Use of Tranexamic Acid in Liposculpture: A Double-Blind, Multicenter, Randomized Clinical Trial

Alfredo E. Hoyos, M.D.
Héctor Duran, M.D.
Lazaro Cardenas-Camarena, M.D.
Jorge E. Bayter, M.D.
Laura Cala, M.D.
Mauricio Perez, M.D.
Alejandro Lopez, M.D.
Giancarlo Talleri, M.D.
Rodrigo Domínguez-Millan, M.D.
Ivan R. Mogollon, M.D.

Bogota and Bucaramanga, Colombia; Merida, Yucatan, Zapopan, Jalisco, and México City, México; and Dallas, Texas

Background: Intraoperative hemostasis should be performed with great caution because bleeding is a huge enemy of patient safety during surgery. Tranexamic acid is a lysine synthetic derivate that inhibits fibrinolysis and diminishes the bleeding by blocking the five lysine-binding sites for plasminogen. The authors compare the efficacy of tranexamic acid versus placebo as a hemostatic agent in liposculpture procedures.

Methods: The authors conducted a multicenter, double-blind, randomized, controlled clinical trial in patients who were scheduled for liposculpture in three plastic surgery centers (Colombia and Mexico) between January of 2019 and February of 2020. One hundred forty-one patients were randomly assigned into three groups: intravenous (1 g of tranexamic acid), subcutaneous (1 g of tranexamic acid), and placebo (normal saline). Forty-seven patients were assigned to each group. There were 30 male patients and 111 female patients. The main outcome was to evaluate the amount of postoperative bleeding between groups. The primary outcome was measured by the hemoglobin point loss at day 1 (preoperative hemoglobin minus hemoglobin at day 1 postoperatively) and the hemoglobin (in milligrams per deciliter) point loss at day 5 (preoperative hemoglobin minus hemoglobin at day 5 postoperatively).

Results: The authors found the intravenous intervention group to have a greater hemoglobin level than the other two groups on both the first postoperative day ($p = 0.0001$) and the fifth postoperative day ($p = 0.001$). There were no statistical differences in hemoglobin values between the placebo and the subcutaneous intervention groups.

Conclusion: Intravenous tranexamic acid is a good therapeutic choice to implement on liposculpture procedures to decrease postoperative bleeding. (*Plast. Reconstr. Surg.* 150: 569, 2022.)

Clinical Relevance Statement: The preoperative use of intravenous tranexamic acid not only decreases the bleeding rate after liposuction procedures, but also allows greater lipoaspirate volumes when performing high-definition liposculpture. Further studies are required to support the effectiveness of tranexamic acid within the infiltration solution.

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, I.

Blood loss is inevitable during any surgical procedure regardless of how meticulous the hemostasis; however, its reduction is a key factor for surgical success, because it could progress to severe complications such as hemodynamic decompensation, cardiac arrest, or secondary requirement for blood transfusions. According to the Centers for Disease Control and Prevention, more than 17 million blood product units are transfused every year[1]; although a convenient technique for blood reposition during major bleeding, it often involves some complications such as anaphylaxis, blood-borne infections, and others.[2]

From Total Definer Research Group and the Dhara Clinic; Clinica el Pinar; private practice; and Corporea Health & Aesthetics, Plenus Medical Group Merida.
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Hemostatic agents play a pivotal role in surgical timing, where the topical, systemic, and energy-based agents are the most frequently used among the vast majority.[3–5] Tranexamic acid is a lysine synthetic derivate that inhibits fibrinolysis (antifibrinolytic) by blocking the five lysine-binding sites for plasminogen.[5,6] It competitively binds to kringle domains of plasminogen (zymogen), thereby inhibiting the transformation of plasminogen to the active protease, plasmin. Plasmin degrades clots of fibrin, fibrinogen, and other plasma proteins, including clotting factors V and VIII. As a result, tranexamic acid inhibits the lysis of the fibrin clot[7,8] (Fig. 1).

