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Use of Tranexamic Acid in Head and Neck Free Flap Reconstruction

Fuat B. Bengur[1] | Micah K. Harris[2] | Michael S. Hu[1] | Rula Mualla[2] | Arash Samadi[1] | Olivier Bourguillon[2] | Joshua Smith[2] | Vu T. Nguyen[1] | Michael L. Gimbel[1] | Kevin Contrera[2] | Matthew Spector[2] | Mario G. Solari[1] | Mark W. Kubik[2] | Shaum S. Sridharan[2]

[1]University of Pittsburgh Medical Center, Department of Plastic Surgery—Head and Neck Surgery, Pittsburgh, Pennsylvania, USA | [2]University of Pittsburgh Medical Center, Department of Otolaryngology—Head and Neck Surgery, Pittsburgh, Pennsylvania, USA

Correspondence: Shaum S. Sridharan (sridharans2@upmc.edu)

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ABSTRACT

Introduction: Tranexamic acid (TXA) is commonly used in surgical settings to reduce blood loss. Due to its antifibrinolytic properties, TXA theoretically increases the risk of thrombosis. In this study, the use of TXA was assessed in patients undergoing head and neck free flap reconstruction.

Methods: A cohort of patients from February 2021 to September 2023 received TXA. Patients received 3 g of intravenous TXA intraoperatively, in addition to topical TXA to the donor, recipient, and neck dissection sites. Patients were compared to a retrospective cohort from August 2019 to January 2021. All patients, including those in the retrospective control cohort, met the criteria for TXA.

Results: A total of 397 patients underwent free flap reconstruction (53.6% thigh, 25.6% fibula), of which 185 received TXA and 212 did not. Patients receiving the TXA protocol had a lower perioperative transfusion rate (12.9% vs. 20.7%, $p = 0.042$) and intraoperative estimated blood loss (196.4 ± 102.9 cc vs. 263.7 ± 247.8 cc, $p < 0.001$). There was no difference in postoperative flap vascular compromise in the TXA (7.6%) versus control (10.4%) groups ($p = 0.33$). Postoperative complications, including hematoma and thromboembolic events, were not statistically different between the groups. On multivariate analysis, the use of TXA remained predictive of reduced perioperative transfusion when controlling for BMI > 25, osseous flap, and hypertension.

Conclusion: Patients who received TXA demonstrated decreased perioperative transfusion after head and neck free flap reconstruction with no increase in flap vascular compromise or major thromboembolic events. Implementation of our protocol to larger cohorts and randomized controlled trials could help identify an optimal dosing regimen and demonstrate long-term efficacy.

1 | Introduction

Microvascular free tissue transfer is a reliable method of complex head and neck reconstruction, with flap success rates above 95% at high volume centers (Bui et al. 2007; Kubo et al. 2002; Suh et al. 2004). Given the complexity and length of these surgeries, bleeding is a major concern. Various methods are used intraoperatively to achieve and maintain hemostasis, including cauterization, suture ligation, as well as hemostatic agents such as oxidized regenerated cellulose (Boucher and Traub 2009).

Fuat B. Bengur and Micah K. Harris contributed equally to this work.

However, hemostasis and blood loss remain a challenge in many cases.

Tranexamic acid (TXA) is an antifibrinolytic agent that acts as a lysine analogue to bind to plasminogen and plasmin and block the action of plasmin on fibrin (Brown et al. 2018; Porte and Leebeek 2002). It has successfully been used in various surgical specialties, particularly in the acute care and trauma setting, demonstrating a reduction in the need for transfusions and intraoperative blood loss, while not having an impact on the overall venous thromboembolism (VTE) rate (Hamele et al. 2020; Khan et al. 2018; Lewis et al. 2016; Morrison et al. 2012). Given its success, the use of TXA has rapidly expanded to various reconstructive surgeries including craniofacial and orthognathic reconstruction (Eustache and Riffaud 2019; Mei and Qiu 2019; Murphy et al. 2016; Siotou et al. 2019), aesthetic surgeries (Cansancao et al. 2018; Cohen et al. 2021; Wokes et al. 2021) and breast reconstruction (Weissler et al. 2020). A recent systematic review demonstrated a clear benefit with the use of TXA in a wide variety of plastic surgery procedures to decrease blood loss regardless of the administration route, with no increased risk of thrombosis (Elena Scarafoni 2021). Within otolaryngology, a meta-analysis of randomized controlled trials demonstrated a reduction in perioperative bleeding and transfusion with TXA administration following surgeries including neck dissection and parotidectomy (Alsubaie et al. 2022).

