

The Role of Using Tranexamic Acid (TXA) during Thyroidectomy to Control Bleeding in Patients Diagnosed with Controlled Toxic Goiter

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Introduction: Toxic goiter is a condition that is characterized by an excessive production of thyroid hormones by the gland, which may be diffusely enlarged, multinodular, or a solitary nodule at one lobe of the thyroid gland.

Aim of work: To compare the amount of bleeding during and after thyroidectomy operations in patients diagnosed with toxic goiter among two groups, the first group with perioperative TXA injection and the second group with placebo injection and to assess tranexamic acid (TXA) role of hemostasis.

Patients and methods: This study was conducted at the general Surgery departments of Ain Shams University Hospitals and the National Institute of Diabetes and Endocrine diseases. 36 patients with toxic goiter presented to us in the outpatient clinic and fulfilling the inclusion criteria in the absence of any of the exclusion criteria all underwent total thyroidectomy operation after controlling their medical status and anesthesiology department approve their fitness of surgery.

Results: This study showed that in group 1, the mean Pre-surgery hemoglobin level was 13.08 ± 2.53 post-surgery hemoglobin level was 12.5 ± 2.42 . In group 2, the mean Pre-surgery hemoglobin level was 13.53 ± 2.44 , post-surgery hemoglobin level was 12.1 ± 0.36 . There were significant differences between both groups as regards laboratory data.

Conclusion: injecting (TXA) has a beneficial effect During thyroidectomy. Moreover, based on the results of the present study, injecting this amount of (TXA) had No significant effect on post-surgery hemoglobin levels. finally, and to get more data and more valuable statistics, more studies on a larger number of cases (May be multicenter) with the same method of postoperative assessment and standardization of both inclusion and exclusion criteria.

Key words: Toxic Goiter, total Thyroidectomy, tranexamic acid.

Introduction

Toxic goiter is a disorder characterized by overproduction of thyroid hormones from the gland which may be diffusely enlarged, multinodular or solitary nodule at one lobe, it can be associated with other autoimmune disorder as it happens in patients diagnosed with Graves' disease.¹

Management of such disorders usually starts by controlling the other systems affections and anti-thyroid drugs and radioactive iodine sometimes, but it still the challenging surgical options which is characterized by more abundant vascularity and excessive adhesion.²

Total thyroidectomy is the most performed operation in the field of endocrine gland surgery. It is the optimum treatment for many thyroid disorders.³ Bleeding and hematoma development have great significance due to the extensive vascularization of the thyroid tissue, and its proximity to the airway.³ Although it's rare but these complications can emerge as a life-threatening condition.⁴

Post-thyroidectomy bleeding is not common; the risk is stated between 0.1-1.4percent.⁵ Hematomas or bleeding can occur immediately postoperatively or up to a day after it, but the majority occurs within

the first 6 hours post- operatively.⁵

Throughout the history of surgery, various methods have been used for hemostasis in parallel to technical improvements. The purpose of all these techniques is to prevent or stop bleeding as it happens, and to prevent development of a postoperative neck hematoma formation.⁶

Tranexamic acid (TXA) is an inexpensive and relatively safe antifibrinolytic drug that has a half-life of 2 hours, with a maximum concentration of approximately 1 hour after administration. The fibrinolytic effects last from 8 to 17 hours.⁴

The peri-operative use of this drug is becoming more common, according to some studies that showed patients receiving TXA were less to require a blood transfusion after head and neck cancer surgeries.⁸

Aim of work

The aim of this study is to compare the amount of bleeding during and after thyroidectomy operations in patients diagnosed with toxic goiter among two groups, the first group with perioperative TXA injection and the second group with placebo injection and to assess tranexamic acid (TXA) role of hemostasis.

Patients and methods

Type of study: Comparative, Prospective and Controlled Randomized Study.

Study setting: Ain Shams University Hospitals and National Institute of Diabetes and Endocrine diseases.

Study period: 6 months.

Study population

Inclusion Criteria: All patients who were diagnosed with toxic goiter of the thyroid gland either Graves' disease or secondary toxic goiters, who were candidate to total-thyroidectomy operation.