The usual tranexamic acid routes of administration are local, intravenous, and oral. It is almost exclusively excreted through the kidney, with a half-life of 1.5 to 3 hours.[9] Most common adverse events are gastrointestinal (nausea, vomiting, diarrhea), hemodynamic changes (hypotension or hypertension), seizures, allergy reaction or anaphylaxis, visual disturbances, and prothrombotic states.[10,11] The major contraindication for the use of tranexamic acid are as follows: intracranial bleeding, history of thromboembolic disease, allergy to tranexamic acid, and known defective color vision (color blindness).[7,11] Blood serum levels of tranexamic acid required to inhibit 80 percent of fibrinolysis in vitro start at approximately 10 μg/ml; these concentrations correlate to an intravenous dosage of 10 mg/kg, which provides an antifibrinolytic concentration of tranexamic acid that remains almost 8 hours in the blood and up to 17 hours in tissues.[12,13]

Tranexamic acid has been broadly used in clinical practice since 1962, and it became very popular after 2010 when the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 study showed a decreased overall mortality in patients after trauma.[6] As a result, its use has been extended among surgical specialties as diverse as orthopedics, cardiothoracic surgery, obstetrics, and even plastic surgery, where its use has been limited to craniofacial procedures. Thus, we designed a multicenter, randomized, double-blind clinical trial to evaluate the efficacy of tranexamic acid as a hemostatic agent in liposculpture procedures.

PATIENTS AND METHODS

Study Design

We conducted a multicenter clinical trial from January of 2019 to February of 2020 at three plastic surgery locations: (1) Dhara Clinic, in Bogota, Colombia; (2) Centro Medico de las Americas Clinic, in Merida, Mexico; and (3) Innovare Hospital, in Jalisco, Mexico. Patients were assigned randomly into three groups: intravenous intervention (intravenous tranexamic acid), subcutaneous intervention (subcutaneous tranexamic acid), and control (placebo with normal saline). The surgeon, anesthesiologist, and patient were blinded for each treatment.

Inclusion criteria were as follows: liposculpture scheduled as a unique procedure; VASER-assisted, high-definition liposculpture performed by all surgeons; surgery duration between 2 and 5 hours; age between 20 and 45 years; and body mass index between 20 and 30 kg/m^2. Exclusion criteria were as follows: cosmetic procedures other than or in addition to liposculpture; a medical history of thromboembolic events or any other hematologic disease; currently taking aspirin and use of aspirin within 14 days before surgery; use of any anticoagulant within 5 days before surgery; a medical history of epilepsy or under current treatment for it; known allergy to tranexamic acid or any of its components; American Society of Anesthesiologists classification of III or intravenous; and prothrombin time and/or activated partial thromboplastin time greater than 1.5 times the baseline.

Interventions

Sterile syringes with either normal saline or tranexamic acid (1 g) were prepared by the pharmacist before each procedure and arranged in pairs according to the intervention protocol. Both of them were 10 ml in volume and labeled as solution X for intravenous or subcutaneous use. Only the pharmacist was aware of each patient's intervention according to the randomization protocol:

- *Placebo group*: One syringe filled with 10 ml of normal saline was added to the tumescent solution; and another syringe also filled with 10 ml of normal saline was administered through an intravenous route, 30 minutes before starting the procedure.
- *Intravenous group*: One syringe with 10 ml of normal saline was added to the tumescent solution; and one syringe filled with 1 g of tranexamic acid (10 ml) was administered as an intravenous single dose, 30 minutes before starting the procedure.
- *Subcutaneous group*: One syringe filled with 1 g of tranexamic acid (10 ml) was added to a 1-liter bag of tumescent solution (the one used in the anterior torso); and another syringe filled with normal saline (10 ml) was administered through an intravenous route, 30 minutes before starting the procedure.