Despite its widespread use, applications of TXA in head and neck microvascular reconstruction are limited, particularly as TXA has historically been associated with increased thrombosis (Klifto et al. 2020) Outside of head and neck, TXA has repeatedly been shown to not significantly increase the risk of microvascular free flap complications (Lardi et al. 2018) (Valerio et al. 2015). However, only one study has reported on the use of TXA in head and neck reconstruction, in which only 4 of 99 free flap patients received TXA. In the present study, we assessed the use of intraoperative TXA administration on flap-specific outcomes and perioperative transfusion in patients undergoing head and neck microvascular free flap reconstruction.

2 | Methods

We performed a single-center study at the University of Pittsburgh Medical Center between August 2019 and September 2023. The study obtained institutional review board approval. A TXA free flap protocol was developed based on the published literature (Figure 1). Based on this protocol, patients received (1) 1 g IV TXA prior to skin incision, (2) 1 g IV TXA after flap elevation (or at "halfway point"), (3) 200 mL of 3% topical TXA prior to closure, and (4) 1 g IV TXA during skin closure.

Prior to surgery, patients were assessed for eligibility for the TXA protocol. Contraindications included known allergy to TXA, history of intracranial bleed, history of acute thromboembolic disease, history of seizure disorder, elevated creatinine, current use of anticoagulants or antiplatelets (except aspirin). All patients received mechanical thromboembolism prophylaxis with sequential compression devices initiated in the operating room, 120 mg rectal acetylsalicylic acid immediately postoperatively

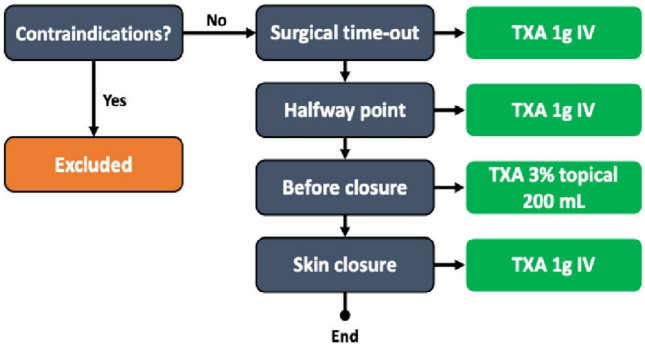

FIGURE 1 | Schematic of the developed tranexamic acid protocol.

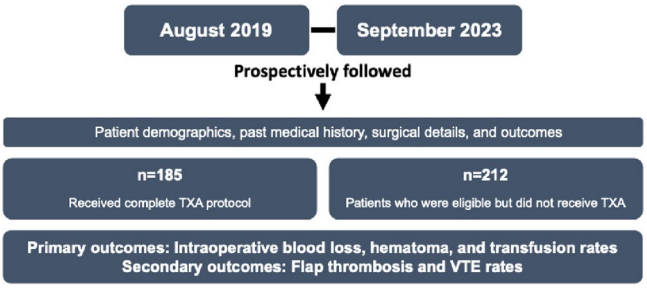

FIGURE 2 | Schematic of the study protocol.

and 81 mg for the first five postoperative days, and a fixed dose of enoxaparin 30 mg BID during hospital stay per institutional guidelines. Data collected included demographical variables (gender, age, body mass index (BMI)), smoking history, medical comorbidities (hypertension (HTN), diabetes mellitus, pulmonary comorbidities, cardiac disease, vascular disease), aspirin use, tobacco use, alcohol abuse, surgical details (etiology, prior treatment, donor site), estimated blood loss (EBL) (anesthesia records), intraoperative and postoperative transfusions, venous thromboembolic events (VTEs) (both pulmonary embolism and deep venous thrombosis), hematoma events, postoperative 30-day recipient and donor site complications.

Primary outcomes were free flap complications and transfusion rate (includes both intraoperative and postoperative). Secondary outcomes were hematoma and VTE rates. Transfusions were generally initiated if the hemoglobin levels of the patients reduced below 7 g/dL, or under 8 g/dL for patients with cardiac comorbidities, though ultimately the decision to transfuse was based on clinical course and patient-specific characteristics. Multiple transfusions during the intraoperative or postoperative period were only counted once for each period, respectively, per patient for the analysis. Free flap pedicle thrombosis was defined as arterial or venous thrombosis requiring surgical exploration of the anastomosis after the index surgery. The hematoma rate included the bleeding events that required return to the operating room for either donor or recipient site.

