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Efficacy of Topical versus Intravenous Tranexamic Acid in Controlling Blood Loss in Patients Undergoing Total Laryngectomy with Neck Dissection: A Randomized Control Trial

DINA MAHMOUD, M.D.; TAREK KADDAH, M.D.; EMAN FOUAD, M.D.; MIRAN MOHAMED, M.Sc. and AMR HUSSEIN, M.D.

The Department of Anaesthesia and Critical Care Medicine, Cairo University

Abstract

Background: Tranexamic acid (TXA) is an anti-fibrinolytic drug widely used to reduce blood loss during major operations, including total laryngectomy with neck dissection. However, there is no final consensus regarding the optimal route of administration of TXA regime whether topical, intravenous or combined.

Aim of Study: The purpose of our study was to compare the efficacy of topical and intravenous (IV) regimen of TXA to control bleedingduring Total Laryngectomy with neck dissection.

Patients and Methods: This randomized controlled trial (RCTs) compared topical with intravenous TXA including patients underwent total laryngectomy with neck dissection. Forty-five patients were enrolled in this study and were divided into 3 different groups. Group (A) received IV TXA on 1mg/ kg before induction, while Group (B) received Topical TXA in the form of irrigation of 2mg/ kg on 200 ml normal saline every one hour after flap elevation for five hours, and Group (C) was the control group.

Results: Total blood loss was significantly lower in Group A than (Group B and Group C) (*p*-value=0.004 and <0.001 respectively) and insignificantly different between Group B and Group C. Duration of operation was significantly lower in Group A than (Group B and Group C). Need for blood transfusion and postoperative hemoglobin levels were insignificantly different among the three groups.

Conclusions: Intravenous TXA was more efficient in reducing blood loss than topical irrigation of TXA.

Key Words: Total laryngectomy – Tranexamic acid – Topical – Intravenous.

Correspondence to: Dr. Dina Mahmoud,
E-Mail: dinamahmoud@kasralainy.edu.eg

Introduction

INTRAOPERATIVE bleeding increases the incidence of damage to vital structures and perioperative complications. Excessive bleeding may be a life-threatening condition and may also need blood transfusion, exposing the patient to additional risks of transfusion reactions and various blood transmitted diseases *[1]*.

Tranexamic acid (TXA) is a hemostatic agent, which inhibits fibrin degradation, by inhibiting the tissue plasminogen activator, which may be beneficial in controlling bleeding during surgery *[2]*. It has been shown to reduce mortality due to traumatic bleeding by a third *[3]*. Although there is no clinical evidence that tranexamic acid increases the risk of thromboembolic events (myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism), it remains a theoretical concern that increased the interest in the topical use of tranexamic acid *[4]*. The direct application of tranexamic acid to the bleeding surface has the potential to reduce bleeding with minimal systemic effects *[5]*.

Total laryngectomy with bilateral block neck dissection is considered one of the major head and neck surgeries. Intraoperative bleeding is considered one of the complications of this surgery, especially considering the type of patients that undergo this surgery whom are usually elderly with multiple co-morbidities, which may lead to intraoperative hemodynamic instability or postoperative complications *[6]*.

Despite multiple randomized controlled trials that had been done to assess the efficacy of tranexamic acid whether intravenous or topically but there is no definite data about using it in total laryngectomy operation. We aimed in this study to

compare the efficiency of topical vs intravenous administration of Tranexamic acid in patients undergoing total laryngectomy with neck dissection.

Patients and Methods

Ethical consideration:

This randomized controlled trial was carried outin Cairo University Hospitals between October 2023 – January 2024 after obtaining ethical committee approval (MS-97-2023), clinical trial registration (NCT06188052) and written informed consent.

Eligibility criteria:

Forty-five patients of either sex, aged between 18-80 years old, ASA physical status I, II undergoing total laryngectomy were included in the study. However, Patients with coagulopathy, a history of thromboembolism, cardiac disease (ischemic heart, valve replacement), or a history of tranexamic acid allergy were excluded.

Randomization:

Online randomization was done where patients were randomized into three equal groups (15 patients in each group), the group assigned with drug preparation were enclosed in sequentiallynumbered concealed envelope. A researcher was responsible for envelope opening, group assignment and drug preparation without any further involvement in the study.

One hour preoperatively, a 20-gauge cannula was inserted into all patients. Tranexamic acid 1mg/kg was given intravenously to patients in group (A). Normal saline was given to group (B) and group (C).

