Effectiveness of Tranexamic Acid Administration on Intraoperative Blood Loss in Elective Craniofacial Surgery

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EXECUTIVE SUMMARY

Abstract: The purpose of this study was to determine if intraoperative use of tranexamic acid (TXA) was associated with estimated blood loss in patients who underwent elective craniofacial surgery.

Introduction: Intraoperative blood loss has been shown to significantly contribute to postoperative morbidity and mortality in patients undergoing surgical procedures. It is the responsibility of the anesthesia clinician to accurately assess and actively replace ongoing blood loss, as well as employ strategies to curtail perioperative hemorrhage. While numerous methods exist to minimize surgical blood loss, such as mild hypothermia and controlled hypotensive techniques, these interventions can prove hazardous in pediatric patients and those with multi-morbidities. Additionally, allogenic blood transfusions possess unique risks in the form of transmissible disease and transfusion complications. It is imperative that the safest, scientifically-proven, most cost-effective, methods be adopted into clinical practice. This will help to ensure optimization of surgical outcomes, reduction in health care costs, and promotion of patients along the wellness continuum. Therefore, antifibrinolytic therapy is being utilized to aid in the reduction of perioperative blood loss. The more recent use of perioperative Tranexamic Acid to decrease surgical blood loss has assisted in achievement of these goals. The findings of this study could be directly applied to patients undergoing elective craniofacial surgery at CAMC and other facilities world-wide. The Certified Registered Nurse Anesthetist (CRNA) will be able to safely implement the results of this evidenced based research into daily practice.

Methodology: A retrospective, quantitative, cohort study design was utilized for this research. A systematic chart review was completed of patients age three months – 35 years old, American Society of Anesthesiologist (ASA) physical classification I-III, who underwent elective craniofacial surgery between June 1, 2008 and June 1, 2018. A total of 108 patients were included in the study and were classified into two groups: Group 1 was comprised of 54 patients who did not receive intraoperative TXA; Group 2 consisted of 54 patients who did receive intraoperative TXA. Primary independent variables were administration of TXA or no administration of TXA. Additional independent variables included age, gender, body mass index (BMI), and ASA physical status. The dependent variables were estimated blood loss and the need for intraoperative blood transfusion. The hypotheses of this study were that intraoperative administration of TXA in patients who underwent elective craniofacial surgery would be associated with decreased estimated surgical blood loss and a decreased need for blood transfusion throughout the operative period versus patients who did not receive intraoperative TXA.

Results: The patient population for this study consisted of 108 patients classified into Group 1 (54 patients who did not receive intraoperative TXA) and Group 2 (54 patients who did receive TXA intraoperatively). Mean age of patients was 9.81 ± 9.06 years. Average BMI was 21.73 ± 6.28 kg/m². Average estimated blood loss, expressed as percentage of EBV, was 13.80 ± 14.71%. No statistical differences were found between the two groups in regard to age and BMI (p = 0.962 and 0.410, respectively). Additionally, there was no statistical significance between Group 1 and 2 in gender and ASA classification (p =0.700 and 0.701, respectively). Step-wise regression showed no statistically significant relationship existed between TXA administration,
transfusion requirements, and estimated blood loss. However, step-wise regression results indicated a significant association between age and estimated blood loss. Logistic regression analysis revealed a significant association between age and blood transfusion \((p = .000)\). Gender, ASA classification, and TXA administration were not significantly associated with intraoperative blood transfusion. As age increased patients were less likely to receive intraoperative blood transfusion \((p = .021)\).

**Discussion:** The results of this study did not support the hypotheses that intraoperative administration of TXA in patients who underwent elective craniofacial surgery would be associated with decreased estimated surgical blood loss and a decreased need for blood transfusion throughout the operative period versus patients who did not receive intraoperative TXA. Since intraoperative administration of TXA was not significantly associated with decrease in blood loss or need for intraoperative blood transfusion, the hypotheses were rejected.

**Conclusion:** The intraoperative administration of TXA was not associated with decreased estimated surgical blood loss or decreased need for intraoperative blood transfusion in patients who underwent elective craniofacial surgery. The results of this retrospective, cohort study concluded that increasing patient age was associated with both decreased likelihood for blood transfusion as well as decreased estimated blood loss.

