Original Article

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Use of Tranexamic Acid to Reduce Bleeding in Head and Neck Reconstructive Surgery

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Author`s Contribution

[1,2,3]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. 2Final approval of the version to be published/Supervision
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ABSTRACT

Objective: To assess the effectiveness of local infiltration of tranexamic acid in reducing intraoperative bleeding in head and neck reconstruction.

Methodology: This prospective study was conducted at Pakistan Institute of Medical Sciences/ Shaheed Zulfiqar Ali Bhutto Medical University between April and October 2024. Sixty six patients undergoing reconstructive surgery for head and neck defects were allocated into two groups: one receiving local infiltration with a 1:1 mixture of lignocaine (20 mg/ml) and TXA (100 mg/ml), and the other receiving a 1:1 mixture of lignocaine (20 mg/ml) and normal saline. Surgical field hemostasis was graded, postoperative hemoglobin drop was measured at 48 hours, and transfusion needs were recorded. Statistical analyses were performed to compare the results of the groups.

Results: The tranexamic acid group demonstrated significantly better surgical field visibility (mean score 1.85 vs. 3.24, $p < 0.01$), a lower mean hemoglobin drop at 48 hours (0.53 g/dl vs. 1.42 g/dl, $p < 0.01$), and reduced transfusion requirements (1 vs. 12 patients). No significant adverse effects were observed during the immediate postoperative period.

Conclusions: Local infiltration of tranexamic acid reduces intraoperative bleeding, improves surgical field visibility, and decreases transfusion requirements without immediate adverse effects. Further studies are recommended to optimize dosing and assess long-term safety.

Keywords: Tranexamic acid, head and neck surgery, reconstructive surgery, bleeding control, local infiltration, surgical hemostasis, intraoperative bleeding, antifibrinolytic agents, surgical field visibility.

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Introduction

Bleeding is a troublesome yet inevitable complication associated with any surgical procedure, including plastic and reconstructive surgery. Intraoperative bleeding affects the surgical technique by obscuring the view of the surgical field, resulting in both increased operative time and a less than optimal outcome. Significant blood loss can cause generalized hypovolemia, leading to reduced vascular supply to the wound and risk of poor wound healing.[1] Increased bleeding mandates the use of more aggressive hemostatic measures during the surgery, such as electrocautery, which in turn increase the risk of pain, swelling and infection. Intraoperative bleeding also affects the recovery period and patients may require special dressings, drain placement and blood transfusions during this time. Furthermore, fear of bleeding may prevent administration of adequate thromboprophylaxis. Hence minimization of intraoperative bleeding is beneficial to both the surgeon and the patient. Modalities

used to control bleeding can either be used to decrease vascular inflow to the operative region, maintain meticulous hemostasis or stabilize the clot by preventing fibrinolysis. Systemic hypotension, use of tourniquets and local infiltration of adrenaline decrease vascular inflow. Use of electrocoagulation, application of pressure and ligation of large bleeding vessels brings about hemostasis. Antifibrinolytic agents promote blood clotting by preventing breakdown of the clot.[2]

One such widely used antifibrinolytic agent is tranexamic acid (trans-4-aminomethyl cyclohexane carboxylic acid) (TXA). It is readily available, low cost and has a favorable safety profile. A synthetic analogue of lysine, it reduces degradation of polymerized fibrin in the clot by reducing conversion of plasminogen to plasmin. It has been routinely used for several years with intravenous, oral and topical routes all available. There are concerns about possible side effects after systemic administration.[3] Local infiltration on the other hand is an ideal mode of administration. It provides an effective dose at the site of action while avoiding adverse effects.

