Use of tranexamic acid in reduction mammoplasty: a randomized controlled trial
Study Protocol

Prepared by: Amy Yao, MD (Plastic Surgery resident)

Version Date: August 25, 2021

1) Background

Breast reduction mammoplasty (BRM) is among the most commonly performed procedures in plastic surgery, with reliable surgical techniques and consistent results.[1] However, postoperative hematoma is one of the most common complications following BRM.[2-4] Despite meticulous hemostasis, up to 7,000 breast reduction patients develop a hematoma per year, leading to significant acute and long-term consequences. Hematoma-related complications include unplanned surgery, need for blood transfusion, wound healing issues, and unfavorable surgical outcomes. Though blood transfusions may be indicated, transfusion-related complications include hemolytic reactions, immunologic complications, and mortality.[5] The primary prevention of perioperative blood loss is therefore of critical importance.

Tranexamic acid has emerged in the literature as a promising agent that reduces perioperative blood loss and need for transfusion. Tranexamic acid is an antifibrinolytic agent that acts by stabilizing clot formation.[6] Tranexamic acid is currently FDA approved to reduce bleeding after tooth extraction in hemophiliacs, as well as to reduce heavy menstrual bleeding. Multiple randomized controlled trials in cardiac, orthopedic, and orthognathic surgery have demonstrated that tranexamic acid significantly reduces intraoperative bleeding and need for subsequent blood transfusion, without an increased risk of thromboembolic events including myocardial infarction, deep vein thrombosis, or pulmonary embolism.[7-11] Moreover, tranexamic acid has been shown to be cost-effective in the surgical setting, not only by reducing direct hospital costs (drug and blood products), but also by decreasing subsequent costs such as shortening length of stay and lowering the incidence of complications.[12] However, despite its consistently reported efficacy, low cost, and favorable safety profile, tranexamic acid remains underutilized in plastic surgery. This underutilization may be due to a relative lack of plastic surgery-specific research, coupled with unfamiliarity and concern regarding its safety profile. There is a need for high-level research investigating the use of tranexamic acid in plastic surgery.

We propose a prospective, double-blinded randomized controlled study of the efficacy of tranexamic acid in patients undergoing reduction mammoplasty. Our primary outcome variable will be rate of hematoma development. Our secondary outcome variables will be rate of blood transfusion, incidence of deep venous thrombosis, and rate of thromboembolic events. We will also collect a broad range of preoperative variables, surgical details, and other characteristics that may impact the perioperative bleeding risk. We hope to contribute to the growing body of literature supporting tranexamic acid to reduce unwanted surgical bleeding. Given the paradigm shifts evidenced by the recent surge in interest regarding tranexamic acid across multiple surgical subspecialties, better

understanding of the efficacy of tranexamic acid in plastic surgery may have powerful implications for surgical outcomes in our field.

2) Significance

The current proposal builds logically upon the prior research at our institution, which has been conducted by the PI and the Co-Investigator (Dr. Amy Yao). We have sought to identify risk factors for hematoma development following reduction mammoplasty in our patient population, which has higher rates of obesity, hypertension, and diabetes compared to the national average. We have identified a hematoma rate of 7% in our patient population per a retrospective chart review, which is consistent with the prior literature. The PI's research focuses on optimizing surgical outcomes in breast-related procedures, providing a strong and pertinent research background for the proposal.

There is a large body of evidence supporting the use of tranexamic acid to reduce perioperative blood loss and need for transfusion in trauma, orthopedic, and cardiac surgery.[7-11] Within the field of plastic surgery, previous research has focused on craniomaxillofacial surgery, though there have been preliminary studies of tranexamic acid's utility in burn surgery and aesthetic surgery.[6,13] Though virtually all authors endorse the integration of tranexamic acid into clinical practice based on their findings, there have been few adequately powered randomized studies in plastic surgery.[14,15] Furthermore, the majority of prior studies utilized primary outcome variables of unclear clinical significance. In a 2015 randomized controlled trial of 30 patients undergoing reduction mammoplasty, Ausen *et al* described an average 10 cc decrease in 24-hour drain output from topical TXA-treated breasts compared to contralateral controls, which was found to be statistically significant, but otherwise with uncertain clinical implications.[16] In their discussion, Ausen *et al* write that their study was inadequately powered to determine whether or not tranexamic acid could prevent postoperative hematoma.