**Key Words:** antifibrinolytic drugs, blood loss, craniofacial surgery, tranexamic acid, transfusion
INTRODUCTION

Background and Significance

According to the American Society of Plastic Surgeons (ASPS), almost 220,000 craniofacial and maxillofacial surgeries were performed in the United States (U.S.) in 2016 (American Society of Plastic American Society of Plastic Surgeons, 2017). These procedures include craniosynostosis correction, cleft lip and palate repair, and orthognathic surgery. Anomalies of the craniofacial region can be congenital or acquired and involve a wide range of defects (Davis, Cladis, & Motoyama, 2011).

Surgical correction for craniofacial abnormalities has been linked to significant perioperative blood loss due to the vascularity of the surgical field (Choi, Irwin, & Samman, 2009). Intraoperative bleeding not only poses a threat to homeostasis but has a direct effect on surgeon efficacy (Christabel et al., 2014). Additionally, risks of allogenic blood transfusion can include transmission of infectious disease and transfusion associated complications (Sankar, Krishnan, Veerabahu, & Vikraman, 2012). Prevention and treatment of excessive bleeding in the operating room (OR) is paramount for a positive clinical outcome. While the necessity of blood transfusion is sometimes unavoidable, it is prudent to employ strategies to curtail the use of these scarce resources (Faverani et al., 2014).

Various methods to decrease intraoperative bleeding have been utilized including hypothermia, hypocapnia, mild hypotensive technique, autologous transfusion, and normovolemic hemodilution. (Meara et al., 2005). However, due to the risks associated with some of these methods in vulnerable populations, it would be judicious to explore alternative techniques to decrease intraoperative bleeding, such as antifibrinolytic therapy (Song et al., 2013). Antifibrinolytic medications, such as tranexamic acid (TXA), work by competitive
inhibition of plasmin to fibrin binding sites as well as inhibition of plasminogen to plasmin conversion (Dunn & Goa, 1999).

Literature Review

TXA is a synthetic lysine analogue with initial studies dating back to 1962 (Slaughter & Greenberg, 1997). It has 6 to 10 times the binding capacity of other synthetic antifibrinolytic drugs and has been shown to be more cost effective than aprotinin. TXA has been used to reduce operative bleeding in a variety of settings, such as open-heart surgery, orthopedics, menorrhagia, gastrointestinal bleeding, liver transplantation, transurethral resection of the prostate (TURP), and craniofacial surgery (Dunn & Goa, 1999). Reported elimination half-life of TXA is approximately 1-1.5 hours and studies support continuous intravenous administration of antifibrinolytic therapy during the perioperative stage to ensure therapeutic blood concentrations are achieved (Slaughter & Greenberg, 1997).

A 1974 study completed on healthy volunteers revealed that TXA distribution followed an open, two-compartment model with glomerular filtration being the primary route of elimination after a single intravenous dose (Eriksson, Kjellman, Pilbrant, & Schannog, 1974). Further studies indicated over 95% of each dose is eliminated as chemically unaltered drug in the urine. Therefore, dosage adjustment should be considered in patients with documented renal insufficiency. Recommendations for general fibrinolysis include a single intravenous dose of 10mg/kg or 1g of TXA (Dunn & Goa, 1999). Agreement is lacking in regard to timing of administration. However, most literature supports preoperative administration of TXA, with the decision for continuous infusion at the discretion of the clinician (Choi et al., 2009).

Concerns regarding the potential of antifibrinolytic therapy to promote thromboembolic events have been cited by numerous studies. Pharmacologically, TXA serves to stabilize formed
blood clots by slowing fibrinolysis and has not been reported to exhibit prothrombotic effects. Therefore, it does not appear that TXA contributes to the risk of perioperative thrombosis (Slaughter & Greenberg, 1997).

