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Original contribution

Blood loss and transfusion requirements with epsilon-aminocaproic acid use during cranial vault reconstruction surgery☆,☆☆

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ABSTRACT

Objective: To determine whether epsilon-aminocaproic acid (EACA) load of 50 mg·kg^{-1} before skin incision, and infusion of 25 mg·kg^{-1}·h^{-1} until skin closure during cranial vault reconstruction (CVR) were associated with decreased estimated blood loss and transfusion requirements.
Background: Antifibrinolytic medications decrease bleeding and transfusion requirements during cardiothoracic and orthopedic surgeries with high blood loss, but practical reductions in blood loss and transfusion requirements have not been consistently realized in children undergoing CVR. Current dosing recommendations are derived from adult extrapolations, and may or may not have clinical relevance.
Method: Retrospective case-controlled study of 45 consecutive infants and children undergoing primary craniosynostosis surgery at Covenant Children's Hospital during years 2010-2014. Exclusion criteria included revision surgery, and chromosomal abnormalities associated with bleeding disorders. Blood loss and blood transfusion volumes as a percent of estimated blood volume were compared in the presence of EACA while controlling for age, suture phenotype, use of bone grafting, and length of surgery. Secondary outcomes measures included volume of crystalloid infused, length of hospital stay, and any postoperative intubation requirement.
Results: When analyzed based on length of surgery, EACA did reduce blood loss and blood transfusion ($R^2 = 0.19$, $P = .005$ and $R^2 = 0.18$, $P = .010$, respectively) with shorter surgeries.
Conclusions and relevance: Using a standardized dosing regimen of EACA during craniosynostosis surgery, we found statistical significance in blood loss and transfusion requirements in surgeries of the shortest duration. We suspect this may be due to our selected dosing regimen, which may be lower than recently recommended. This study contributes to the growing body of evidence supporting EACA in CVR for craniosynostosis.

1. Introduction

Primary surgery to correct craniosynostosis in infants and children can typically be divided into early surgery (cranial vault reconstruction [CVR] without bone grafting at 3-6 months of age) vs late surgery (CVR with bone grafting at ages >6 months of age, and often around 9-12 months of age). Minimally invasive approaches often involve smaller incisions and may employ the use of endoscopy and include limited strip craniectomies or suturectomies coupled with either surgically implanted springs or postsurgical molding helmets to affect change. In late surgery, the osteogenic capacity of the dura is limited and the bone is more vascular and less moldable requiring multiple craniotomies, bone flaps, and reshaping of bone grafts followed by fixation with rigid resorbable plates and screws. The CVR with bone grafting requires longer operations with greater expected blood loss. Early surgery must be weighed against smaller patient size and blood volumes. With transfusion rates between 40% and 90% for more extensive CVR with bone grafting, these infants are routinely exposed to risks of transfusion, including both infectious and noninfectious transfusion reactions [1,2].

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In healthy infants, initial clotting factor levels and platelet counts are usually normal and procoagulant processes are balanced by anticoagulant processes. Antifibrinolytic therapy prevents existing beneficial clots from being broken down along the traumatized edges of bone and tissue, thereby leading to reduced microvascular bleeding. According to a large practice survey in 2011, only 30% of institutions in the United States routinely used antifibrinolytic medications for craniosynostosis surgery, despite established use in other high blood loss surgery, such as cardiac and scoliosis surgeries [3]. Two categories of antifibrinolytic medications have been used for decreasing blood loss. One category includes the serine protease inhibitor aprotinin, which inhibits clot breakdown while also possessing some anti-inflammatory properties. It had been extensively used in adults and children, but was removed from the North American market in 2008 after a large study in high-risk adult cardiac surgery showed increased mortality [4]. It is still used in Europe, and has recently been reestablished in Canada for pediatric indications, but remains unavailable in the United States. The second category consists of lysine-analogs, and includes tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA). Uncertainty in effective dosing of TXA and EACA may have led to decreased use of these antifibrinolytics, and only recently have there been reports of efficacy [5-7]. A large meta-analysis of TXA in craniosynostosis surgery showed a reduction in packed red blood cell (PRBC) infusion, and decreased rates of bleeding [5]. Studies for aprotinin and EACA also show reduced bleeding and transfusion requirements during craniosynostosis surgery [7,8]. A positive study of EACA in craniosynostosis surgery by Oppenheimer et al [7] did not mention dosing regimen used.

After introducing the use of EACA to our craniosynostosis program in October 2012, we subjectively felt like we were seeing less blood loss and decided to objectively quantify the effect of EACA use. Conducting a retrospective chart review enabled us to objectively study our hypothesis. Using a standardized dosing regimen, we hypothesized that we would find a reduction in blood loss and transfusion requirements across all craniosynostosis cases, but expected to see greater reductions in the age <6-month group.