Tranexamic acid has been found to be effective in reducing postpartum hemorrhage following caesarean section[4] and is now commonly used in cardiac surgery.[5] Applications in trauma[6] and dental procedures[7] have also been reported. It is also recently being utilized in aesthetic procedures[8] and burn surgery.[9] But its potential use in soft tissue reconstructive procedures is still largely untapped. The head and neck region owing to its extensive blood supply is a source of significant intraoperative bleeding. In this regard, local infiltration of tranexamic acid during operations in this highly vascular area may provide a beneficial reduction in bleeding. Therefore, in this study we set out to investigate whether local infiltration of tranexamic acid is effective in reducing intraoperative bleeding during reconstructive procedures of the head and neck, as compared to a control. To assess this we documented the satisfaction of the surgeon with the view of the operative field and the reduction in hemoglobin level postoperatively. Additionally we noted any need for blood transfusion in the postoperative period.

Methodology

This comparative study was conducted at the Pakistan Institute of Medical Sciences/Shaheed Zulfiqar Ali Bhutto Medical University between April and October 2024, following approval from the hospital's Ethical Review Board (No. F.1-1/2015/ERB/SZABMU/1259 dated 03-04-24). Patients were included in the study if they underwent surgery involving reconstruction of face, scalp, or neck defects, were between 14 and 80 years of age, and had not been on any anticoagulant medication for at least five days prior to the surgery.

Patients were excluded if they had a known allergy to tranexamic acid, a personal or familial history of coagulation disorders, or uncontrolled hypertension defined as a systolic blood pressure greater than 200 mmHg.

A total of sixty six patients were included, thirty three in each group, after determining the sample size using WHO sample size calculator, with a level of significance of 5% and power of test of 80%. Written informed consent was obtained from all patients. Before the procedure the following details were recorded: demographic data, comorbid conditions, history of allergies, family history and the use of any anticoagulant medication including the last dose taken. During the procedure the site of defect and the reconstructive procedure being performed were recorded. Patients were allocated into two groups. In one group local infiltration was done with a mixture of 20 mg/ml lignocaine and 100 mg/ml tranexamic acid in a 1:1 ratio. In the second group local infiltration was done with a mixture of 20 mg/ml lignocaine and 0.9% normal saline in a 1:1 ratio. This resulted in an effective concentration of tranexamic acid of 50 mg/ml in the first group. In both groups the final mixture had a concentration of 1% of lignocaine to alleviate postoperative pain. Infiltration was done in the subcutaneous plane, 15 minutes before making the first surgical incision. Both recipient and donor sites were infiltrated with the mixture. The total amount injected was proportional to the size of the defect, varying from 2 ml to 7 ml. All patients were operated on, infiltrated with the prepared solution and assessed for adequacy of surgical field hemostasis by the same surgeon (one of the authors). Electrocoagulation and ligation of visible bleeding vessels were used as per routine in such procedures. No other hemostatic measures were employed. Pulse rate and blood pressure were continuously monitored from the time of injection till the end of procedure.

The operating surgeon was asked to give a subjective evaluation of the view of the surgical field according to the following ordinal scale, where a lower score indicates better hemostasis:

1- Excellent: better hemostasis than expected in this type of procedure

2- Good: hemostasis as expected in this type of procedure with minimal oozing

3- Moderate: hemostasis less than optimal for this type of procedure with moderate oozing

4- Poor: hemostasis less than optimal for this type of procedure with diffuse severe oozing

Blood samples were collected immediately before infiltration of solution, at 24 hours following the procedure, and at 48 hours following the procedure to determine the preoperative and postoperative hemoglobin values and the drop in hemoglobin levels. All patients remained admitted in the hospital for at least 2 days following the operation and need for transfusion of blood products during this time was also recorded. In addition any side effects observed during this recovery period or at one week follow up were noted.

Statistical analysis was performed using IBM SPSS Statistics 20. T-tests were performed to compare the outcome values of the two groups, considering a p value of <0.05 to be statistically significant. A Pearson correlation coefficient was calculated to determine whether there was a positive correlation between variables, considering a p value of <0.01 to be significant.

Results

The demographic data of the study participants are summarized in Table I. Both groups were comparable in terms of gender distribution and age.

Table I: Patient demographic data.