A secondary examination was completed of 35,478 pediatric patients who received TXA during a single hospital encounter between 2009 and 2013. Data were collected using the Pediatric Health Information System (PHIS) which contains information from 36 U.S. children’s hospitals affiliated with the Children’s Hospital Association. Of those included in the study, 1275 patients received TXA for craniofacial surgery. Results also denoted a broad range of indications for tranexamic use in the pediatric population (Nishijima et al., 2016).

A randomized, double-blind trial was conducted on 66 patients who underwent palatoplasties from January through December 2014 at the Facial Defects Awareness Center of the Professor Fernando Figueira Internal Medicine Institute (CADEFI) in Brazil. Patients in the study group received a 10mg/kg TXA bolus followed by a 1mg/kg continuous infusion for the duration of surgery. Control group patients received a placebo. In this clinical trial, intraoperative blood loss was calculated as a percentage of the patient’s estimated total circulating blood volume. Results indicated an 11.9% diminution in intraoperative bleeding in the study group compared to the control group (Arantes, Pereira, de Melo, Alonso, & Duarte, 2017).

In 2009, Choi, Irwin, and Samman studied 73 patients scheduled for orthognathic surgery. The purpose of the clinical trial was to determine if a correlation existed between single dose preoperative TXA and intraoperative blood loss. Anesthetic plan for all patients involved a mild controlled hypotensive technique. The intervention group received 20mg/kg TXA prior to surgery start and the control group received 0.9% normal saline. Average blood loss total in the treatment group was 878.6 ml compared to 1257.2 ml in the control group – a difference of 422
ml. These results were calculated to be statistically significant and indicated the usefulness of TXA in intraoperative blood loss reduction (Choi et al., 2009).

A similar prospective, randomized, triple-blinded study was performed with isolated Le Fort I osteotomies in Chennai, India in 2013. Hypotensive anesthesia was also utilized in this trial. A sample size of 49 patients were included with age range 18-34 years. Thirty minutes prior to induction, Group 1 (control) received a placebo of saline and Group 2 (intervention) received 10mg/kg TXA. Operating time and total blood loss was significantly reduced in Group 2 compared to Group 1. Total blood loss in the intervention group revealed a 45% reduction when compared to the control group. Additionally, lab values revealed a significant variance in preoperative and postoperative hemoglobin and packed cell volume. These findings also suggest single intravenous preoperative administration of TXA may diminish the need for postoperative blood transfusion (Christabel et al., 2014).

Multiple other studies have supported the use of antifibrinolytic therapy for orthognathic surgery. Mohammadi and Hasheminasab (2012) demonstrated a positive correlation between preoperative administration of TXA and blood loss reduction during bimaxillary osteotomy surgery. A 2012 study analyzed the difference in surgical field visibility, case duration, and total blood loss among patients undergoing orthognathic surgery who received TXA in conjunction with hypotensive anesthesia versus hypotensive technique alone. Statistical significance existed when comparing estimated blood loss and quality of the surgical field between the two groups (Sankar et al., 2012). Further, meta-analysis completed by Song et al. (2013) confirmed the efficacy of TXA in reducing intraoperative blood loss during orthognathic surgery.

The use of TXA has also been shown to be effective in reducing blood loss in patients who underwent craniosynostosis correction. A 2010 study completed in France showed a
statistically significant difference in volume and number of transfused packed red blood cells among 40 children who received a 15mg/kg bolus of TXA followed by a 10mg/kg/hr infusion versus saline placebo. Patients in this study also received erythropoietin pre-operatively per institution protocol (Dadure et al., 2011). Similarly, a 2015 single-center study in Germany reported a significant decrease in blood loss and packed red blood cell transfusion after TXA administration in 40 patients who underwent fronto-orbital advancement. In this study, the intervention group received a 10mg/kg bolus followed by 5mg/kg/hr continuous infusion while the control group received no TXA (Engel et al., 2015).