Study protocol:

On arrival at the operating room, pulse oximetry, continuous electrocardiogram, and noninvasive blood pressure measurement device were connected to the patient. Pre-medications were given; metoclopramide (10mg) and dexamethasone (8mg) preoperatively. The induction was done by sevoflurane and succinylcholine 0.5mg/kg. After intubation, fentanyl 2mic/kg and atracurium 0.5mg/kg were given, followed by 0.08mg/kg Morphine sulfate. Anesthesia was maintained by isoflurane 1.5% and atracurium 0.1mg/kg/30min. After flap elevation (using local infiltrations of epinephrine 1/100000), the surgical site was irrigated by 40ml of tranexamic acid 2mg/kg dissolved in 200ml normal saline every 1 hour for the first 5 hours in group (B), and by normal saline in the group (A) and group (C).

The data collector was blinded to the group assignment and was responsible for assessment of intraoperative bleeding and blood loss measurement as the combined total of the volume of drainage in the suction canister and the weight of the sponges used (minus the dry weight of the sponges and any irrigation that was used). Intraoperative hemodynamics were recorded (HR, SBP and DBP arterial blood pressure) at induction and every 15 minutes. Hemoglobin was measured preoperatively and 2 hours postoperatively and the need for blood transfusion was recorded.

Drug complications were assessed (stroke or myocardial infarction) for 72 hours postoperatively. Also, demographic data and duration of operation were recorded.

Sample size:

Our primary outcome was the total amount of blood loss. In a previous study [7], the median (range) total intraoperative blood loss in the control group was 403 (261-545) mL. So, the mean± SD was calculated as 403±71 mL.We calculated a sample size that could detect a mean difference of at least 80 mL (20% difference) between the study groups. Using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium), a sample size of 36 patients was needed to have a study power of 90% and an alpha error of 0.05. However, to allow the comparisons between the control group and each treatment group, an adjusted P (Bonferroni correction) of 0.025 was considered significant for the primary outcome and the required sample size was increased to 42 patients. The number was increased to 45 envelopes (15 envelopes per group) to compensate for possible dropouts.

Statistical analysis:

Analysis of data was performed using Statistical Package for social science (SPSS) software, version 26 for Microsoft Windows (SPSS Inc., Chicago, IL, USA). Categorical data were reported as frequency and percentages and were analyzed using the chi-squared test. Continuous data were checked for normality using the Kolmogorov-Smirnov test. Distributed data were presented as means ± standard deviations and were analyzed using one-way analysis of variance (ANOVA) with Tukey's post hoc test for pairwise comparison. Skewed data were expressed as medians (quartiles) and were analyzed using the Kruskal-Wallis test. A two-way repeated measures ANOVA was used to evaluate dose (between-groups factor with Tukey's post hoc test for pairwise comparison) and time (repeated measures)". A *p*-value of 0.05 or less was considered significant.

Results

In this study, 61 patients were assessed for eligibility, 10 patients did not meet the criteria and 2 patients refused to participate in the study and 4 patients were postponed. The remaining patients were randomly allocated into three equal groups (15 patients in each group). Patients were followed-up and analyzed statistically as shown in Fig. (1).