2. Methods

We compared cases from October 2012 through August 2014 (22-month period) which did receive EACA, to controls from January 2010 through September 2012 (preceding 34-month period) which had not received EACA. Cases and controls were not matched a priori, but were conveniently similar. This study method was chosen to produce results that would inform continuing blood conservation management of these cases in our institution, and might inform development of prospective trials.

Being a retrospective study, the need for review was waived by institutional review boards of St Joseph Health System and Texas Tech University Health Sciences Center. Patients undergoing primary craniosynostosis surgery from January 2010 through September 2014 were identified using clinic and surgical lists and assigned to case or control status depending on whether intraoperative EACA was used. There were 29 non-EACA controls during the first time period, and 14 EACA cases during the second time period.

Exclusion criteria included revision surgery, chromosomal abnormality associated with bleeding disorders (1 patient, Noonan syndrome), and use of TXA (1 patient when EACA was unavailable). Estimated blood volume (EBV) in milliliters was calculated as 80 mL × weight in kilograms. Primary outcome measures included estimated blood loss (EBL) as a percentage of EBV (EBL/EBV%) and transfusion of PRBCs in milliliters as a percentage of EBV (PRBC/EBV%). Secondary outcome measures included postoperative intubation, amount of crystalloid infused, and length of stay. Subgroup stratification was employed by age greater than or less than 6 months, suture phenotype, and use of bone grafting.

2.1. Epsilon-aminocaproic acid dosing

Use of EACA was standardized to include a loading dose of 50 $mg{\cdot}kg^{-1}$ via syringe infusion pump over 30 minutes starting after placement of the first peripheral intravenous cannula during and was completed before skin incision. Infusion rate of 25 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ was continued until final skin layer closure.

2.2. Laboratory analysis

Preoperative laboratory values were drawn before the day of surgery in most patients. A few patients had blood drawn with start of first peripheral intravenous cannula after induction of anesthesia. Intraoperative blood gas analysis was conducted approximately every 60 minutes with a calibrated bench technique by a respiratory therapist who was on-site in the operating room.

2.3. Blood product transfusion management

We did not have a uniform blood transfusion algorithm during these study years. In general, we replaced visual blood loss in milliliters 1:1 with PRBCs from skin incision until incision closure. Transfusion and fluid requirements determination was performed by the anesthesiologist in consultation with surgical team. Either an arterial line or central line was placed for each patient from which hourly blood gas analysis was performed and transduced pressures were used for clinical decision-making.

2.4. Surgical techniques

Age permitting, we now offer small incision(s) approach with endoscopic assistance for early surgery beginning in early 2014. Two of the sagittal synostosis cases presented here aged <6 months were endoscopically repaired. The surgical duration of these first 2 endoscopic cases was similar to the open technique, and they were not excluded from review. Before early 2014, T-cell receptor without bone grafting was performed in patients <6 months of age using an open bicoronal approach with strip craniectomy of the diseased synostotic suture. Anterior and posterior biparietal wedge craniectomies, out-fracturing of the parietal bone flaps with or without barrel staving of the parietal bones was performed. For pronounced occipital cupping, a prone approach was used and the occipital bone was barrel-staved. For more pronounced frontal bossing, supine positioning and frontal barrel staving were performed. Late surgery (patients >6 months of age) was also approached via open bicoronal incision and then CVR with multiple bone grafts and cranioplasties including fronto-orbital reshaping and advancements for coronal and metopic synostosis.

3. Results

Of 43 suture surgeries, 22 (51%) were sagittal, 5 (12%) were coronal, 12 (28%) were metopic, 1 (2%) was squamosal, and 3 (7%) had more than one affected suture. Fourteen (33%) cases received EACA, and 29 (67%) controls were made up of patients not receiving EACA.

3.1. Blood product transfusion

Mean preoperative hemoglobin was $12 \pm 1.1\ g{\cdot}dL^{-1}$. Mean end of surgery hemoglobin was $9.9 \pm 1.4\ g{\cdot}dL^{-1}$. Mean discharge hemoglobin was $9.9 \pm 1.3\ g{\cdot}dL^{-1}$ and these values were not significantly different between cases or controls. No patient received more than 1 unit of blood intraoperatively. Two patients did not receive intraoperative blood transfusion, one of whom received a postoperative transfusion. Postoperative blood transfusion was given to 2 case and 4 control patients. Decision to transfuse postoperatively was not based on a trigger algorithm. Some patients were sent home with hemoglobin level of less