A unique, randomized, double-blind study of 60 patients investigated the ability of TXA to control common side effects of rhinoplasty (intraoperative bleeding, periorbital ecchymosis, and eyelid edema) that were commonly managed with corticosteroids. 10mg/kg of TXA or placebo was administered intravenously immediately prior to surgery start. All patients received dexamethasone 8mg every 8 hours postoperatively. Mean intraoperative bleeding (calculated by hematocrit and estimated blood loss), eyelid edema, and periorbital ecchymosis was appreciably reduced in the intervention group in contrast to the control group (Ghavimi, Taheri Talesh, Ghoreishizadeh, Chavoshzadeh, & Zarandi, 2017).

Benefits to use of antifibrinolytic therapy reach further than direct patient outcomes. The unit dose cost of antifibrinolytic drugs compared to one unit of packed red blood cells can be substantial. Therefore, even a one-unit reduction in transfusion requirements per patient is advantageous. This aggregate expense reduction may assist with unburdening of the health care system, especially for those who do not possess a third-party plan (Sepah et al., 2011).

In 2015, the National Clinical Guideline Centre released evidence-based guidelines and recommendations regarding blood transfusion including a cost-effective analysis of cell salvage
and tranexamic acid use. An economic evidence profile of tranexamic acid showed an incremental cost reduction of £54 (approximately $75.84) when perioperative intravenous tranexamic acid was used instead of placebo (National Clinical Guideline Centre, 2015). A cost-benefit analysis, in conjunction with a Process Improvement Project, that was completed by Demos et al. (2017) showed individual patient savings of approximately $128, per encounter, with hospital-wide standardization of preoperative TXA administration. Additionally, $55,884 was reported in annual institution savings following project implementation (Demos et al., 2017).

Statement of the Problem

While an array of techniques have been used to decrease intraoperative bleeding in the OR, it is imperative that the safest, scientifically-proven, most cost-effective, methods be adopted into clinical practice. This will help to ensure optimization of surgical outcomes, reduction in health care costs, and promotion of patients along the wellness continuum. The more recent use of perioperative TXA to decrease surgical blood loss has assisted in achievement of these goals. The findings of this study could be directly applied to patients undergoing elective craniofacial surgery at CAMC and other facilities world-wide. The Certified Registered Nurse Anesthetist (CRNA) will be able to safely implement the results of this evidenced based research into daily practice.

Research Objectives

The goal of this research was to determine if the intravenous administration of TXA was associated with less total estimated blood loss in patients who underwent craniofacial surgery. The purpose of this study was to determine if intraoperative use of tranexamic acid (TXA) was associated with estimated blood loss in patients who underwent elective craniofacial surgery.
METHODOLOGY

Hypothesis

The hypotheses for this study were:

1. Intraoperative administration of TXA in patients who underwent elective craniofacial surgery will be associated with decreased estimated surgical blood loss versus patients who did not receive intraoperative TXA.

2. Intraoperative administration of TXA in patients who underwent elective craniofacial surgery will be associated with a decreased need for intraoperative blood transfusion versus patients who did not receive intraoperative TXA.

Research Design

The study design was a retrospective, quantitative, cohort study conducted at Charleston Area Medical Center (CAMC). This study design was employed due to cost effectiveness, ability to compare multiple variables within the information snapshot, and timeliness of data collection. Electronic medical records (EMR) of patients meeting inclusion criteria were reviewed, which allowed for comparison of clinical characteristics and patient demographics.

Sample

A chart review was conducted on patients age 3 months-35 years with ASA classification of I-III who underwent elective craniofacial surgery between June 1, 2008 and June 1, 2018 at CAMC. One hundred and eight patients who met inclusion criteria were separated into two groups: Group 1 was comprised of 54 patients who did not receive intraoperative TXA; Group 2 consisted of 54 patients who received any dose of intraoperative TXA. Patients eligible for inclusion were identified utilizing The International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes 01.25 (craniectomy), 01.24 (craniotomy), 01.23
(craniectomy, reopening of site), 02.01 (craniectomy, linear/strip), 02.06 (cranioplasty), 73.8 (craniectomy, fetal), 76.69 (osteotomy, facial bone), 76.66 (osteoplasty, maxilla, total), 76.65 (osteoplasty, maxilla, segmental), 76.64 (osteoplasty, mandible), 76.63 (osteoplasty, mandible body), 76.62 (osteoplasty, ramus, open) 76.61 (osteoplasty, ramus, closed), 76.91 (bone graft to facial bone), 76.92 (insertion of synthetic implant in facial bone) and applicable International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-PCS) codes (Appendix A).