This study would be the first randomized controlled trial to evaluate the use of tranexamic acid in reducing the rate of hematoma development in patients undergoing reduction mammoplasty. We plan to expand on the findings of Ausen *et al* by selecting hematoma development as the primary outcome variable. Selecting reduction mammoplasty patients as the study population allows us to evaluate each patient as their own internal control, thereby eliminating potential confounders associated with an increased risk of hematoma, such as hypertension.[14] Moreover, breast procedures have been identified as an independent risk factor for hematoma development compared to trunk, extremity, or facial plastic surgery procedures.[3] With the large volume of body contouring surgery at our institution, as well as the higher rates of medical comorbidities associated with hematoma formation present in our patient population, we are uniquely equipped to conduct this study. This innovative study will provide high-level evidence regarding the use of tranexamic acid in plastic surgery in an elegant model.

3) Study Design

a) <u>Study Objectives</u>

The primary goal of this proposal is to determine the efficacy of tranexamic acid in reducing the rate of hematoma formation after breast reduction surgery. This will be a double-blinded, randomized controlled study. The research will be achieved by randomizing one breast in a bilateral breast reduction to receive topical tranexamic acid, while the other breast will not receive the study drug. Both the surgical team and the patient will be blinded to which side has received the study drug. The patient will then be followed for the standard postoperative period and the rate of hematoma development will be recorded. Patient demographics, comorbidities, treatment history, and surgical details will be collected from these charts and analyzed for their impact on perioperative blood loss. **We hypothesize that use of topical tranexamic acid will decrease the rate of hematoma formation and the rate of blood transfusion without increasing the incidence of deep vein thrombosis or thromboembolic events.**

b) Target Population and Recruitment Methods

Consecutive patients presenting for breast reduction mammoplasty performed by plastic surgeons affiliated with Montefiore Medical Center will be offered enrollment in the study. Potential study participants will be recruited at their preoperative consultation appointments that take place at the Hutchinson Metro Center campus. Written informed consent (detailed below) will be obtained from all participants before inclusion. As this proposal involves greater than minimal risk to patients, we will have a Data and Safety Monitoring Plan in place prior to beginning the study.

c) Inclusion and Exclusion Criteria

Inclusion criteria include: being over the age of 18 and being scheduled for reduction mammoplasty at the Hutchinson Metro Center campus of Montefiore Medical Center.

Exclusion criteria include: oncologic breast reductions, unilateral breast reductions, history of thromboembolic disease, history of bleeding diatheses, history of stroke, current pregnancy, severe comorbidity (defined as American Society of Anesthesiologists (ASA) fitness grade IV or above).

d) Primary and Secondary Outcomes

Primary outcome: development of hematoma within 30 days of surgery
Rationale: Topical tranexamic acid has been shown to reduce perioperative blood loss and need for transfusion. A recent randomized controlled trial showed that topical tranexamic acid significantly decreased 24-hour drain output following reduction mammoplasty, though the clinical significance of this was unclear.

- *We hypothesize that breasts treated with topical tranexamic acid will have a lower rate of hematoma development compared to the contralateral control.*

Secondary outcom*e:* incidence of blood transfusion within 30 days of surgery, incidence of deep vein thrombosis, and incidence of pulmonary embolism
Rationale: Tranexamic acid is an antifibrinolytic, and therefore acts by inhibiting fibrinolysis and stabilizing clot formation. There has historically been concern that

use of tranexamic acid will increase the incidence of thromboembolic events such as deep venous thrombosis and pulmonary embolism.

- *We hypothesize that patients treated with topical tranexamic acid will not have an increased rate of thromboembolic events compared to nationally published rates and those of our own historical controls.*

e) Study Timelines

We anticipate that data collection from the treatment arm will take 8 months and analysis and manuscript preparation will take another 4 months.