Exclusion criteria

Patients unfit for surgery or refuse to consent, with anemia, thrombocytopenia, hepatic disorders, coagulopathy, increased bleeding tendency disorders, Tranexamic acid contraindicated patients (History of thromboembolic or ischemic event as pulmonary embolism, deep venous thrombosis, ischemic cerebrovascular accident, acute myocardial infarction, or ischemic retinopathy), or Patients with history of previous neck surgery, or previous radiation therapy.

Sampling method: Patients of clinically diagnosed Toxic Goiter of thyroid gland who presented to the department of general surgery at Ain Shams university hospitals and National institute of diabetes and endocrine diseases.

Sample size: 36 patients because of a confidence level of 95% and type I error of .05, the sample size calculated to achieve power of the study of .90 and type II error of .10. The expected incidence of identification of TXA role in lowering bleeding tendency is 20% in conventional operation. However, the maximum expected incidence of TXA role is 50%. The calculated sample size was 16 patients in each group. To guard against drop out, the sample size will be 18 patients in each group.

Ethical considerations: Detailed explanation of the procedure to the patient was done. Written consent had been taken from the patients according to ethical committee considerations. All patients signed a consent reviewing the tests, medications and procedures including all complications and test results (Informed Consent).

Study tools

The patients with thyroid lesions were evaluated in order that starts with Medical history taking and the proper clinical examination that may require radiological investigations as: (e.g: Neck Ultra-Sound / Technetium scan) and Laboratory

investigations as: Preoperative routine labs, thyroid hormones levels, thyroid antibodies levels with other work out as indirect laryngoscope and ultrasound guided fine needle aspiration cytology FNAC may be needed and indicated.

Surgical technique

24 hours before the surgery the patients' hemoglobin was recorded for Both groups which their operations consisted of total extra-capsular thyroidectomy and were performed by the same experienced endocrine surgeons involved in the study. the thyroid was approached via a low transverse collar incision. After elevation of the Sub-platysma flap, superiorly and inferiorly, the strap muscles were divided in the midline and elevated sharply from the underlying thyroid gland.

The dissection of the thyroid began with ligation division of the middle thyroid vein.

The superior pole vessels were ligated, the inferior thyroid artery was ligated after identification of the recurrent laryngeal nerve, Attention was directed toward visualization of the inferior and superior parathyroid glands.

The dissection was carried out across the midline and completed by mobilizing the isthmus and pyramidal lobe of the thyroid.⁹ And this was repeated for the other Lobe.

Intra-operative assessment: The following parameters were recorded during surgery: Operative time (Skin incision to skin closure), intra-operative exposure of the recurrent laryngeal nerve and parathyroid glands, blood loss. It describes the primary methods for determining blood loss, including visual assessment, photometric analysis, gravimetric blood loss determination, blood loss formulas using hemoglobin and hematocrit monitoring.¹⁰

Patients which were at group 1 (TXA recipients), for each one of them 20 mg/kg of TXA was diluted by 20cc normal saline and applied intravenous during the surgery. The amount of bleeding during surgery was calculated by estimating the number of gauzes with the standard size of 10 cm ×10 cm that were completely soaked with blood during surgery. Each completely blood-soaked gauze holds 20 cc of blood.

Post-operative measures: Patients were managed in a high-dependency care setting to provide close supervision during the first 24 hours. Beta-blocker therapy continued for 5–7 days with its dose titrated to the patient's heart rate.¹¹

postoperative bleeding measured based on the amount of blood collected in the Hemovac drains till withdrawn in maximum period of 72 hours after

the surgery.

For both groups of patient's hemoglobin was recorded 24 hours before and after the surgery.

Statistical analysis

Data was analyzed using SPSS (statistical package for social sciences) version 22. Qualitative data was presented as number and percent, Quantitative data was tested for normality by Shapiro-wilk test then described as mean and standard deviation for normally distributed data and median and range for non-normally distributed. The appropriate statistical test was applied according to data type with the following suggested tests: Chi-Square for categorical variable.

Statistical package

Statistical package for social sciences (SPSS) program (version 22).