Demographic	Tranexamic acid + lignocaine N= 33	Normal saline + lignocaine N= 33
Male/Female	23/10	22/11
Mean± SD (age)	43.85±9.66	45.88 ± 9.01

The hemostasis scores for the two groups differed significantly, as shown in figure I.

The mean surgical field hemostasis score for the tranexamic acid group was much lower at 1.85 (SD = 0.566) as compared to the normal saline group at 3.24 (SD = 0.561). An independent samples t-test showed this difference to be significant with $p < 0.01$, $t = -10.053$, table II. The 95% confidence interval of the difference between means ranged from -1.671 to -1.117. A Pearson correlation coefficient computed to assess the relationship between infiltration of tranexamic acid and a lower hemostasis score, showed a positive correlation between the two variables, $r = 0.782$, $n=66$ and the correlation was found to be significant at $p < 0.01$.

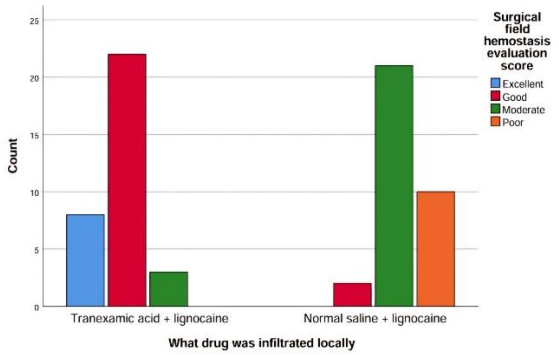

Figure I. Surgical field hemostasis scores according to group.

For the tranexamic acid group, the majority of patients suffered a drop in hemoglobin in the range of 0.1-1.0 g/dl. While in the normal saline group this was in the range of 1.1-2.0 g/dl. An independent samples t-test was performed to determine the significance of the difference between the mean drop in hemoglobin level after 48 hours between the two groups. This showed a significant difference, $p <0.01$, $t= -12.800$, 95% confidence interval -1.0335 to -0.7544, table II.The mean preoperative and postoperative hemoglobin levels for both groups are given in table III.

Table III: Preoperative and postoperative hemoglobin levels.

Mean hemoglobin level (g/dl)	Tranexamic acid + lignocaine	Normal saline + lignocaine
Preoperative	12.16 (1.10)	11.94 (0.81)
24 hours after operation	11.92 (1.09)	11.24 (0.91)
48 hours after operation	11.65 (1.16)	10.52 (0.97)

Table II: Comparison of surgical field hemostasis score and drop in hemoglobin between groups.

	Tranexamic acid + lignocaine	Normal saline + lignocaine	Mean difference (95% CI)	t	Standard error difference	P value
Surgical field hemostasis score	1.850 (0.566)	3.240 (0.561)	-1.394 (-1.671 to -1.117)	-10.053	0.139	.000
Drop in hemoglobin level at 48 hours	0.530 (0.239)	1.424 (0.322)	-0.8939 (-1.0335 to -0.7544)	-12.800	0.698	.000

Decreased transfusion requirements were observed in the postoperative period for patients in the tranexamic acid group, with only 1 patient requiring transfusion compared to the 12 patients in the normal saline group, table IV.

Table IV: Comparison of blood transfusion requirements in the postoperative period between the groups.

Units of blood transfused	Tranexamic acid + lignocaine	Normal saline + lignocaine
0	32	21
1	1	10
2	0	2

**Transfusion in the form of packed red cells, each unit containing about 350 ml volume*

Discussion

The more favorable surgical field hemostasis scores, relatively less reduction in hemoglobin levels and reduced frequency of transfusion observed by us in patients given a subcutaneous mixture of lignocaine and tranexamic acid, point towards reduced intraoperative blood loss in these patients. These findings can be explained by the fact that tranexamic acid competitively blocks the lysine binding sites on plasminogen, preventing binding between fibrin and plasminogen, and hence activation of plasminogen. It also competitively inhibits tissue plasminogen activator and inhibits plasmin induced platelet activation. There is normally an equilibrium between clot formation and clot degradation. Tranexamic acid effectively shifts this balance in favor of clot formation.