4) Study Population

a) Study Population

The study population will comprise all patients over the age of 18 scheduled to undergo breast reduction surgery at the Hutchinson Medical Center campus of Montefiore Medical Center, who meet the inclusion and exclusion criteria outlined above. No patients from before the beginning of electronic medical record use at Montefiore Medical Center will be used, as it will not be possible to explore these patients' medical records. As this proposal involves greater than minimal risk to patients, we will have a Data and Safety Monitoring Plan in place prior to beginning the study.

b) Vulnerable Populations

Include	Exclude	Vulnerable Population Type
	X	Adults unable to consent
	X	Individuals who are not yet adults (e.g., infants, children, teenagers)
	X	Wards of the State (e.g., foster children)
	X	Pregnant women
	X	Prisoners

c) Informed Consent Process

It will be documented at an 8th grade reading level that they are being asked to enroll in a study involving research. The purpose of the research is to investigate the off-label use of an antifibrinolytic on perioperative blood loss and hematoma formation. It will be explained that the procedure will include the topical administration of tranexamic acid at the conclusion of their operation, which is above and beyond the standard of care for body contouring procedures.

- Potential benefits include the reduction in perioperative blood loss, a lower risk of hematoma formation, and a decrease in possible transfusion requirement
- Potential risks include a slight increase in the following risks: seizure, pulmonary embolism, deep venous thrombosis (DVT), and allergic reaction. Though the proposed research involves greater than minimal risk to the subjects, several prior randomized controlled trials have demonstrated the overall safety of the study drug:
    - For example, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial, a major multicountry,

prospective, placebo-controlled trial of 20,211 adult trauma patients showed that tranexamic acid provided a mortality benefit without an increased risk for thromboembolic events[17]
    - The Aspirin and Tranexamic Acid for Coronary Artery Surgery trial of 4,631 patients showed that the use of tranexamic acid does not increase the risk of thromboembolic events; however, it did show that the incidence of seizures increased from 0.1% to 0.7% (p=0.002), though this largely occurred in patients undergoing open chamber procedures, a known independent risk factor for seizure
- An additional risk to subjects in this study is a breach of confidentiality. This will be protected against with the use of well-trained research staff, encrypted and password protected data, and a locked linking file.

d) Protection of Human Subjects
The alternative to participating in this study includes proceeding with the standard of care in reduction mammoplasty, without the administration of topical tranexamic acid. Confidentiality of records identifying the participant will be maintained. In the event of a research-related injury, the participant will be instructed to contact the PI. In the event of potential complications that may ensue, including those that are known potential complications following reduction mammoplasty such as hematoma development and wound healing issues, the participant will be treated with the appropriate medical treatment per standard of care. There will be no compensation for participating in this study, nor will compensation be available in the event of a postoperative complication. Contact information for the research team will be provided in the event the participant wishes to ask pertinent research questions. Participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled. Significant new findings developed during the course of the research which may affect the participant's willingness to continue participation will be provided to the participant.

e) Sources of Research Material
This project relies on the scheduling system used by the Epic electronic medical record system. Patients presenting for breast reduction surgery who are deemed eligible and scheduled for surgery from the plastic surgery clinic will be offered enrollment in the study.

5) Participant Recruitment

a) Plan for Participant Recruitment
All patients over 18 presenting for breast reduction surgery who are deemed eligible and scheduled for surgery from the plastic surgery clinic will be offered enrollment in the study, unless they meet exclusion criteria as outlined above.

b) Data Management and Confidentiality

Although creation of the data-set will require use of patient names and medical record numbers, these will be stripped as soon as data-collection is complete and a linking file will be kept under lock and key by the primary investigator. The data set will be stored on Montefiore's encrypted server. Only the study team will have access to the stored data, and only the study team will have access to the linking file. Data will be stored until the data is analyzed and scholarly output is generated. All members of the research team have undergone appropriate Human Subjects Protection training.

c) Provisions to Monitor the Data to Ensure the Safety of Subjects/Data Safety and Monitoring Plan

There will be regularly scheduled monitoring reviews by a Data Safety Monitoring Board (DSMB) at 6-month time intervals to review rates of adverse events, which will determine if the study poses sufficiently low risk to proceed. The DSMB will be comprised of two members of the Department of Surgery who are not affiliated with the study (Dr. Sheldon Feldman, MD and Dr. Prashanth Sreeramoju, MD), as well as a biostatistician from the Albert Einstein College of Medicine/Montefiore Medical Center (Dr. Shankar Viswanathan, DrPH). The incidence of venous thromboembolism (VTE) in reduction mammoplasty ranges from 0.22% to 2.9%. A recent National Surgical Quality Improvement Program study describes a 0.17% rate of pulmonary embolism and a 0.07% rate of deep vein thrombosis in BRM patients.[18] Furthermore, the incidence of seizure in the general population is estimated at 3%.[19] With an anticipated sample size of 100 patients, if more than 2 patients (1.5%) develop either a deep vein thrombosis, pulmonary embolism, or seizure postoperatively, the study will be paused while further investigation regarding safety takes place. In the case of increased incidence of adverse events that warrant further investigation, the study will be paused and the PSF grant office will be kept apprised. We do not anticipate increased risk for thromboembolic events or seizure, given the well-described safety profile of tranexamic acid even in hypercoagulable populations such as bedbound or cancer patients, and given that we are using a low, topical dosage with fractional systemic absorption.