Results

This study was conducted at the General Surgery Departments of Ain Shams University Hospitals and the National Institute of Diabetes and Endocrine diseases from June 2022 to June 2023 and was held on 36 patients.

Demographic data of studied cases

shows that in group 1, the mean age was 52.5 ± 5.1 , 16.7% were male. In group 2, the mean age was 52.4 ± 5.0 , 22.2% were male.

There were insignificant differences between both groups as regard age or sex (Table 1).

According to Anthropometric data

shows that in group 1, the mean Weight was 77.5 ± 6.1 , BMI was 25.1 ± 2.1 . In group 2, the mean Weight was 74.6 ± 6.3 , BMI was 24.4 ± 2.0 . There were insignificant differences between both groups as regard weight or BMI (Table 1).

Vital signs data of studied cases after the procedure was done

shows insignificant differences between both groups as regard the vital signs (Table 2).

Laboratory data of studied cases

shows that in group 1, the mean fT4 (pmol/l) was 24.3 ± 5.0 , T3 was 3.98 ± 1.02 , TSH was 0.085 ± 0.015 . In group 2, the mean fT4 (pmol/l) was 26.2 ± 3.6 , T3 was 4.08 ± 0.86 , TSH was 0.083 ± 0.19

There were slight significant differences between both groups as regard Laboratory data (Table 3).

Bleeding data of studied cases:

shows that in group 1, the mean bleeding after surgery was 63.7 ± 6.2 , Bleeding during surgery was 67.47 ± 5.14 . In group 2, the mean bleeding after surgery was 81.2 ± 9.5 , Bleeding during surgery was 87.01 ± 10.2 . hence, there were significant differences between both groups as regard Bleeding after surgery and Bleeding during surgery (Table 4).

Bleeding data according to hemoglobin records of studied cases:

shows that in group 1, the mean bleeding after surgery was 63.7 ± 6.2 , Bleeding during surgery was 67.47 ± 5.14 . In group 2, the mean bleeding after surgery was 81.2 ± 9.5 , Bleeding during surgery was 87.01 ± 10.2 . hence There were significant differences between both groups as regard Bleeding after surgery and Bleeding during surgery (Table 5).

Bleeding data according to hemoglobin records of studied cases:

shows that in group 1, the mean Pre-surgery hemoglobin level was 13.08 ± 2.53 , post-surgery hemoglobin level was 12.5 ± 2.42 . In group 2, the mean Pre-surgery hemoglobin level was 13.53 ± 2.44 , post-surgery hemoglobin level was 12.1 ± 0.36 . Hence There were significant differences between both groups as regards laboratory data (Table 6).

Correlation between bleeding during thyroidectomy operations and different parameters in patients diagnosed with toxic goiter:

shows Correlation between bleeding during thyroidectomy operations and different parameters in patients diagnosed with toxic goiter. So, There were significant correlation bleeding during thyroidectomy operations and Pre-surgery hemoglobin level (Table 7).

Correlation between bleeding according to hemoglobin records after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter: shows Correlation between bleeding according to hemoglobin records after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter. So, There were significant correlation bleeding after thyroidectomy operations and Post -surgery hemoglobin level (Table 8).

Univariate Correlation between bleeding after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter: there were significant correlations between bleeding after thyroidectomy operations and

different parameters in patients diagnosed with toxic goiter (Table 9).

Multivariate Correlation between bleeding after thyroidectomy operations and different

parameters in patients diagnosed with toxic goiter: there were significant correlations between bleeding after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter (Table 10).

Table 1: Demographic data of studied cases

	Group 1 (n=18)	Group 2 (n=18)	P value
Age			
Mean± SD	52.5±5.1	52.4±5.0	0.93
Sex			
Male	3 (16.7%)	4 (22.2%)	0.67
Female	15 (83.3%)	14 (77.8%)	

Table 2: Anthropometric data of studied cases

	Group 1 (n=18)	Group 2 (n=18)	P value
Weight			
Mean± SD	77.5±6.1	74.6±6.3	0.895
BMI			
Mean± SD	25.1±2.1	24.4±2.0	0.84