Patients who were enrolled and completed the full protocol from February 2021 to September 2023 (TXA group) were compared with a retrospective group of patients from August 2019 to January 2021 (control group) who did not receive TXA but would have met the inclusion criteria listed above (Figure 2). Patients who did not complete the full protocol were excluded from the study. Reasons

for not completing the complete protocol included missing the topical dose or missing any of the IV doses.

3 | Statistical Analysis

Descriptive statistics included mean ± standard deviation (SD) for continuous variables and frequencies and proportions for categorical variables. All analyses were performed using SPSS v27 (IBM). Chi-squared was performed for categorical variables with Fisher's exact test, and independent samples T-test was performed for numerical variables. A value of $p < 0.05$ was considered statistically significant. Variables that were found to be significant on univariate regression analyses were then included in multivariate linear and logistic regression models to identify significant outcome predictors.

4 | Results

The study included a total of 397 patients, 185 of which met our inclusion criteria and were studied on the TXA protocol (TXA group), versus 212 retrospective control patients who met criteria but did not receive TXA (control group). Forty-two patients were excluded due to TXA contraindications, the most common being current anticoagulation or antiplatelet use (52.4%), followed by elevated creatinine (28.6%), and history of acute thromboembolic disease (14.3%). The mean age, BMI, gender distribution, cardiac comorbidities, diabetes, aspirin use, tobacco use, and alcohol abuse rates were not statistically different between groups (Table 1). The most common donor site for free flap harvest was the anterolateral thigh (56.2% in TXA group vs. 51.4% in control, $p = 0.38$) followed by the fibula (23.2% in TXA group vs. 27.8% in control, $p = 0.29$). Preoperative hemoglobin was not statistically different between the TXA (13.3 ± 2.1 g/dL) and control groups (13.9 ± 3.3 g/dL, $p = 0.24$). Perioperative hemoglobin for which transfusion was performed was also not statistically different between the TXA (7.1 ± 0.97 g/dL) and control groups (7.2 ± 0.41 g/dL, $p = 0.36$).

TABLE 1 | Demographic variables.

Variable	Control ($n = 212$)	TXA ($n = 185$)	p
Age (y)	61.1 ± 13.1	62.6 ± 11.9	0.12
Gender (male)	123 (66.5%)	146 (68.9%)	0.61
Mean BMI (kg/m^2)	26.9 ± 6.8	26.2 ± 6.5	0.16
Preop Hgb (g/dL)	13.9 ± 3.3	13.3 ± 2.1	0.24
Cardiac comorbidities	119 (64.3%)	133 (62.7%)	0.74
Diabetes	49 (22%)	35 (16.7%)	0.19
Aspirin use	13 (7%)	24 (11.3%)	0.14
Tobacco use	129 (70.1%)	164 (78.1%)	0.07
Alcohol abuse	60 (33.1%)	56 (27.1%)	0.19

Abbreviations: BMI, body mass index; Hgb, hemoglobin; Preop, preoperative; TXA, tranexamic acid.

When comparing the TXA versus control groups (Table 2), the rate of flap vascular compromise during hospitalization was no different (7.6% vs. 10.4%, $p = 0.331$). The overall rate of intraoperative vascular pedicle revision was 5%, with rates between the TXA versus control groups not being statistically different (3.8% vs. 5.7%, $p = 0.82$). Patients receiving the TXA protocol were found to have lower perioperative (including intraoperative and postoperative) transfusion rates (12.9% vs. 20.7%, $p = 0.042$). Intraoperative EBL was also found to be lower in the TXA group (196.4 ± 102.9 cc vs. 263.7 ± 247.8 cc, $p < 0.001$). Univariate logistic regression analyses were then conducted for all variables to identify significant predictors of perioperative transfusion. Variables with p-value < 0.1 were included on subsequent multivariate analysis. On multivariate analysis, TXA administration remained a significant predictor of decreased perioperative transfusion (OR 0.35, 95% CI = 0.14–0.86, $p = 0.022$) when controlling for overweight to obese (> 25) BMI

TABLE 2 | Intraoperative and postoperative outcomes.