d) Provisions to Protect the Privacy Interests of Subjects

We will be requesting a waiver of consent and HIPAA authorization for recruitment purposes (so as to find eligible participants for the study), but we are not seeking a waiver for the study as a whole as we are obtaining informed consent from the study participants.

e) Economic Impact on Subjects

None

7. Protocol Methodology

We have based our research strategy on that of the previously published randomized controlled trial performed by Ausen et al.[16] The randomization will be performed electronically by the Albert Einstein College of Medicine Clinical Research Center. Patients will be randomized to receive topical tranexamic acid to one breast and placebo (topical saline) to the other, after obtaining hemostasis but prior to closure

during reduction mammoplasty. The study drug will be prepared and randomized with the assistance of the Einstein Investigational Drug Service as detailed below.

A custom order for the study drug will be created in Epic. Each week, the list of patients scheduled to undergo reduction mammoplasty the following week will be provided to the pharmacy. The Investigational Drug Service at Einstein will prepare randomization kits comprised of two identical 20cc syringes labeled "LEFT" or "RIGHT" based on the existing randomization table. Our pharmacy carries a standard vial of tranexamic acid at a concentration of 100mg/mL, with 10mL per vial (total 1g of TXA). We will dilute the tranexamic acid to a volume capable of moistening the typical wound surface of reduction mammoplasty; 20 mL has been shown to sufficiently moisten at least 1500cm^2.[16] The side pre-randomized to treatment will contain 10cc of 100mg/mL of tranexamic acid diluted in 10cc of normal saline (0.9% sodium chloride). The other vial will contain 20cc of of normal saline. Tranexamic acid is colorless, therefore the two syringes will appear identical.

The randomization kits will be brought to the operating facility the day prior to surgery and will be kept under lock and key. The randomization kits will be labeled with a unique identification number, separate from patient medical record numbers, and will expire twenty-four hours after pickup. At the end of each week, unused randomization kits will be returned. The pharmacy will prepare a dispensing log and transfer log, to be stored at the Investigational Drug Service headquarters. The dispensing and transfer log will be signed at each visit and the database (including the number of the randomization kit corresponding to each patient) will be closely maintained by the PI.

All personnel involved in the operation and postoperative follow-up, including the attending physician, resident and physician assistant team, and clinic staff are to be blinded to the randomization. The randomization code will not be broken until 30 days after the last patient has undergone surgery.

There is not yet a consensus on the recommended dosing of tranexamic acid. Prior comparative trials and meta-analyses indicate that topical tranexamic acid has comparable or superior efficacy to that of intravenous dosing,[20-23] with the added benefit of minimizing systemic exposure. The plasma concentration of topical tranexamic acid is less than one-tenth the amount after intravenous administration.[24,25] Prior research suggests that a dose of 1 gram is sufficient to achieve an antifibrinolytic effect.[13] Higher doses have generally fallen out of favor due to meta-analyses showing that they do not yield any greater benefit, and that higher dosage (>80 mg/kg total dose) led to an increased risk of seizures.[26] We will therefore administer 1 gram of topical TXA to the treated breast.

The reduction mammoplasty will be performed per our standard protocol. After achieving adequate surgical hemostasis, the contents of the vials will be applied to the raw wound surface of each breast. Drains will be placed bilaterally, per our protocol, and the incisions will be closed in the standard fashion. The patients will have

surgical brassieres fitted postoperatively and will have routine follow-up scheduled in clinic. It is standard in our practice to have patients present for follow-up at one week postoperatively. Patients are instructed to record their daily drain output, and drains are typically removed once 24-hour output falls below 30cc.

Subject treatment assignments will remain blinded until the final subject has completed follow up and all data has been recorded and validated. Urgent, immediate unblinding due to medical emergency may be authorized by the Investigator. When possible, the treatment assignment will be provided to the treating physician in order to maintain the blind for the Investigator and study staff.