Table 3: Vital signs data of studied cases after the procedure was done

	Group 1 (n=18)	Group 2 (n=18)	P value
Heart rate (beat/ minute)			
Mean± SD	79.88±7.01	77.69±6.22	0.895
Temperature (° C)			
Mean± SD	37.1±0.20	36.4±0.28	0.84
Systolic blood pressure (mmHg)			
Mean± SD	123.15±14.29	121.2±15.5	
Diastolic blood pressure (mmHg)			
Mean± SD	82.2±5.5	80.96±6.1	0.8
Respiratory rate (cycle/ minute)			
Mean± SD	18.51 ±0.91	19.47 ±0.90	0.44

Table 4: Laboratory data of studied cases

	Group 1 (n=18)	Group 2 (n=18)	P value
ft4 (pmol/l)			
Mean± SD	24.3±5.0	26.2±3.6	0.185
ft3 (pmol/l)			
Mean± SD	3.98±1.02	4.08±0.86	0.48
TSH (mU/l)			
Mean± SD	0.085±0.015	0.083±0.19	0.81

Table 5: Bleeding data of studied cases

	Group 1 (n=18)	Group 2 (n=18)	P value
Bleeding after surgery			
Mean± SD	63.7±6.2	81.2 ± 9.5	<0.001
Bleeding during surgery			
Mean± SD	67.47±5.14	87.01±10.2	<0.001

Table 6: Bleeding data according to hemoglobin records of studied cases

	Group 1 (n=18)	Group 2 (n=18)	P value
Pre-surgery hemoglobin level			
Mean± SD	13.08±2.53	13.53±2.44	0.805
Post-surgery hemoglobin level			
Mean± SD	12.5±2.42	12.1±0.36	0.022

Table 7: Correlation between bleeding during thyroidectomy operations and different parameters in patients diagnosed with toxic goiter

	Bleeding during thyroidectomy	
	r	P
Age	0.15	0.445
Weight	0.19	0.09
Pre-surgery hemoglobin level	0.918860	0.0001

Table 8: Correlation between bleeding according to hemoglobin records after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter

	Bleeding after thyroidectomy	
	R	P
Age	0.142	0.42
Weight	0.18	0.102
Post-surgery hemoglobin level	0.98	0.0001

Table 9: Univariate Correlation between bleeding after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter

Pre-surgery hemoglobin level	Correlation	-0.348
	Significance	<0.0001
Post-surgery hemoglobin level	Correlation	-0.471
	Significance	<0.0001

Table 10: Multivariate Correlation between bleeding after thyroidectomy operations and different parameters in patients diagnosed with toxic goiter

Variable	Value	
Pre-surgery hemoglobin level	Correlation	71.305
	Significance	<0.0001
Post-surgery hemoglobin level	Correlation	20.495
	Significance	<0.0001

Discussion

Toxic goiter is a condition that is characterized by an excessive production of thyroid hormones by the gland, which may be diffusely enlarged, multinodular, or a solitary nodule at one lobe of the thyroid gland.

It is possible for toxic goiter to relate to other autoimmune conditions, as is the case with patients who have been diagnosed with Graves' disease. Patients who have been diagnosed with Hashimoto's thyroiditis also have a higher risk of developing toxic goiter.

In most cases, the first step in treating disorders of this nature is to manage any symptoms affecting the body's other systems. The most successful therapy is still challenging surgical choices, which are characterized by more abundant vascularity and severe adhesion. Although anti-thyroid medications and radioactive iodine are often employed, the most effective treatment is still challenging surgical options.

The total thyroidectomy is the technique that is conducted most commonly in the field of surgery involving endocrine glands. This is because the thyroid gland is one of the most important glands in the body. It is the treatment of choice for a diverse range of disorders affecting the thyroid.

Any bleeding that takes place or the formation of a hematoma is of essential concern because of the high vascularization of the thyroid tissue and its near proximity to the airway. These difficulties, despite the fact that they are not particularly prevalent, have the potential to develop into a condition that threatens one's life.

Patients who have thyroidectomy have a risk that ranges from 0.1 to 1.4% of experiencing bleeding following the procedure. but the vast majority of hematomas and bleeding occur during the first six hours after surgery.