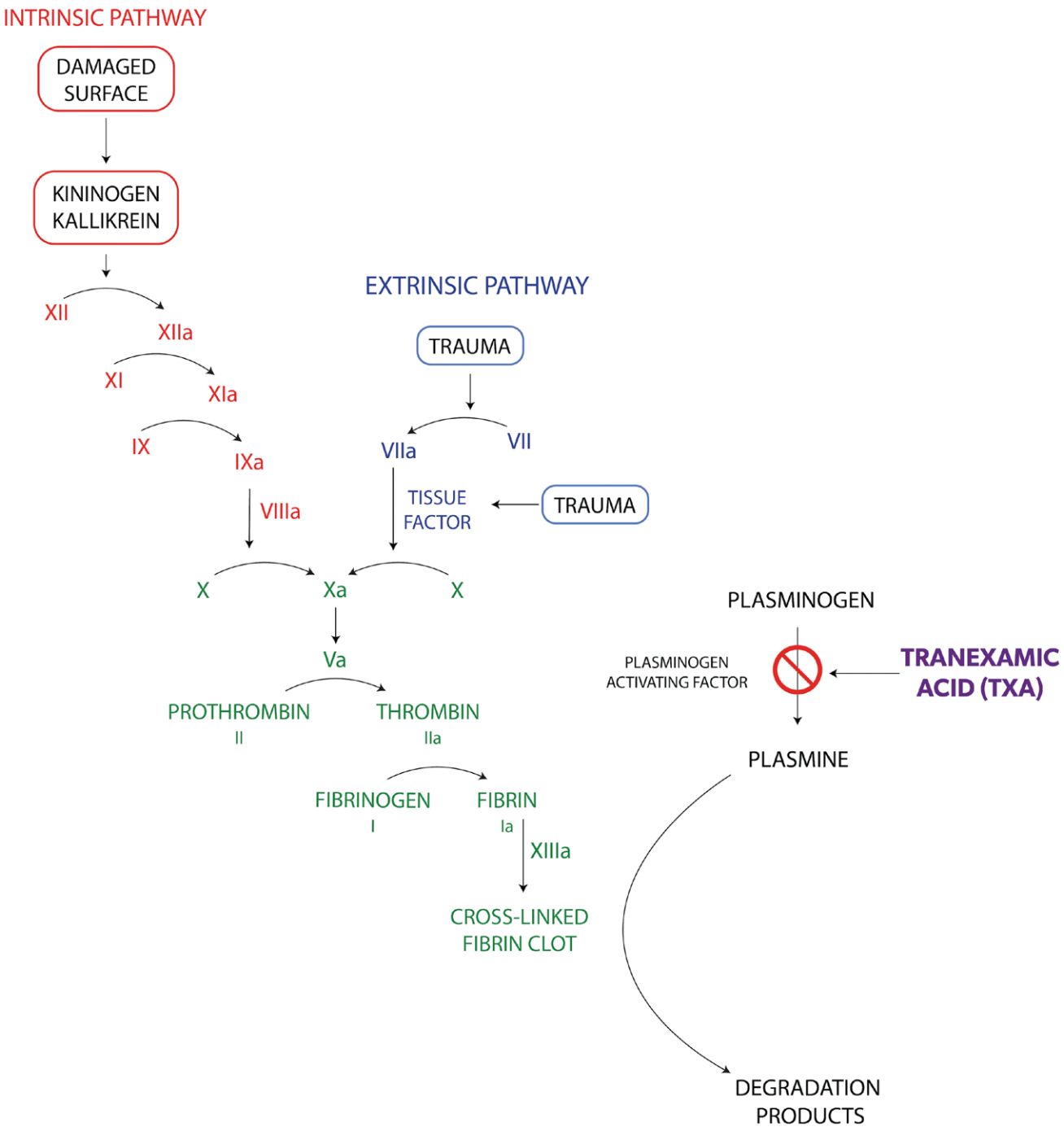

Fig. 1. Mechanism of action of tranexamic acid.

All patients underwent general anesthesia, thromboprophylaxis with heparin in a 40-mg subcutaneous single dose, intraoperative sequential compression stockings, and perioperative antimicrobial coverage according to each surgical center antimicrobial protocols.

Randomization

Each participant was given an identification number and assigned randomly into one of the three groups (placebo, intravenous tranexamic acid, and subcutaneous tranexamic acid) by a computational online app (www.randomizser.org). Research Randomizer uses the "Math.random" method within the JavaScript programming language as the core method for generating its random numbers, which are generated by a computer algorithm.[14] The pharmacist at the surgery center labeled each pair of the syringes according to the patient identification number with solution X for either intravenous or subcutaneous administration.

Outcomes

The primary outcome was the difference regarding hemoglobin (Hb) loss points between groups. All patients had hemoglobin and hematocrit tests taken before surgery and 24 hours and 5 days postoperatively. We determined the hemoglobin loss points by using the following formulas:

- $Hb_{R1} = Hb_1 - Hb_0$.
- $Hb_{R5} = Hb_5 - Hb_0$.