Variable	TXA ($n = 185$)	Control ($n = 212$)	p
Perioperative transfusion	24 (12.9%)	44 (20.7%)	**0.04**
Estimated blood loss	196.4 ± 102.9	263.7 ± 247.8	**< 0.001**
Operative duration (min)	627.7 ± 131.1	637.1 ± 136.1	0.25
Ischemia duration (min)	124.9 ± 31.3	128.1 ± 38.4	0.19
Flap vascular compromise	14 (7.6%)	22 (10.4%)	0.33
RTOR	13 (7%)	18 (8.4%)	0.35
Overall flap failure	5 (2.7%)	5 (2.3%)	0.54
Hematoma	8 (4.3%)	14 (6.6%)	0.32
Donor	2 (1.1%)	6 (2.8%)	0.22
Recipient	6 (3.2%)	9 (4.2%)	0.61
Donor site			
Infection	0 (0%)	3 (1.4%)	0.25
Dehiscence	3 (1.6%)	2 (0.9%)	0.67
Skin graft loss	0 (0%)	2 (0.9%)	0.19
Recipient			
Infection	5 (2.7%)	8 (3.8%)	0.59
Dehiscence	6 (3.2%)	7 (3.3%)	0.97
Pulmonary embolism	4 (2.2%)	6 (2.8%)	0.78
Deep vein thrombosis	2 (1.1%)	3 (1.4%)	0.88

Note: Bold value indicates statistical significance $p < 0.1$.
Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; TXA, tranexamic acid.

(OR 0.34, 95% CI = 0.15–0.76, $p = 0.009$), osseous flap (OR 2.51, 95% CI = 1.15–5.46, $p = 0.02$), and hypertension (OR 2.33, 95% CI = 1.01–5.41, $p = 0.047$) (Table 3).

The rate of donor site (3.3% vs. 1.6%, $p = 0.33$) and recipient site complications (7.1% vs. 10.8%, $p = 0.21$) were also not statistically different. Specifically, the donor site hematoma (1.1% vs. 2.8%, $p = 0.22$), recipient site hematoma (3.2% vs. 4.2% $p = 0.61$), and overall hematoma (4.3% vs. 6.6%, $p = 0.32$) rates were not statistically different. The rates of pulmonary embolism (2.2% vs. 2.8%, $p = 0.78$) and deep vein thrombosis (1.1% vs. 1.4%, $p = 0.88$) during postoperative hospitalization were not statistically different. Mean operative duration (627.7 ± 131.1 min vs. 637.1 ± 136.1 min, $p = 0.25$) and mean ischemia duration (124.9 ± 31.3 vs. 128.1 ± 38.4, $p = 0.19$) were not statistically different.

5 | Discussion

Despite the use of TXA in other free flaps, its use has not been well described in head and neck reconstruction. Here, we found that the administration of TXA resulted in a lower rate of perioperative transfusion without any increase in free flap vascular compromise.

The safety profile of TXA in microvascular free flap reconstruction has been explored outside of head and neck. Klifto et al. reported a significant reduction in blood loss and perioperative transfusion with the use of TXA in free flap reconstruction of the breast and extremities, with no increased rate of flap thrombosis (Klifto et al. 2020). Lardi et al. evaluated their series of 98 free flaps in 83 patients for microvascular breast reconstruction. In the TXA group, 50 patients received TXA up to 3 g IV and had a significantly lower blood loss, without an increase in thrombosis rate (Lardi et al. 2018) Similarly, in our cohort of 185 patients who received TXA, we identified a decreased rate of perioperative transfusion and lower EBL. Compared with the previous studies, we used a standard higher dose of TXA with the systemic component of 3 g, in addition to the topical administration of 6 g in a 200 mL solution. Despite the increased dose, we rates of intraoperative and postoperative flap vascular compromise were not significantly different, further highlighting the safety of TXA.

To our knowledge, the only prior study describing the use of TXA with head and neck free flap reconstruction was by Rogers et al. who retrospectively reviewed a series of 99 patients that underwent free flap surgery for head and neck cancer, of which only 4 were administered 1 g of IV TXA intraoperatively. Moreover, flap-specific outcomes were not reported, and no conclusions regarding TXA could definitively be made (Rogers et al. 2019). Chen et al. performed a prospective randomized trial on the use of TXA for patients undergoing ablative head and neck procedures without any free flap reconstruction (Chen et al. 2008). With the use of a protocol including one dose of preoperative TXA (intravascular 10 mg/kg) before incision followed by continuous infusion of 1 mg/kg/h during the surgery, they did not find a significant difference in reducing the postoperative bleeding rates. Kulkarni et al. assessed TXA in patients undergoing composite mandibulectomy and concurrent neck dissection with pedicled flap reconstruction (Kulkarni et al. 2016). They used one-time 10 mg/kg of TXA in 100 mL of saline intraoperatively, before the surgical incision. Despite seeing a reduced postoperative blood loss with the use of TXA, the authors did not identify a significant difference in the need for transfusions.