Throughout the course of the history of surgery, many different methods have been utilized to produce hemostasis. This is in keeping with the development of increasingly complex surgical procedures. All of these procedures are intended to either stop bleeding as it occurs or prevent bleeding from occurring in the first place, as well as stop the formation of a postoperative hematoma in the neck. All of these procedures are also intended to stop the creation of a postoperative hematoma in the chest.

TXA is an antifibrinolytic medicine that is not only inexpensive but also carries a little risk of adverse effects. Its half- life is two hours, and around one hour after administration, it achieves its maximum concentration. Its half-life is two hours. The

fibrinolytic treatment persist for 8 to 17 hours later.

According to the findings of a number of different researches, the administration of this medicine to surgical patients is becoming an increasingly common practice. According to the findings of these studies, patients with head and neck cancer who were administered TXA were significantly less likely to require a blood transfusion following surgical procedures.

The aim of our study is to asses tranexamic acid (TXA) role of hemostasis and to compare the amount of bleeding during and after thyroidectomy operations in patients diagnosed with toxic goiter among two groups, the first group with perioperative TXA injection and the second group with placebo injection.

This study showed that in group 1, the mean age was 52.5 ± 5.1 , 16.7% were male. In group 2, the mean age was 52.4 ± 5.0 , 22.2% were male. There were insignificant differences between both groups as regard age or sex.

Similar to our results,⁹ aimed to demonstrate the effect of intraoperative topical tranexamic acid on postoperative drainage output for thyroid surgery. They included 57 patients in their study. There were 27 patients in the TXA group, of which 20 were female (74.1%) and 7 were male (25.9%). The age range was 12-78, the mean age was 47 years. The control group included 30 patients, 24 (80%) women, and 6 (20%) men. The age range was 21-71 and the mean age was 45.38.

In agreement with our results, Abdul-Hamid et al. (2020)¹³ aimed to assess outcomes of postoperative haematoma following the administration of perioperative tranexamic acid during thyroid surgery. A total number of 260 patients were included in the study; 106 were given TXA and 154 patients were not given any. There were insignificant differences between both groups as regard age or sex.

Alipour et al. (2020)¹⁴ aimed to determine and compare the effectiveness of tranexamic acid (TXA) medication on controlling BL during and after total thyroidectomy. They carried out as a double-blind clinical trial on 83 patients affected with benign and malignant pathologies which were candidates for total thyroidectomy surgical operation. Patients were randomly divided into two groups including TXA recipients, for which 20 mg/kg of TXA was diluted to 20 cc with normal saline before surgery, and the control group which did not receive TXA. In their study, 83 patients were evaluated in two groups, 20 (24.1%) of which were male and 63 (75.9%) were female, and considering $P = 0.565$, there was no significant difference between the two evaluated groups. Regarding the average age

of the patients, the control group had an average age of 47.85 ± 14.1 , while the average age of the experimental group was 46.16 ± 11.3 , and $P = 0.55$ shows no significant difference regarding the average age in the two evaluated groups.

This study reported that in group 1, the mean bleeding after surgery was 63.7 ± 6.2 , bleeding during surgery was 67.47 ± 5.14 . In group 2, the mean bleeding after surgery was 81.2 ± 9.5 , Bleeding during surgery was 87.01 ± 10.2 . There were significant differences between both groups as regard Bleeding after surgery and Bleeding during surgery.

Abdul-Hamid et al. (2020)¹³ study suggested that administering one dose of 1g TXA intravenously during thyroid surgery reduces the risk of post-operative haematoma. There were no adverse reactions in any of our patients from receiving TXA.

All the bleeds in this study were not from a named vessel but rather a general slow bleed and we do not expect a TXA to change the outcome from bleeding from a named vessel.

Alipour et al. (2020)¹⁴ showed that in terms of the amount of patients' bleeding during surgery in the two evaluated groups, the experimental group (TXA) with an average bleeding of 25.27 ± 9.52 cc and the control group with an average bleeding of 34.58 ± 14.06 cc was reported, which considering $P = 0.016$ obtained from the t-test, a statistically significant difference was observed between the two groups, indicating that the group treated with TXA had lost significantly less blood during surgery in comparison to the control group.