8. Data Analysis

We hypothesize that use of topical tranexamic acid will decrease total perioperative blood loss, hematoma formation, and transfusion rates without increasing the incidence of deep vein thrombosis or thromboembolic events.

a) Chart review data:

Patient charts will be abstracted for baseline demographic data and medical comorbidities that may independently increase the risk of developing a postoperative hematoma. Data to be abstracted from the medical record includes: demographic data (including patient gender, age, ethnicity), medical data (including body mass index, comorbidities (e.g. hypertension, diabetes, hyperlipidemia, coronary artery disease), smoking history, history of neoadjuvant radiation therapy or chemotherapy, history of thromboembolic disease, bleeding diatheses, or use of anticoagulant medications), surgical data (including type of operation performed, surgical team involved, weights of tissue removed, estimated blood loss, drain outputs in the immediate postoperative period, date that drain(s) were removed) and complications within 30 days of the index operation including hematoma requiring operative washout or bedside evacuation, seroma, cellulitis, nipple-areolar complex necrosis, fat necrosis, delayed wound healing, deep vein thrombosis and pulmonary embolism. Patients with insufficient records or those who are lost to follow-up will be excluded from the final analysis.

b) Statistical Analysis

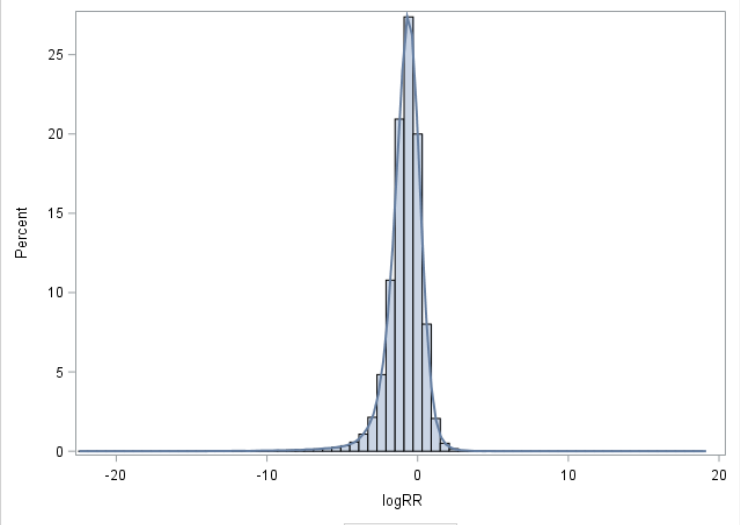
We have partnered with our institution's Department of Surgery faculty biostatisticians on the statistical methods for this proposal. Based on a Bayesian approach, **a sample size of 100 patients will be sufficient to adequately power this study.**

The primary objective of this pilot study is to explore whether, and to what extent, treatment using TXA decreases the risk of hematoma in patients undergoing breast reduction mammoplasty (BRM) compared to a saline placebo. A double-blind within-subjects design will be used with each patient receiving both treatments and thus serving as their own control. A simple randomization scheme will determine which treatment will be used for each side (left or right) for each patient. A Bayesian approach will be employed to estimate the posterior probability distribution of the

relative risk reduction in post-surgical hematoma between treatment rate between treatment with TXA and control. This posterior probability distribution provides the information necessary to answer the salient questions informative about the presence and strength of an efficacy signal for TXA; specifically, what is the probability that treatment with TXA reduces the risk of hematoma, compared to control by an amount δ for any $0< \delta <1$. Note that the probability that the relative risk < 1 corresponds to the probability that treatment with TXA is superior to the control. A description of this approach follows.

Prior to data collection and consistent with a null hypothesis of no difference between treatments we assume that the effect of treatment with TXA is equal to the effect of treatment with control. This assumption is formalized by assuming that the probability of developing a hematoma is the same for each treatment. The Bayesian approach considers this prior probability of developing a hematoma to be a random variable, which we specify to be a beta distribution with parameters 0.35 and 4.65, translating into a mean of 0.07 (the assumed hematoma rate for both treatments under the "null" hypothesis) and a standard deviation of about 0.10. Since patients will be treated with both treatments, the prior probabilities of developing a hematoma are not assumed to be independent. In our approach, we assume a conservative correlation of 0.30.