TABLE 3 | Predictors of perioperative transfusion on multivariate analysis.

	Odds Ratio	95% CI	*p*
TXA	0.35	0.14–0.86	0.022
BMI > 25	0.34	0.15–0.76	0.009
Osseous flap	2.51	1.15–5.46	0.020
Hypertension	2.33	1.01–5.40	0.047

Abbreviations: BMI, body mass index, TXA, tranexamic acid.

Despite its historical association with thrombosis, TXA has interestingly been shown in recent studies to have antithrombotic effects as well. In in vitro studies, TXA has mechanistically been shown to modify the activity of fibrinolytic and thrombotic pathways, pointing to a regulatory mechanism rather than simply a pro-thrombotic effect. Results from large randomized controlled trials have corroborated these studies. In the CRASH-2 (Clinical Randomization of an Antifibrinolytic in Increased Hemorrhage 2) trial, TXA was administered to bleeding trauma patients in an effort to reduce surgical bleeding. While the results showed a significant reduction in death due to bleeding, it also showed fewer vascular occlusive deaths with TXA and a significant reduction in myocardial infarctions (Roberts et al. 2011). These data may explain why TXA has repeatedly been shown to be safe in the setting of microvascular free flaps.

Similar to previous studies, high BMI was found to be protective for perioperative transfusion requirements in our cohort (Crippen et al. 2018). This may be related to cachectic head and neck patients presenting with anemia and malnutrition related to a diminished ability to self-replete hemoglobin. Additionally, the use of osseous flaps (free fibula) was found to be associated with increased perioperative transfusion requirements, which could be related to the increased operative duration and extent of dissection with the harvest of fibula flaps (Lindeborg et al. 2020). Finally, hypertension was predictive of increased perioperative transfusion, as higher pressures can lead to increased bleeding intraoperatively. The use of TXA was also found to be an independent predictor of reduced perioperative transfusion requirements, which further highlights the added benefit of the described protocol. Combined with the data regarding BMI, future studies focusing on the optimal dosing per body weight of the patients could identify a weight-based dosing protocol to potentially further improve outcomes and reduce the need for transfusions in this patient cohort.

Lastly, TXA is a cheap agent to administer with an average cost of $15/1 g at our institution. The total cost of TXA for patients with our current protocol was $135. Therefore, TXA has the

major benefit of being an effective agent in the prevention and treatment of bleeding and reducing healthcare costs by potentially minimizing perioperative transfusion requirements.

6 | Limitations

First, our study was fundamentally a retrospective analysis, as the TXA protocol was implemented at a certain timepoint and subsequently compared to a retrospective cohort. Surgeons were not blinded to which patients received TXA, which may have led to an increased focus on achieving intraoperative hemostasis or an underestimation of the intraoperative EBL, or an increase in the clinical threshold for postoperative transfusion for the TXA group. Patients in the TXA and control cohorts were not matched, though demographic variables were found to be not statistically different. A power analysis was not done prior to patient enrollment to determine sample size; given that we expected vascular thrombosis, return to OR, hematoma, and DVT/PE rates to be similar between TXA and control groups, a post hoc analysis was done to estimate the number of patients needed to determine statistical equivalence, which showed that 84 patients in the experimental group were needed. Despite being a commonly utilized metric, estimated blood loss was collected from the anesthesia assessment forms and could be highly variable dependent on the surgical/anesthesia team available during the surgery. Lastly, despite the reduced transfusion requirement, we did not observe a reduction in clinical postoperative bleeding events.

7 | Conclusion

In conclusion, we demonstrated that a low-cost protocol TXA administration protocol is safe and feasible in major head and neck free flap reconstruction without an increase in flap failure or thrombosis rates. There may be an association with reduced intraoperative blood loss and perioperative transfusion requirements. Implementation of our protocol to larger cohorts and randomized controlled trials could help identify an optimal dosing regimen and demonstrate long-term efficacy.

Acknowledgments

The authors have nothing to report.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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