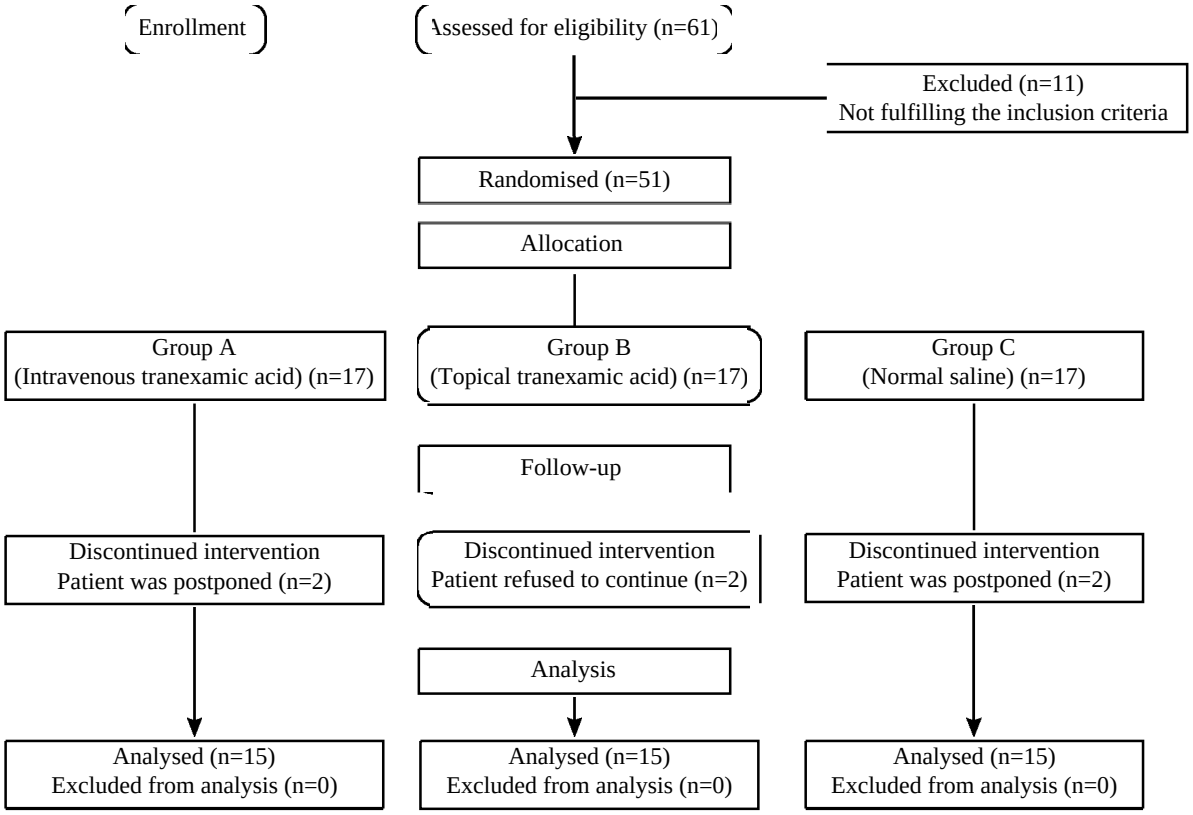

Fig. (1)

The Demographic data (age, sex, weight) were insignificantly different among the three groups. Duration of operation was significantly lower in Group A than (Group B and Group C) (*p*-value=0.007 and 0.005 respectively) and insignificantly different between Group B and Group C as shown in Table (1).

Total blood loss was significantly lower in Group A than (Group B and Group C) (*p*-value=0.004 and <0.001 respectively) and insignificantly different between Group B and Group C. Need for blood transfusionwasinsignificantly different between the 3 groupsas shown in Table (2).

Postoperative hemoglobin levels were insignificantly different among the three groups as shown in Table (3).

Table (1): Demographic data and duration of operation of the studied groups.

	Group A (n=15)	Group B (n=15)	Group C (n=15)	*p*-value	Post Hoc
Age (years):					
Mean ± SD	62.5±7.06	60.6±10.9	63.8±13.24	0.714	
Range	52 - 74	40 - 82	47 - 91		
Sex:					
Male	14 (93.33%)	15 (100%)	14 (93.33%)	0.593	
Female	1 (6.67%)	0 (0%)	1 (6.67%)		
Weight (Kg):					
Mean ± SD	73.7±4.81	72.1±4.85	68.7±7.18	0.066	
Range	65 - 80	65 - 80	60 - 80		
Duration of operation (h):					
Mean ± SD	5±1.13	6.2±1.15	6.1±0.92	0.005*	p_1=0.007*
Range	3 - 7	4 - 7	5 - 7		p_2=0.005*
					p_3=0.861

*Denotesstatistically significant (*p*-value <0.05).
*p*1 : Comparing group A to group B.
*p*2 : Comparing group A to group C.
*p*3 : Comparing group B to group C.

Table (2): Total blood loss and need for blood transfusion of the studied groups.

	Group A (n=15)	Group B (n=15)	Group C (n=15)	*p*-value	Post Hoc
Total blood loss (mL):					
Mean ± SD	347.3±181.95	586.7±240.14	633.3±135.84	0.001*	p_1=0.004*
Range	100 - 600	200 - 1150	400 - 850		p_2<0.001*
					p_3=0.517
Need for blood transfusion:					
Yes	3 (20%)	7 (46.67%)	6 (40%)	0.283	
No	12 (80%)	8 (53.33%)	9 (60%)		

*Denotesstatistically significant (*p*-value <0.05). *p*2 : Comparing group A to group C.
*p*1 : Comparing group A to group B. *p*3 : Comparing group B to group C.

Table (3): Postoperative Hb of the studied groups.

	Group A (n=15)	Group B (n=15)	Group C (n=15)	*p*-value
Postoperative Hb (mg/dl):				
Mean ± SD	11.2±1.82	10.3±1.42	11±1.71	0.263
Range	7 - 13.8	7.8 - 12.8	8.4 - 13.7	

Discussion

Total laryngectomy with additional neck dissection is considered as major head and neck surgery. During head and neck surgery, precise hemostasis ensures a clear view on the surgical field. Minimalizing blood loss and operative time are beneficial both for the patient and costeffectiveness [6].

The rate of overall complications during total laryngectomy is estimated by 45%. Postoperative complications entail bleeding, dysphagia and stomal complications [8]. Complication rates for neck dissection vary greatly according to the extent of the surgery and the levels involved [9], especially in salvage surgery [10]. More effective hemostasis and a consequently better view on the surgical field may lead to less complications.