Terms in the equations are as follows: Hb_0, preoperative hemoglobin; Hb_1, postoperative hemoglobin at day 1; Hb_5, postoperative hemoglobin at day 5; Hb_{R1}, hemoglobin point loss 1 day postoperatively; and Hb_{R5}, hemoglobin point loss 5 days postoperatively. We also performed a subgroup analysis to determine the difference in hematologic parameters (hemoglobin and hematocrit) between the groups.

Sample Size and Statistical Analysis

Sample size was calculated using the online app from sealed envelope,[15,16] where 96 patients were required to have a 90 percent chance of detecting (significant at the 5 percent level) a difference between the mean postoperative hemoglobin value from 10.5 g/dl in the control group to 11.5 g/dl in the experimental group and an estimated standard deviation of 1.5 g/dl. Because we planned two experimental approaches—subcutaneous tranexamic acid and intravenous tranexamic acid—141 patients were randomized into three groups: (1) intravenous tranexamic acid group ($n = 47$), (2) subcutaneous tranexamic acid group ($n = 47$), and normal saline group ($n = 47$). A total of 30 male and 111 female patients were enrolled. Preoperative hemoglobin levels of 13 ± 1 and 14 ± 1 were considered as normal for men and women, respectively.

Each group demographic and clinical characteristics and hematologic parameters were analyzed before surgery, in the immediate postoperative period, and at the fifth postoperative day. The descriptive analysis was made through means and medians according to the distribution of variables. For categorical variables, counts and percentages were used. The quantitative variables with parametric distribution were compared by using analysis of variance; for variables with nonparametric distribution, the Kruskal-Wallis test was used. Qualitative variables frequencies were compared using the chi-square test. We used a box plot to illustrate the differences between each group's central tendency (mean or median) of the hemoglobin values depending on its distribution. A two-tailed test was performed for bilateral hypothesis with a significance level less than 0.05. Data were tabulated in Microsoft Excel (Microsoft Corp., Redmond, Wash.) and statistical analysis was performed using the STATA (StataCorp LLC, College Station, Texas) general-purpose statistical software package (version 15.0).

Ethical Considerations

All patients provided informed consent for the procedure, including authorization for the use of photographs for research purposes. The study adhered to the principles of the Declaration of Helsinki, local guidelines, and protocols for human subjects. The study was approved by the ethics committee at each of the participating plastic surgery centers. During the preoperative consultation, the protocol interventions were clearly explained to each of the 141 patients enrolled in the study.

RESULTS

There were no statistically significant differences between the groups regarding clinical and demographic variables such as, age, body mass index, surgical time, infiltrated volume, extraction volume, and fat extraction volume, which ensured the homogeneous distribution among groups (Table 1). First, we analyzed the differences in

Table 1. Demographic and Clinical Characteristics by Group

Characteristic	Placebo Group	IV TXA Group	SQ TXA Group	*p*
No.	47	47	47	
Gender, no. (%)				0.090
Female	42 (89.4)	35 (74.5)	34 (72.3)	
Male	5 (10.6)	12 (25.5)	13 (27.7)	
Age, yr				0.671
Median	34.0	34.0	34.0	
IQR	27.0–39.0	31.0–40.0	27.0–41.0	
Mean BMI, kg/m^2	25.4 (3.0)	25.7 (2.9)	24.6 (2.7)	0.187
Surgical time, min				0.296
Median	175.0	205.0	195.0	
IQR	150.0–215.0	150.0–260.0	150.0–240.0	
Mean infiltrated volume, cc	4969.1 (1608.4)	5726.4 (2024.5)	5495.7 (1943.7)	0.135
Mean extraction volume, cc	4144.2 (1429.4)	3988.1 (1326.8)	3930.0(1531.3)	0.755
Mean fat extraction volume, cc	2751.7 (1322.5)	2921.1 (1126.0)	2872.5 (1427.0)	0.809

IV, intravenous; TXA, tranexamic acid; SQ, subcutaneous; IQR, interquartile range; BMI, body mass index.