**Inclusion Criteria**

1. Male or female patients age 3 months-35 years old
2. American Society of Anesthesiologists (ASA) physical classification I-III
3. Patients who underwent craniofacial surgery and did or did not receive intravenous TXA

**Exclusion Criteria**

1. Patients less than 3 months or greater than 35 years old
2. Patients with bleeding disorders, clotting disorders, or hemostasis abnormalities
3. Patients taking TXA at time of craniofacial surgery
4. Patients who received preoperative blood transfusions
5. ASA physical classification greater than III

**Procedure**

A retrospective chart review was conducted from electronic medical records on patients who underwent elective craniofacial surgery at CAMC from June 1, 2008 through June 1, 2018. Pertinent data were collected utilizing patients’ perioperative anesthesia and surgery records. Collected data included age, gender, BMI, ASA classification, TXA administration, estimated blood loss, and administration of intraoperative blood transfusion. Age was measured in years.
Gender classification was male or female. BMI (kg/m$^2$) was calculated using patient height and weight obtained from the anesthesia record. A classification system using yes and no was employed to indicate if patients received intraoperative TXA. Yes indicated the patient received intraoperative TXA and no indicated the patient did not receive TXA. The yes and no system was also used to record intraoperative blood transfusion. Yes indicated the patient received intraoperative blood transfusion of packed red blood cells and no indicated the patient did not receive intraoperative blood transfusion of packed red blood cells. Estimated blood loss (EBL) in milliliters was converted into a percentage of blood volume loss (PBVL) by dividing EBL by the patient’s estimated total blood volume (EBV). EBV was calculated using the following:

<table>
<thead>
<tr>
<th>Age</th>
<th>EBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate (1-28 days)</td>
<td>100 ml/kg</td>
</tr>
<tr>
<td>Infants (1-11 months)</td>
<td>80 ml/kg</td>
</tr>
<tr>
<td>Child 1-12 years</td>
<td>75 ml/kg</td>
</tr>
<tr>
<td>Adult &gt;12 years</td>
<td>70 ml/kg</td>
</tr>
</tbody>
</table>

Source: Miller & Pardo, 2011

The ASA physical status classification is a system developed by the American Society of Anesthesiologists to determine the general health of the patient prior to surgery (American Society of Anesthesiologists, 2014). The classifications are:

I. A normal healthy patient.

II. A patient with mild systemic disease.

III. A patient with severe systemic disease.

IV. A patient with severe systemic disease that is a constant threat to life.

V. A moribund patient who is not expected to survive without the operation.

VI. A declared brain-dead patient whose organs are being removed for donor purposes.
Data Collection and Instrumentation

Microsoft Excel was utilized by the researcher to systematically organize collected data. Each patient was assigned a number in the order the data will be collected. The assigned number in no way linked the patient to the data collected. Each patient’s EMR was accessed to obtain specific data from the perioperative anesthesia and surgery records. Information gathered from these records assisted with delineation of patients into one of two groups: 1. Received intraoperative TXA, 2. Did not receive intraoperative TXA. SPSS software was utilized to determine the statistical relevance of collected data.

Statistical Design and Analysis

The purpose of this study was to determine if intraoperative administration of TXA was associated with decreased blood loss in patients who underwent elective craniofacial surgery. Step-wise regression was used to determine if a relationship existed between TXA therapy, PBVL, and transfusion administration. Age, BMI, gender, and ASA classification were also included in the regression analyses. A t-test was performed to determine if the two groups shared similarities in age and BMI. A Chi-squared test was used to determine if the two groups were similar in gender and ASA classification. A p-value <0.5 was considered statistically significant.

