reduction in sagittal synostosis as a discrete population, the low rate of transfusion we observed is also useful as a preliminary benchmark by which to assess other means of reducing transfusion in CVR for sagittal synostosis. Parsing out the effects of the individual pharmaceutical agents on transfusion reduction in our study is difficult given our multifaceted protocol and the retrospective nature of our analysis. The higher preoperative Hb we observed in protocol patients is attributable to the administration of EPO along with iron supplementation and likely functions to give patients a greater buffer period before transfusion is needed. The best indicator of the success of TXA administration would be an exact measurement of surgical blood loss. In our study, we instead used estimated blood loss, which was the only measure available to us retrospectively. Accurately estimating surgical blood loss poses various well-characterized difficulties [22]. In craniosynostosis surgery, in particular, blood loss estimation is made especially difficult by insensible losses as osteotomies are made [15]. Therefore, the clinical significance of the intergroup difference in estimated blood loss is uncertain. Analysis is further complicated by our shift in transfusion triggers from automatic transfusion to situation-dependent transfusion based on the patient's clinical status. This change represents an uncontrolled paradigm shift that likely accounts for at least some of the observed reduction in transfusion rates. Despite these challenges to analysis, we did observe that the two groups did not have significantly different intraoperative Hb nadirs, suggesting that combination of EPO and TXA allowed the study group to tolerate surgery without suffering any greater hemodynamic strain intraoperatively than the control group.

Efforts to reduce transfusions in craniosynostosis patients have spanned decades. However, as Vergnaud et al. have opined, the end goal of zero transfusions in these patients may only be feasible in those with isolated sagittal craniosynostosis [28]. Indeed, coupled with the increasing use of minimally invasive techniques like endoscopic assistance, which has been shown to reduce operative time, blood loss, and hospital stay, the volume of research on reducing transfusions by pharmacologic means has rendered this goal more realistic [5, 24]. Though, for our study, we analyzed patients undergoing open CVR, we have initiated the use of this protocol in our patients undergoing endoscopic repairs as well. Future studies could seek to analyze this protocol with minimally invasive approaches, or with preoperative autologous blood donation, ANH, and/or CS as demonstrated by Velardi et al. [26, 27].

Other than the limitations in assessing blood loss and the confounding effects of our new transfusion practices and retrospective study design that were previously discussed, our study was also limited by its sample size. The administration of preoperative EPO requires an initial consultation with hematology, extra weekly appointments, and lab draws prior to injection. These demands can be difficult for families that have unreliable transportation, or who live hours from larger healthcare systems capable of rendering this level of care, which is a common occurrence given the wide geographic region we serve. All of these factors can reduce an already small pool of patients in which the success of this protocol could be assessed. The financial burden of EPO/TXA therapy relative to the burden of transfusion is a topic of potential future investigation.

Conclusions

Our protocol of preoperative erythropoietin with iron and perioperative tranexamic acid and altered transfusion practices resulted in a 14.3% rate of transfusion in patients undergoing

repair of sagittal craniosynostosis and did not negatively impact their postoperative course relative to an automatic transfusion control. Given the dearth of studies examining pharmacologic means of reducing transfusion in sagittal synostosis in isolation from other more complex and surgically challenging forms of craniosynostosis, we hope this study serves to provide another data point by which future studies may seek to address this issue in a prospective manner. It further demonstrates that very low rates of transfusion are possible in sagittal craniosynostosis patients who require CVR and that transfusion need not be viewed as an inevitable event in CVR. This is valuable to keep in mind when presented with patients who due to age or other circumstances are not candidates for minimally invasive approaches.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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