This prior probability is combined with the observed data, the number of observed hematomas under each treatment (a binomial random variable) to yield an estimated posterior probability distribution for each hematoma rate. These estimated rates will be used to estimate the posterior distribution for the relative risk, and its natural logarithm which has the advantage of being approximately normally distributed and less skewed given the low expected hematoma rates.



An illustration of the estimated probability distribution for the natural logarithm of the relative risk is shown (left) under the "alternative" hypothesis that treatment with TXA reduces the rate of hematoma by a relative 50% compared to control based on a sample of 100 patients, the proposed sample size. The distribution is obtained by simulation using 100,000 replications. The sample size of 100 was chosen to ensure a high probability of detecting an efficacy signal (a relative risk of 0.5 or less) should it exist. Specifically, with a sample size of 100, the probability of estimating a relative risk < 1, or natural logarithm of the relative risk < 0 (i.e., estimating that treatment with TXA is superior to treatment with control) is approximately 80%, corresponding to an odds of 4:1. This 80% probability corresponds to the frequentist notion of power.

Note that the prior odds (assuming equal rates of hematoma) of observing a relative risk less than one is 1:1. Also, the the probability of observing odds of 4:1 in favor of TXA under the assumption of equal hematoma rates using each treatment is approximately 20%. This 20% is a false positive rate corresponding to the frequentist Type I error rate.

We will perform a corresponding frequentist analysis using conditional logistic regression to estimate the odds ratio and corresponding 95% confidence interval for developing a hematoma using TXA compared to control. Our use of a non-informative prior ensures that these results will be consistent with those provided by the Bayesian approach, and thus enhance interpretation of the trial's results. Descriptive statistics, using both numerical and graphical summaries, will be used to describe the sample with respect to demographics, baseline characteristics, and important outcomes.

Secondary endpoints will be analyzed using classical frequentist methods, with generalized linear models used to assess treatment group difference in blood transfusion, incidence of deep vein thrombosis, and incidence of thromboembolic events.

9. Data Safety Monitoring Plan

There will be regularly scheduled monitoring reviews at 6-month time intervals to review rates of adverse events, which will determine if the study poses sufficiently low risk to proceed. The DSMB will be comprised of two members of the Department of Surgery who are not affiliated with the study (Dr. Sheldon Feldman, MD and Dr. Prashanth Sreeramoju, MD), as well as a biostatistician from the Albert Einstein College of Medicine/Montefiore Medical Center (Dr. Shankar Viswanathan, DrPH). The incidence of venous thromboembolism (VTE) in reduction mammoplasty ranges from 0.22% to 2.9%. A recent National Surgical Quality Improvement Program study describes a 0.17% rate of pulmonary embolism and a 0.07% rate of deep vein thrombosis in BRM patients.[18] Furthermore, the incidence of seizure in the general population is estimated at 3%.[19] With an anticipated sample size of 100 patients, if more than 2 patients (1.5%) develop either a deep vein thrombosis, pulmonary embolism, or seizure postoperatively, the study will be paused while further investigation regarding safety takes place. In the case of increased incidence of adverse events that warrant further investigation, the study will be paused and the PSF grant office will be kept apprised. We do not anticipate increased risk for thromboembolic events or seizure, given the well-described safety profile of tranexamic acid even in hypercoagulable populations such as bedbound or cancer patients, and given that we are using a low, topical dosage with fractional systemic absorption.

Although creation of the data-set will require use of patient names and medical record numbers, these will be stripped as soon as data-collection is complete and a linking file will be kept under lock and key by the primary investigator. The data set will be stored on Montefiore's encrypted server. Only the study team will have access to the

stored data, and only the study team will have access to the linking file. Data will be stored until the data is analyzed and scholarly output is generated. All members of the research team have undergone appropriate Human Subjects Protection training.