Ethical Considerations

The study was approved by the CAMC and West Virginia University-Charleston Division Institutional Review Board on June 29, 2018.
RESULTS

Presentation, Analysis, and Interpretation of Data

Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No TXA Group (Group 1)</th>
<th>TXA Group (Group 2)</th>
<th>P-Value (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>9.77</td>
<td>9.86</td>
<td>0.962</td>
</tr>
<tr>
<td>Gender (n/%)</td>
<td></td>
<td></td>
<td>0.700</td>
</tr>
<tr>
<td>Male</td>
<td>27 (50%)</td>
<td>29 (54%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27 (50%)</td>
<td>25 (46%)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>22.23</td>
<td>21.23</td>
<td>0.410</td>
</tr>
<tr>
<td>ASA (n/%)</td>
<td></td>
<td></td>
<td>0.701</td>
</tr>
<tr>
<td>I</td>
<td>17 (32%)</td>
<td>18 (33%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>33 (61%)</td>
<td>34 (63%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4 (7%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>Mean PVBL</td>
<td>12%</td>
<td>15%</td>
<td>.273</td>
</tr>
<tr>
<td>Received Intraoperative Blood</td>
<td>16 (30%)</td>
<td>20 (37%)</td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, statistically significant

The patient population for this study consisted of 108 males and females between the ages of three months to 35 years who underwent elective craniofacial surgery from June 1, 2008 through June 1, 2018 at CAMC. Group 1 was comprised of 54 patients who did not receive intraoperative TXA. Group 2 was comprised of 54 patients who did receive TXA intraoperatively. Mean age of patients was 9.81 ± 9.06 years. Average BMI was 21.73 ± 6.28 kg/m². PVBL was 13.80 ± 14.71%.

A t-test determined no statistical difference between the two groups in regard to age and BMI (p = 0.962 and 0.410, respectively). Additionally, a Chi-squared test confirmed there was no statistical difference between Group 1 and 2 in gender and ASA classification (p =0.700 and 0.701, respectively). Demographic results are represented in Table 1.
Step-wise linear regression was used to determine if a relationship existed between TXA administration, transfusion administration, PVBL, and age. The analysis revealed a significant association between age and estimated blood loss with a coefficient of -.847. This showed that for every increase in age by one year, PVBL decreased by .847. Linear regression analysis for factors affecting estimated blood loss are represented in Table 2.

Logistic regression analysis was used to determine if age, gender, TXA administration, ASA 1, and ASA 2 were associated with intraoperative blood transfusion administration and revealed a significant association between age and blood transfusion only (p = .000). Gender, ASA classification, and TXA administration were not significantly associated with intraoperative blood transfusion. Logistic regression analysis results for factors affecting intraoperative blood transfusion are represented in Table 3.
Table 4. Logistic Regression Step 1

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>Sig.</th>
<th>Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-.572</td>
<td>.248</td>
<td>5.339</td>
<td>1</td>
<td>.021*</td>
<td>.564</td>
</tr>
<tr>
<td>Constant</td>
<td>1.460</td>
<td>.424</td>
<td>11.851</td>
<td>1</td>
<td>.001</td>
<td>4.305</td>
</tr>
</tbody>
</table>

*p < 0.05, statistically significant

Step 1 in the Logistic regression (Table 4) showed that as age increased patients were less likely to receive intraoperative blood transfusion (p = .021).

DISCUSSION

Discussion of Study Results

The results of this retrospective, cohort study indicated that there was no statistically significant association between the intraoperative administration of TXA and PVBL. Additionally, there was no correlation between intraoperative administration of TXA and the need for intraoperative blood transfusion. Groups 1 and 2 were not statistically different in age, gender, BMI, or ASA Classification. Mean estimated blood loss was similar between the two groups. The findings of this study were not consistent with literature reviewed.

Step-wise linear regression revealed a statistically significant association between age and estimated blood loss. As patient age increased by one year, EBVL decreased by a factor of .847. Logistic regression determined a significant association existed between age and blood transfusion. As patient age increased, the likelihood for blood transfusion decreased.