preoperative hemoglobin and hematocrit levels between the three groups. We found that the intravenous tranexamic acid group had a lower mean preoperative hemoglobin value than the control group and the subcutaneous group, with a statistically significant difference (p = 0.003) (Table 2). In addition, when plotting the postoperative hemoglobin at day 1 values, the intravenous tranexamic acid group showed higher hemoglobin and hematocrit levels compared to those in the subcutaneous tranexamic acid and control groups, with statistically significant results (p = 0.006 and p =0.049, respectively) (Table 2 and Fig. 2), which clinically means that the intravenous tranexamic acid group presented less blood loss compared to the other groups. Afterward, the average hemoglobin levels at 5 days postoperatively were also found to be higher in the intravenous tranexamic acid group compared to those of the subcutaneous tranexamic acid and control groups; nonetheless, the p value was not statistically significant (p = 0.268) (Table 2 and Fig. 3).

After applying the formulas for hemoglobin point loss analysis (see Statistical Analysis section), the intravenous tranexamic acid group showed less postoperative hemoglobin loss than the other two groups on both hemoglobin point loss 1 day postoperatively and 5 days postoperatively values with statistically significant results (p = 0.000 and p = 0.001, respectively) (Table 3 and Figs. 4 and 5). Finally, we compared the results of mean hematocrit, hemoglobin, and hemoglobin point loss values among all groups to acknowledge any other important difference; however, there were no other statistically significant differences than the formerly reported, when compared together (Table 4).

Complications

No major complications were reported. Any complication related to blood clotting was considered secondary to the use of tranexamic acid. Regardless of the route, if intravascular blood flow impairment was suspected, it was considered a complication. Major bleeding and severe hematoma were also considered complications. Fortunately, only minor complications such as prolonged swelling and bruising were reported [n = 9 (6.4 percent)]; however, they are beyond the scope of this article.

DISCUSSION

Because clinical studies support the use of tranexamic acid for patients with a high risk of bleeding,[6] we came up with the idea that maybe

Table 2. Hematologic Parameters by Group

Characteristic	Placebo Group	IV TXA Group	SQ TXA Group	*p*
Hb_0 (mg/dl), mean (SD)	14.4 (1.1)	13.8 (1.2)	14.6 (1.2)	0.003*
HCT_0 (mg/dl), mean (SD)	43.4 (3.4)	41.8 (3.6)	43.4 (4.3)	0.065
Hb_1 (mg/dl), mean (SD)	10.6 (1.3)	11.6 (1.3)	11.2 (1.5)	0.006*
HCT_1 (mg/dl), median (IQR)	32.0 (28.6–36.4)	34.6 (31.3–38.0)	32.9 (29.9–36.1)	0.049*
Hb_5 (mg/dl), mean (SD)	11.5 (1.7)	12.0 (1.4)	11.8 (1.4)	0.268
HCT_5 (mg/dl), mean (SD)	34.5 (5.6)	36.1 (4.3)	35.8 (4.7)	0.221

IV, intravenous; TXA, tranexamic acid; SQ, subcutaneous; Hb_0, preoperative hemoglobin; HCT_0, preoperative hematocrit; Hb_1, first-day postoperative hemoglobin; HCT_1, first-day postoperative hematocrit; IQR, interquartile range; Hb_5, fifth-day postoperative hemoglobin; HCT_5, fifth-day postoperative hematocrit.
*Statistically significant results.

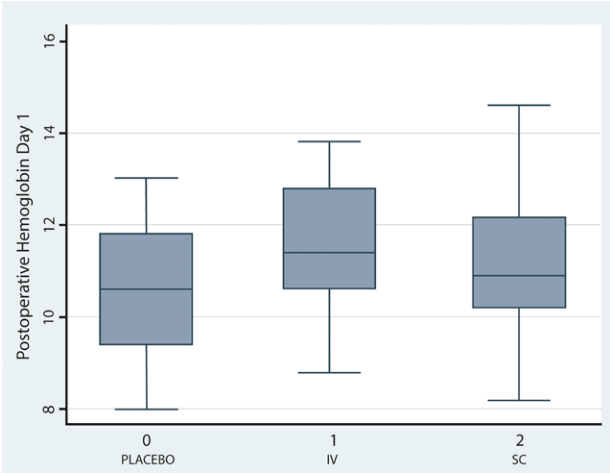

Fig. 2. Hemoglobin level central tendency by group at postoperative day 1. *IV*, intravenous; *SC*, subcutaneous.