Our results appear to be in agreement with those of a previous study by Zilinsky et al. on the subcutaneous injection of this drug in mohs micrographic surgery for head and neck skin cancer.[10] They reported a decreased bloodstain to defect ratio and improved hemostasis in patients receiving the drug.[10] Furthermore the effects were more pronounced in patients who were on routine anticoagulant drugs.[10] Similarly Chang et al. found the local infiltration of diluted tranexamic acid effective in clearing the surgical field and reducing postsurgical complications.[11]

In experimental models, tranexamic acid inhibited fibrinolysis when given in a concentration of 10 – 100 micromol/L.[12] The dosage of tranexamic acid is route dependent. Recommended intravenous dose for the treatment of local fibrinolysis is 0.5 – 1.0 g, at the rate of 1 ml/minute, 2 – 3 times daily.[13] Recommended intravenous dose for the treatment of general fibrinolysis is 1.0 g by slow IV injection every 6 – 8 hours.[13] However the effective dose for local action when injected subcutaneously is disputed. In a randomized controlled study on the use of topical tranexamic acid in patients undergoing total knee arthroplasty, 0.5 g, 1 g, 2 g, and 3 g solutions were topically applied to different patient groups.[14] Their results showed that drop in hemoglobin levels, total blood loss, and frequency of transfusion significantly decreased in all groups with application of ≥ 1 g of topical tranexamic acid compared to the control group but there was no significant dose dependent decrease beyond this dose.[14] It is however still unclear whether concentration of drug, duration of exposure to it, or both factors influence its local effect on the tissue. Further testing with varied drug concentrations injected subcutaneously is required to ascertain the ideal drug dosage.

Tranexamic acid is not metabolized in the body and is excreted mainly in the urine. Adverse effects reported in literature include gastrointestinal upset,[13] anaphylaxis, color vision disturbances,[13] arterial and venous thrombosis,[15] dermatitis, wound healing complications[16] and convulsions.[3] In addition it may also have a hypopigmentation effect as it inhibits melanin synthesis by interfering with UV induced plasmin activity in keratinocytes, an action which is utilized in the treatment of melasma.[17] None of the mentioned side effects were observed in our patients during admission or at one week follow up. However, a longer observation duration is required in the postoperative period to confirm the safety of tranexamic acid.

As tranexamic acid has been shown to halt angiogenesis in vitro,[18] there were concerns about a negative outcome on graft and flap survival. But we noted no significant differences in outcome of the reconstructive procedure. Of the patients that underwent full thickness skin grafting, two in the tranexamic acid group suffered loss of 30% and 70% graft surface area respectively, and a single patient in the normal saline group had a loss of 50% of the graft surface area. One patient from the normal saline group showed necrosis of distal edge of the flap. This was managed with debridement and dressings. One patient, belonging to the tranexamic acid group, developed a serous collection deep to the flap. The collection was drained and the flap survived.

Traditionally adrenaline is injected along with local anesthetic at the incision site in surgery of highly vascular regions of the body, including the head and neck. Adrenaline exerts its effect by causing immediate vasoconstriction of the surrounding vessels and is short acting. The effect of tranexamic acid however is more

sustained and long lasting. Since the two drugs have different mechanisms of action, they could work in a complementary manner when used together and this should be investigated in future studies.

While this study gives valuable insight, it is not without limitations. The generalizability of our results is limited by the fact that the data was collected from a single center, by a single surgeon. Potential bias may have been introduced by using consecutive patients rather than randomized, blinded, age-matched controls. Additionally, the short follow-up period restricts the assessment of long term side effects. The study also did not explore the optimal dosage needed for maximum efficacy.

Conclusion

Local infiltration of tranexamic acid significantly reduced intraoperative bleeding, improved surgical field visibility, and decreased transfusion requirements in head and neck reconstructive surgery, with no immediate adverse effects observed. It appears to be a safe and effective adjunct in such procedures, though further studies are needed to determine optimal dosing and long-term safety.

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