While craniofacial surgeries include a wide variety of procedures, this study focused primarily on patients who underwent craniosynostosis correction and elective orthognathic surgeries. It should be noted that majority of patients included in this study who were less than one year of age (n = 39) underwent craniosynostosis correction. This type of corrective surgery is associated with significant blood loss requiring blood transfusion (Engel et al., 2015). This may help explain the regression results that indicated increased age was associated with decreased
blood loss and likelihood for intraoperative blood transfusion. Conversely, no patients over the age of three (n=56) received intraoperative blood transfusions. Majority of these patients underwent elective orthognathic surgery. In this study, no patients who underwent orthognathic surgery received intraoperative blood transfusions. Additionally, craniosynostosis correction was the only procedure in which intraoperative hemoglobin and hematocrit levels were monitored through blood specimen collection. Trending of these laboratory values may have contributed to the decision to administer packed red blood cells, although cases existed when blood was administered prior to the obtainment of these values.

Although there were only five different lead/primary surgeons included in this study, additional required neurological surgeon assistance during craniosynostosis correction may have affected overall procedural blood loss due to surgical technique. Furthermore, variation in anesthetic techniques were noted. Inhalation agents utilized were sevoflurane or desflurane. Maintenance of anesthesia and pharmacologic choice for controlled hypotension included sufentanil, propofol, esmolol, or nitroglycerine.

Pediatric dosing of TXA for initial bolus and subsequent infusion varied among anesthesia providers. Initial TXA bolus ranged from 10-20 mg/kg. Subsequent infusion rates ranged from 5-10 mg/kg/hr. Adult dosing of TXA began with an initial bolus of 1g. Subsequent infusion rates varied widely based on surgeon preference, with some providers requesting no infusion after initial intraoperative bolus. Although variation in dosage of intraoperative TXA was noted, administered dose was consistent with research guidelines and recommendations noted in literature review.
Study Limitations

There were several study limitations that were identified throughout the research process. The retrospective study design limited results to association of variables instead of causation. Incomplete documentation excluded patients in this research, which contributed to the small sample size. However, sample size utilized in this study matched and, in some cases, exceeded sample sizes in literature reviewed cases. Additionally, TXA had only been used clinically in elective craniofacial surgeries at CAMC since 2015, owing to the limited sample size for the TXA group.

This study design also did not allow for standardization of anesthetic techniques such as pharmacologic method of controlled hypotension. Estimation of blood loss is a subjective measurement among anesthesia providers, as variable amounts of irrigation were used, and lap pads, tapes, and sponges were not weighed for accurate fluid measurement. Finally, dosing of TXA and surgical provider was not standardized.

IMPLICATIONS AND RECOMMENDATIONS

The results of this study did not support the hypotheses that intraoperative administration of TXA in patients who underwent elective craniofacial surgery would be associated with decreased estimated surgical blood loss and a decreased need for blood transfusion throughout the operative period versus patients who did not receive intraoperative TXA. Since intraoperative administration of TXA was not significantly associated with decrease in blood loss or need for intraoperative blood transfusion, the hypotheses were rejected. It would be beneficial to conduct a prospective study on this topic in order to reduce limitations present in this study. Anesthetic techniques and TXA dosage could be standardized among all patients as well as utilization of a
metric scale for more accurate blood loss estimation. Moreover, patients undergoing the same surgical procedure could be studied.

CONCLUSION

The intraoperative administration of TXA was not associated with decreased estimated surgical blood loss or decreased need for intraoperative blood transfusion in patients who underwent elective craniofacial surgery. The results of this retrospective, cohort study concluded that increasing patient age was associated with both decreased likelihood for blood transfusion as well as decreased estimated blood loss.
REFERENCES