Thus, it was possible and feasible to administer anti-fibrinolytic agent to reduce blood loss after total laryngectomy. Anti-fibrinolytic agent including aprotinin, tranexamic acid, and epsilon-amino-caproic acid. Of these, TXA was potentially the most effective and relatively safe alternative [11].

Intravenous administration of TXA involves systemic delivery of the drug, allowing for widespread distribution throughout the body. This route of administration is convenient and widely used in various surgical settings [12]. While local administration of TXA involves direct application of the drug to the surgical site. This approach allows for high drug concentrations at the bleeding site, effectively inhibiting fibrinolysis and reducing blood loss. Local TXA is commonly administered in various forms such as topical application, intraarticular injection, or as part of a wound irrigation solution [13].

According to the results of the current study, the duration of operation was significantly lower in Group A than (Group B and Group C) (*p*-value =0.007 and 0.005 respectively) and insignificantly different between Group B and Group C. Total blood loss was significantly lower in Group A than (Group B and Group C) (*p*-value=0.004 and <0.001 respectively) and insignificantly different between Group B and Group C. Need for blood transfusion and hemoglobin levels were insignificantly different among the three groups.

Our results were comparable to that conducted on patients underwent total knee arthroplasty [14], intertrochanteric fracture [15,16] and shoulder arthroplasty [17] as they concluded that the usage of intravenous tranexamic acid has a beneficial role on decreasing blood loss during and after surgery.

A study comparing intravenous to topical irrigation of TXA conducted on patients underwent hysterectomy found that no significant intergroup difference, regarding hemoglobin levels, which was in concordance with our study [18].

Other studies comparing the efficacy of topical and intravenous administration of tranexamic acid conducted on total knee arthroplasty [19,20], concluded that both routes controlled blood loss efficiently which was not in concordance with the results of our study and this may be referred to the use local injection of TXA and not the topical irrigation.

To the best of our knowledge, our randomized controlled trailwas the first to prove the role of intravenous and topical irrigation of tranexamic acid in controlling intraoperative bleeding in patients undergoing total laryngectomy operation.

However, the current study had some limitations. It is conducted in a single center. We evaluated only 2 different regimens of tranexamic acid; therefore, future studies are needed to identify the optimal regimen in larger sample size of different-populations.

Conclusion:

Topical TXA and intravenous TXA were both effective as the need for blood transfusion and surgeon satisfaction were similar in both routes after total laryngectomy with neck dissection, however intravenous TXA was more efficient in reducing blood loss than topical TXA.

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فعالية حمض الترانكسيميك الموضعى مقابل الوريد فى السيطرة على فقدان الدم فى المرضى الذين يخضعون لاستئصال الحنجرة الكلى مع تشريح الرقبة: دراسة مراقبة عشوائية

الخلفية: يزيد النزيف أثناء العملية الجراحية من حدوث تلف فى الهياكل الحيوية ومضاعفات ما بعد الجراحة مثل العدوى أو الورم الدموى. قد يكون النزيف المفرط حالة مهددة للحياة وقد يحتاج أيضًا إلى نقل دم بعد العملية الجراحية، مما يعرض المريض لمخاطر إضافية من تفاعلات نقل الدم والاتصال بمختلف الأمراض المنقولة بالدم.

تعتبر عملية استئصال الحنجرة الكاملة مع تشريح الرقبة واحدة من العمليات الجراحية الرئيسية للرأس والرقبة. يعتبر النزيف أثناء العملية من عوامل الخطر لهذه العملية خاصة أن الأشخاص الذين يخضعون لهذه العملية هم من كبار السن ويعانون من أمراض مصاحبة متعددة. قد يؤدى النزيف أثناء العملية الجراحية إلى عدم استقرار الدورة الدموية أثناء العملية أو مضاعفات ما بعد الجراحة مثل ضعف التئام الجروح وتكوين ناسور البلعوم.

الهدف من الدراسة: لقد صممنا هذه الدراسة بهدف إثبات دور حمض الترانيكساميك الموضعى والوريدى فى السيطرة على النزيف أثناء العملية الجراحية لدى المرضى الذين يخضعون لعملية استئصال الحنجرة الكاملة مع تجنب مخاطر إعطاءه عن طريق الوريد.

الطريقة: أجريت هذه الدراسة العشوائية مزدوجة التعمية على ٤٥ مريضاً يخضعون لعملية استئصال الحنجرة الكاملة. تم تقسيم المرضى إلى ٣ مجموعات متساوية.

الخلاصة: كان كل من حمض الترانيكساميك الموضعى وحمض الترانيكساميك الوريدى فعالين حيث كانت الحاجة إلى نقل الدم ورضا الجراح متشابهة فى كلا الطريقين بعد استئصال الحنجرة الكلى مع تشريح الرقبة ، ولكن حمض الترانيكساميك عن طريق الوريد كان أكثر كفاءة فى تقليل فقد الدم من حمض الترانيكساميك الموضع.