Regarding the amount of bleeding after surgery, the average bleeding based on the volume of blood collected in the Hemovac drain was 32.5 ± 4.15 cc for the experimental group and 35.48 ± 4.88 cc for the control group, which considering $P = 0.5$ obtained from the t-test, there was no significant difference between the two groups.

Das et al. (2015)⁸ conducted as a double-blind case-control study on 80 patients undergoing head and neck cancer surgeries revealed a significant difference of the hemoglobin level before and after surgery in the two groups of TXA-receiving and control, which is not consistent with the results of the present study. The amount of bleeding during and after surgery in the two groups studied by Das was also significantly different which is consistent with the present study regarding the case of bleeding during surgery. It is notable that Das's study only admitted the patients affected with malignant pathologies and comprehensive neck dissections had been performed in most operations.

This study showed that in group 1, the mean Pre-surgery hemoglobin level was 13.08 ± 2.53 , post-surgery hemoglobin level was 12.5 ± 2.42 . In group 2, the mean Pre-surgery hemoglobin level was 13.53 ± 2.44 , post-surgery hemoglobin level was 12.1 ± 0.36 . There were significant differences between both groups as regard Laboratory data.

Abdul-Hamid et al., (2020)¹³ study suggests that administering one dose of 1g TXA intravenously during thyroid surgery reduces the risk of post-operative hematoma. There were no adverse reactions in any of our patients from receiving TXA.

All the bleeds in this study were not from a named vessel but rather a general slow bleed and we do not expect a TXA to change the outcome from bleeding from a named vessel.

Alipour et al. (2020)¹⁴ showed that the pre-surgery hemoglobin levels were 13.08 ± 1.53 mg/dl in the TXA-receiving group and 13.53 ± 1.44 mg/dl in the control group and considering the obtained $P = 0.156$, there was no significant difference between the two groups. Furthermore, the post-surgery hemoglobin levels were 12.22 ± 1.42 mg/dl in the TXA-receiving group and 12.52 ± 2.36 mg/dl in the control group which, considering the obtained $P = 0.492$, were not significantly different.

Conducting a systematic review in 2018, De Vasconcellos et al. (2018)¹⁵ investigated the effect of TXA on the amount of bleeding during rhinoplasty surgery and according to the results of this study, bleeding during surgery in the TXA-receiving group was significantly less than the control group, which is consistent with the results of the present study.

In a study conducted by Kalkarni et al. (2016) on 240 patients undergoing head and neck cancer surgeries, one group of patients was injected with 10 cc/kg of diluted TXA before surgery and the other group was injected with the same amount of normal saline. According to the results, there was no significant difference between the two groups in terms of bleeding during surgery, but there was a significant difference between the TXA-receiving group and the control group regarding the amount of bleeding over 24 h after surgery, both results inconsistent with the results of the present study.

Thakur et al. (2019)¹⁶ conducted a study to investigate the effect of TXA on the amount of bleeding during and after head and neck surgeries. Ninety-two patients were admitted to the study and divided into Group 1 and Group 2 based on the type of surgical procedure. Fifty patients that had undergone total thyroidectomy, total parotidectomy, and various neck dissections were placed in Group 1, and 42 patients that had undergone subtotal thyroidectomy, lobectomy, and superficial

parotidectomy were placed in Group 2. In each group, patients were divided into two groups of TXA-receiving and control. According to the results, there was no statistically significant relationship between the control and experimental groups of Group 1 and Group 2 regarding bleeding during and after surgery, which was consistent with the results of the present study in terms of bleeding after surgery but inconsistent with the present results in terms of bleeding during surgery.

Conclusion

According to the results of the present study, the amount of bleeding during surgery significantly reduced in the group that received 20 mg/kg of TXA before surgery, compared to the control group, and although post-surgery bleeding in the TXA-receiving group also decreased in comparison to the control group, the difference was not statistically significant. Moreover, based on the results of the present study, injecting this amount of (TXA) has a beneficial effect During thyroidectomy.

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