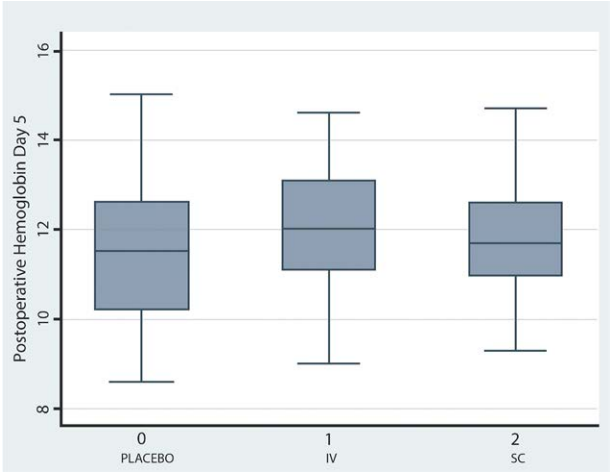

Fig. 3. Hemoglobin level central tendency by group at postoperative day 5. *IV*, intravenous; *SC*, subcutaneous.

patients scheduled for procedures with a bleeding possibility could benefit from its use. We designed a multicenter, randomized, controlled trial to evaluate the effectiveness of tranexamic acid in reducing the postoperative bleeding in patients undergoing liposuction. Physiologically, there is a perfect balance between the coagulation cascade and fibrinolysis; however, if this cascade is disrupted, pathologic conditions could develop (e.g., hypercoagulability states or spontaneous bleeding). Surgical procedures represent a iatrogenic disruption of the balance, by generating broad trauma with subsequent blood loss, which could deteriorate to possibly require transfusions.[17] Thus, controlling intraoperative bleeding has become a crucial factor to diminish complications, and so meticulous hemostasis is mandatory. Tranexamic acid has anti-inflammatory action through the inhibition of acute-phase reactants such as interleukin-6 and C-reactive protein, reducing postoperative edema. Patients treated with tranexamic acid during surgery express lower D-dimer levels than those who do not, which indirectly indicates plasmin formation and suggests lower fibrinolytic activity that will result in less ecchymosis and bleeding.[8] Concentrations of 100 μg/ml in vitro are required to achieve a 98 percent inhibition of fibrinolysis[13]; this usually requires a rise in the intravenous dose, which could increase the risk of seizures.[18–20] Although tranexamic acid use is very common in other surgical fields such as cardiac surgery and orthopedics, in plastic surgery, it is limited to a few procedures (e.g., rhinoplasty and rhytidectomy[21,22]) as a local hemostatic agent,[23–25] resulting in less hematoma formation.

Our study has shown less postoperative hemoglobin loss with the use of intravenous tranexamic acid compared to the use of subcutaneous tranexamic acid and normal saline, which means that less bleeding occurred during and after the procedure in the intravenous tranexamic acid group, resulting in a safer procedure for the patient. We did not have any adverse effects (major or minor) in any of the three groups of intervention. The fact that preoperative hemoglobin levels were lower in the intravenous tranexamic acid group compared to those in the control and subcutaneous tranexamic acid groups, in addition to the higher hemoglobin point loss 1 day postoperatively and hemoglobin point loss 5 days postoperatively, actually supports the outstanding benefit of intravenous administration of tranexamic acid before surgery. Ausen et al. reported that tranexamic acid blood concentrations were less than 5.2 μg/ml in patients undergoing abdominoplasty and treated with local tranexamic acid. As we mentioned before, the tranexamic acid serum concentration

Table 3. Differences Regarding Hemoglobin Loss among Groups

Characteristic	Placebo Group	IV TXA Group	SQ TXA Group	*p*
Hb_0–Hb_1 (mg/dl), mean (SD)	3.8 (1.5)	2.2 (0.8)	3.4 (1.1)	0.000*
Hb_0–Hb_5 (mg/dl), median (IQR)	3.1 (1.4–4.3)	1.8 (0.8–2.5)	2.7 (1.8–3.8)	0.001*

IV, intravenous; TXA, tranexamic acid; SQ, subcutaneous; Hb_0, preoperative hemoglobin; Hb_1, first-day postoperative hemoglobin; Hb_5, fifth-day postoperative hemoglobin.
*Statistically significant results.