10. References

1. Surgeons ASoP. ASPS National Clearinghouse of Plastic Surgery Procedural Statistics. 2019; https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-full-report-2019.pdf. Accessed November 3, 2020.
2. Hussien M, Lee S, Malyon A, et al. The impact of intraoperative hypotension on the development of wound haematoma after breast reduction. *British journal of plastic surgery.* 2001;54(6):517-522.
3. Kaoutzanis C, Winocour J, Gupta V, et al. Incidence and Risk Factors for Major Hematomas in Aesthetic Surgery: Analysis of 129,007 Patients. *Aesthet Surg J.* 2017;37(10):1175-1185.
4. Nguyen BN, Barta RJ, Stewart CE, et al. Toradol following Breast Surgery: Is There an Increased Risk of Hematoma? *Plastic and reconstructive surgery.* 2018;141(6):814e-817e.
5. Goodnough LT, Brecher ME, Kanter MH, et al. Transfusion medicine. First of two parts--blood transfusion. *The New England journal of medicine.* 1999;340(6):438-447.
6. Brown S, Yao A, Taub PJ. Antifibrinolytic Agents in Plastic Surgery: Current Practices and Future Directions. *Plastic and reconstructive surgery.* 2018;141(6):937e-949e.
7. Dadure C, Sauter M, Bringuier S, et al. Intraoperative tranexamic acid reduces blood transfusion in children undergoing craniosynostosis surgery: a randomized double-blind study. *Anesthesiology.* 2011;114(4):856-861.
8. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *The Cochrane database of systematic reviews.* 2007(4):CD001886.
9. Murphy GR, Glass GE, Jain A. The Efficacy and Safety of Tranexamic Acid in Cranio-Maxillofacial and Plastic Surgery. *The Journal of craniofacial surgery.* 2016;27(2):374-379.
10. Murkin JM. Lessons learned in antifibrinolytic therapy: The BART trial. *Semin Cardiothorac Vasc Anesth.* 2009;13(2):127-131.
11. Arantes GC, Pereira RMR, de Melo DB, et al. Effectiveness of tranexamic acid for reducing intraoperative bleeding in palatoplasties: A randomized clinical trial. *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery.* 2017;45(5):642-648.
12. Guerriero C, Cairns J, Perel P, et al. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One.* 2011;6(5):e18987.
13. Rohrich RJ, Cho MJ. The Role of Tranexamic Acid in Plastic Surgery: Review and Technical Considerations. *Plastic and reconstructive surgery.* 2018;141(2):507-515.
14. Weissler JM, Banuelos J, Jacobson SR, et al. Intravenous Tranexamic Acid in Implant-Based Breast Reconstruction Safely Reduces Hematoma without Thromboembolic Events. *Plastic and reconstructive surgery.* 2020;146(2):238-245.
15. Butz DR, Geldner PD. The Use of Tranexamic Acid in Rhytidectomy Patients. *Plast Reconstr Surg Glob Open.* 2016;4(5):e716.

16. Ausen K, Fossmark R, Spigset O, et al. Randomized clinical trial of topical tranexamic acid after reduction mammoplasty. *Br J Surg.* 2015;102(11):1348-1353.
17. collaborators C-t, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 2010;376(9734):23-32.
18. Rubio GA, Zoghbi Y, Karcutskie CA, et al. Incidence and risk factors for venous thromboembolism in bilateral breast reduction surgery: An analysis of the National Surgical Quality Improvement Program. *Journal of plastic, reconstructive & aesthetic surgery : JPRAS.* 2017;70(11):1514-1519.
19. Zack MM, Kobau R. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy - United States, 2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(31):821-825.
20. Wang H, Shen B, Zeng Y. Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled and prospective cohort trials. *The Knee.* 2014;21(6):987-993.
21. Almer S, Andersson T, Strom M. Pharmacokinetics of tranexamic acid in patients with ulcerative colitis and in healthy volunteers after the single instillation of 2 g rectally. *J Clin Pharmacol.* 1992;32(1):49-54.
22. Xie J, Hu Q, Huang Q, et al. Comparison of intravenous versus topical tranexamic acid in primary total hip and knee arthroplasty: An updated meta-analysis. *Thromb Res.* 2017;153:28-36.
23. Fu Y, Shi Z, Han B, et al. Comparing efficacy and safety of 2 methods of tranexamic acid administration in reducing blood loss following total knee arthroplasty: A meta-analysis. *Medicine.* 2016;95(50):e5583.
24. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. *Drugs.* 2012;72(5):585-617.
25. Soslau G, Horrow J, Brodsky I. Effect of tranexamic acid on platelet ADP during extracorporeal circulation. *Am J Hematol.* 1991;38(2):113-119.
26. Murkin JM, Falter F, Granton J, et al. High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. *Anesthesia and analgesia.* 2010;110(2):350-353.