APPENDICES

Appendix A: ICD-10-PCS Codes

Procedures of the skull: 0NS004Z (Reposition skull with internal fixation device, open approach), 0NS005Z (Reposition skull with external fixation device, open approach), 0NS00ZZ (Reposition skull, open approach), 0NS0XZZ (Reposition skull, external approach), 0NB00ZZ (Excision of skull, open approach), 0NU107Z (Supplement frontal bone with autologous tissue substitute, open approach), 0NU10JZ (Supplement frontal bone with synthetic substitute, open approach), 0NU10KZ (Supplement frontal bone with nonautologous tissue substitute, open approach), 0NUM07Z (Supplement right zygomatic bone with autologous tissue substitute, open approach), 0NUM0JZ (Supplement right zygomatic bone with synthetic substitute, open approach), 0NUM0KZ (Supplement right zygomatic bone with nonautologous tissue substitute, open approach), 0NUQ07Z (Supplement left zygomatic bone with autologous tissue substitute, open approach), 0NUQ0JZ (Supplement left zygomatic bone with synthetic substitute, open approach), 0NUQ0KZ (Supplement left zygomatic bone with nonautologous tissue substitute, open approach), 0WU20JZ (Supplement face with synthetic substitute, open approach), 0WU20KZ (Supplement face with nonautologous tissue substitute, open approach), 0NQ0ZZ (Repair skull, open approach), 0N800ZZ (Division of skull, open approach).

Procedures of the orbit: 0UP07Z (Supplement right orbit with autologous tissue substitute, open approach), 0UP0JZ (Supplement right orbit with synthetic substitute, open approach), 0UP0KZ (Supplement right orbit with nonautologous tissue substitute, open approach), 0SP0ZZ (Reposition right orbit, open approach), 0SPXXZZ (Reposition right orbit, external approach), 0UQ07Z (Supplement left orbit with autologous tissue substitute, open approach).
approach), 0NUQ0JZ (Supplement left orbit with synthetic substitute, open approach),
0NUQ0KZ (Supplement left orbit with nonautologous tissue substitute, open approach),
0NSQ0ZZ (Reposition left orbit, open approach), 0NSQXZZ (Reposition left orbit, external
approach).

Procedures of the maxilla: 0NSR04Z (Reposition maxilla with internal fixation device,
open approach), 0NSR04Z (Reposition maxilla with external fixation device, open approach),
0NSR0ZZ (Reposition maxilla, open approach), 0NSRXZZ (Reposition maxilla, external
approach), 0NBR0ZZ (Excision of maxilla, open approach), 0NQR0ZZ (Repair of maxilla, open
approach), 0NUR07Z (Supplement maxilla with autologous tissue substitute, open approach),
0NUR0JZ (Supplement maxilla with synthetic substitute, open approach), 0NUR0KZ
(Supplement maxilla with nonautologous tissue substitute, open approach).

Procedures of the mandible: 0NST04Z (Reposition right mandible with internal fixation
device, open approach), 0NST05Z (Reposition right mandible with external fixation device, open
approach), 0NST0ZZ (Reposition right mandible, open approach), 0NSTXZZ (Reposition right
mandible, external approach), 0NSV04Z (Reposition left mandible with internal fixation device,
open approach), 0NSV05Z (Reposition left mandible with external fixation device, open
approach), 0NSV0ZZ (Reposition left mandible, open approach), 0NSVXZZ (Reposition left
mandible, external approach), 0NBT0ZZ (Excision of right mandible, open approach),
0NBV0ZZ (Excision of left mandible, open approach), 0NQT0ZZ (Repair right mandible, open
approach), 0NQV0ZZ (Repair left mandible, open approach).

Procedures of the jaw: 0W0407Z (Alteration of upper jaw with autologous tissue
substitute, open approach), 0W040JZ (Alteration of upper jaw with synthetic substitute, open
approach), 0W040KZ (Alteration of upper jaw with nonautologous tissue substitute, open
approach), 0W040ZZ (Alteration of upper jaw, open approach), 0WU407Z (Supplement upper jaw with autologous tissue substitute, open approach), 0WU40JZ (Supplement upper jaw with synthetic substitute, open approach), 0WU40KZ (Supplement upper jaw with nonautologous tissue substitute, open approach), 0WU507Z (Supplement lower jaw with autologous tissue substitute, open approach), 0WU50JZ (Supplement lower jaw with synthetic substitute, open approach), 0WU50KZ (Supplement lower jaw with nonautologous tissue substitute, open approach).
Appendix B: Data Collection Tool 1

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### Appendix C: Data Collection Tool 2

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<th>Estimated Blood Volume (EBV) (mL)</th>
<th>Estimated Blood Loss (ml)</th>
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