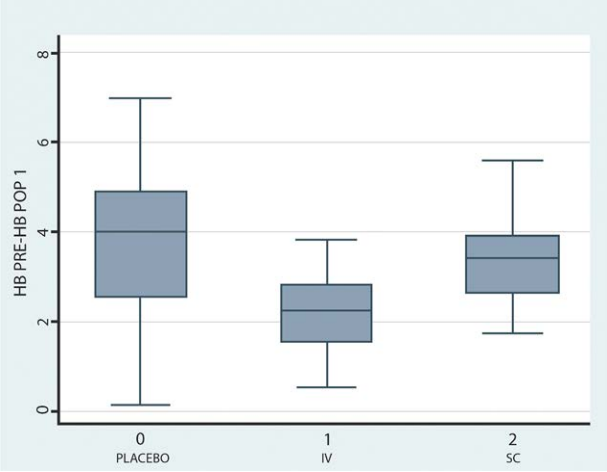

Fig. 4. Hemoglobin (*HB*) preoperatively (*PRE*) minus hemoglobin on postoperative day 1 (*POP 1*). Notice how the intravenous group presented less point of hemoglobin loss. *IV*, intravenous; *SC*, subcutaneous.

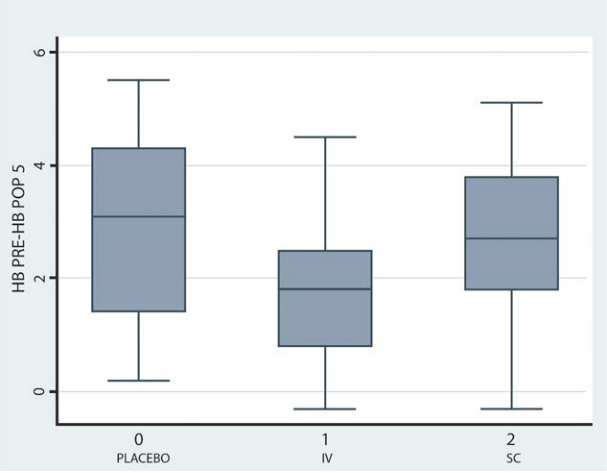

Fig. 5. Hemoglobin (*HB*) preoperatively (*PRE*) minus hemoglobin postoperative day 5 (*POP 5*). The intravenous group showed less hemoglobin loss. *IV*, intravenous; *SC*, subcutaneous.

has to be greater than 10 μg/ml[26] for an adequate fibrinolytic effect. Topical tranexamic acid may be locally effective because of the increased drug concentration in the operative site,[27] which probably diminishes the risk of adverse effects and drug interactions, but those benefits will be absent if large doses of tranexamic acid are used.[28] In our study, we did not find any difference between the subcutaneous tranexamic acid group and the placebo group; however, we did find a statistically significant difference between intravenous tranexamic acid and subcutaneous tranexamic acid, which could be explained by the lower systemic concentrations and irregular plasma levels with the subcutaneous route. Commonly, the subcutaneous route does not reach the minimum concentration necessary to achieve the antifibrinolytic effect required to reduce bleeding but could probably help to decrease the edema and hematoma formation in the postoperative period. However, wetting solution plus subcutaneous tranexamic acid was only used over the anterior torso, which limits the even distribution of the tranexamic acid throughout the treated areas. Further research has to be performed to evaluate this outcome. In contrast, intravenous administration of tranexamic acid during major operations has been shown to reduce the need for blood transfusions by 32 to 37 percent,[29] as shown by Horrow et al, who reported an initial intravenous dose of 10 mg/kg followed by 1 mg/kg/hour to decrease blood loss during cardiac surgery,[30,31] which also supports the use of intravenous tranexamic acid for operations with increased bleeding risk.

A meta-analysis carried out by Ker et al. showed that a total dose of 1 g was probably enough for most adults, and there was not enough evidence to support higher doses, because this would increase the risk of seizures.[30,32] Some studies recommend a high-dose (>80 mg/kg[33,34]) protocol not only to reduce bleeding but also to decrease the use of

Table 4. Comparison between Groups

Variable	NS Group	IV TXA Group	*p*	IV TXA Group	SQ TXA Group	*p*	NS Group	SQ TXA Group	*p*
Hb_0–Hb_1 (mg/dl), median (SD)	4.0 (2.5, 4.9)	2.2 (1.5, 2.8)	<0.001*	2.2 (1.5, 2.8)	3.4 (2.6, 3.9)	<0.001*	4.0 (2.5, 4.9)	3.4 (2.6, 3.9)	0.416
HCT_0–HCT_1 (mg/dl), mean (SD)	11.1 (4.9)	7.3 (3.2)	<0.001*	7.3 (3.2)	10.1 (4.0)	<0.001*	11.1 (4.9)	10.1 (4.0)	0.317
Hb_0–Hb_5 (mg/dl), mean (IQR)	2.9 (1.6)	1.8 (1.1)	<0.001*	1.8 (1.1)	2.7 (1.3)	<0.001*	2.9 (1.6)	2.7 (1.3)	0.517
HCT_0–HCT_5 (mg/dl), mean (SD)	8.9 (6.3)	5.6 (4.0)	0.004*	5.6 (4.0)	7.6 (4.6)	0.033*	8.9 (6.3)	7.6 (4.6)	0.251
Hb_5–Hb_1 (mg/dl), mean (SD)	0.8 (1.0)	0.4 (0.9)	0.036*	0.4 (0.9)	0.6 (1.0)	0.247	0.8 (1.0)	0.6 (1.0)	0.346
HCT_5–HCT_1 (mg/dl), mean (SD)	2.2 (3.6)	1.6 (3.2)	0.473	1.6 (3.2)	2.5 (3.3)	0.190	2.2 (3.6)	2.5 (3.3)	0.592

NS, normal saline; IV, intravenous; TXA, tranexamic acid; SQ, subcutaneous; Hb_0, preoperative hemoglobin; Hb_1, first-day postoperative hemoglobin; HCT_0, preoperative hematocrit; HCT_1, first-day postoperative hematocrit; Hb_5, fifth-day postoperative hemoglobin; HCT_5, fifth-day postoperative hematocrit.
*Statistically significant results.

red blood cell transfusion, fresh frozen plasma, and platelets[35,36]; however, our study showed good results with a low dose (10 to 15 mg/kg).

Our results regarding bleeding control and adverse effects proved to be safe and effective enough to improve patient safety during surgery. With the dose used, we did not have any adverse effects related to the use of tranexamic acid, and we achieved statistically significant outcomes comparing the intravenous tranexamic acid group against the other two, concerning hematologic parameters and hemoglobin loss (Table 4). Moreover, the noncomparable effect of the subcutaneous group could be a limitation of the trial, considering the anti-inflammatory properties of tranexamic acid and its benefits in terms of decreasing ecchymosis and edema when used as a topical agent, although further studies are needed to support these statements. Because other factors play a decisive role in the clinical outcomes and signs and symptoms when bleeding occurs (e.g., oxygen delivery, uploading and oxygen transport, altitude, erythrocyte physiology), further clinical studies are required to support our findings and improve the patient well-being during and after other surgical procedures.

CONCLUSIONS

Tranexamic acid is a safe and effective drug for decreasing surgical bleeding after liposuction. Our randomized controlled trial shows a statistically significant superiority of the intravenous use over the topical and subcutaneous routes. Although a low-dose intravenous tranexamic acid protocol was used, the bleeding rate substantially decreased, and no adverse events were reported, which suggests that it is a worthy measure to implement to improve patient safety during plastic surgery procedures. Further studies will be necessary to compare different tranexamic acid doses for subcutaneous infiltration to attain the local antifibrinolytic effect, which could prevent or decrease bruising and edema formation after liposculpture procedures. Ultimately, new randomized controlled trials are required to compare the cost-benefit and clinical advantages of using tranexamic acid in the infiltration solution versus only intravenous administration versus both.

Alfredo E. Hoyos, M.D.
Carrera 15, No. 83-33, Suite 304
Dhara Clinic
Bogotá 111111, Colombia
alhoyos@gmail.com
Instagram: @alfredohoyosmd
Twitter: @AlfredoHoyosMD

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