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To compare the efficacy of 2.5% and 5% tranexamic acid mouthwash as a hemostatic agent in patients on anticoagulant therapy after oral procedures

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Abstract

Background and Objective: The present study was conducted with the aim to compare the efficacy of 2.5% and 5% tranexamic acid mouthwash as a hemostatic agent in patients on anticoagulant therapy without altering their drug regimen.

Method: This comparative clinical study was done on 120 patients who were undergoing extraction & was on anticoagulation therapy. After extraction of teeth the wound was thoroughly irrigated with 5% (Group I) or 2.5% (Group II) tranexamic acid solution for 2 minutes. They were given tranexamic acid tablets (500mg), 30 tablets, for the preparation of tranexamic acid mouthwash for oral rinsing for 2 minutes. The patients were instructed to enter the degree of bleeding in given recording form for post-operative 7 days on a daily basis according to given visual analogical scale [VAS] reference values.

Results: Postoperatively on day of extraction, out of 50 patients 35 patients in Group I had no bleeding and 15

had oozing, from day 1 to day 7 postoperatively all patients had no bleeding. While in group II out of 50 patients on the day of extraction 14 patients had no bleeding, 31 patients had oozing and 5 patients had accidental low bleeding, post-operatively on day one 27 had no bleeding and 23 had oozing, postoperatively on day two, 48 had no bleeding and 2 had oozing on day 3,4,5,6 and 7 no patients had any complain of bleeding.

Interpretation and Conclusion: In comparison with 5% mouthwash, in 2.5% mouthwash patients have less complains about bad taste of mouthwash, nausea, slight burning sensation, so lower concentration can be beneficial to provide hemostasis when the INR is low (i.e., below 2.5) in patients with oral anticoagulation therapy.

Keywords: Anticoagulant therapy, bleeding assessment, extraction, hemostasis, local anaesthetic agent, tranexamic acid

Introduction

Oral Anticoagulant Therapy (OAT) is widely used for primary prevention of thromboembolic events for various periods to reduce blood coagulability to an optimal therapeutic range for providing some degree of protection from thromboembolic events in patients with atrial fibrillation and prosthetic heart valves and also as a secondary prevention after systemic embolism in patients with rheumatic mitral valve disease, mitral valve prolapse, mitral annular calcification, nonrheumatic mitral regurgitation, and mobile aortic atheromas or aortic plaques larger than 4 mm. [1]

Patients receiving oral anticoagulant therapy who undergo oral surgical procedures may have prolonged and excessive hemorrhage for 2 or 3 days after the initial surgery due to local fibrinolysis, presumably secondary to increased concentrations of plasminogen and plasminogen activators in the external oral environment (epithelial cells in oral mucosa & saliva).As a preventive measure for excessive haemorrhage temporarily withholding or decreasing the dosage of the anticoagulant exposes the patients to the risk of venous thromboembolism and potential systemic emboli from a cardiac source. [2] The risk of serious post-operative hemorrhage has to be balanced against the potential for life threatening thrombo-embolism.

Various protocols have been suggested for treating these patients, including substituting heparin for warfarin with admission of patient to the hospital, decreasing the level of anticoagulation preoperatively, temporarily stopping the warfarin, and not altering the anticoagulant regimen at all. There remains, however, no standard therapeutic approach, and currently it appears that each patient's treatment plan is individually tailored by his or her attending specialist. [2]

In recent years, oral surgical procedures are preferred without any interruption or diminution of the anticoagulant treatment, with emphasizing the efficiency of the local hemostatic materials like Epsilon Amino Caproic Acid (EACA) & Para Amino Methyl Cyclohexane Carboxylic Acid (AMCA) or fibrin glue in addition to gelatin sponge and sutures.[3] AMCA existed in two isomeric forms. The active trans-stereo isomer (Tranexamic acid) is 200 times more active than other.

Tranexamic acid blocks the lysine binding sites of plasminogen which are important for the binding of the plasminogen to fibrin. Preventing this binding stops the activation of plasminogen-by-plasminogen activators, which are absorbed to the fibrin, thus stabilizing the blood clot. It is available in tablet form (500 mg) or as an intravenous injection (per ampule 10.7 gm). The

typical dose is 3 or 4 grams (in divided doses) daily for an adult.[4]

Local anti-fibrinolytic therapy with TXA as a local irrigation (Immediately after the extraction) or as a mouth-wash (6 hourly for 2-7 days) helps in reducing the incidence of post-operative bleeding after oral surgical procedures in patient on OAT[1,21]with negligible systemic absorption.[1,5,6,7] It has additional advantages like avoidance of hospitalization (as needed in heparin therapy), easy availability and less expense, discomfort & follow-up visits (as in cases of long standing sutures). Studies have been done for determining the efficacy of TXA mouthwash in different concentration (4.8%, 5% or 10%).

We performed a randomized clinical comparative study to compare the efficacy of 2.5% & 5% tranexamic acid mouthwash on patients on oral anticoagulation therapy (INR: 1.5-3.0) after extractions.

Materials and method

A comparative clinical study was done on 120 patients on ambulatory basis, treated by the same surgeon in the Department of Oral and Maxillofacial Surgery, Ahmedabad Dental College, Gandhinagar, Gujarat, India. The ethical clearance for the study was taken from an institutionally approved ethical committee. All surgical procedures and postoperative controls had been performed by the same investigator. The study sample consisted of 120 patients who were undergoing extraction & was on anticoagulation therapy within study period of 2015 – 2017. Out of these 20 patients failed to communicate the researcher post-operatively.

The Inclusion criteria includes individuals aged over 18 years of either sex and on anticoagulant therapy with INR1.5-3.0. Patients who had not given informed consent were excluded.

Materials used

- 2.5 & 5% tranexamic acid mouthwash

Method

The patient's medical history was obtained at the first visit & a standardized form was completed for each patient to record the relevant clinical data. Physician reference has been taken. Written-Informed consent was obtained before extractions. Patients were randomized to receive.

Group I: 5% tranexamic acid mouthwash after extraction

Group II: 2.5% tranexamic acid mouthwash after extraction

Blood samples were taken on the day of procedure to evaluate the anticoagulant activity by calculating the International Normalized Ratio (INR). Only patients with an INR (1.5-3.0) were included in study.

Procedure

Pre-operative antibiotic drug was administered half an hour before starting the treatment in all enrolled patients. - Anesthesia was achieved by using of 1.8-mL of 2%lidocaine–containing 1:80,000 adrenaline. Extraction (single or multiple) was done, and mouthwash was prepared during the procedure time. For the preparation of tranexamic acid mouthwash dissolving one tablet, in the 10 ml of distilled water for 5% solution or dissolving one tablet, in the 20 ml of distilled water for 2.5% solution, Patients were instructed not to swallow the solution. The wound was thoroughly irrigated with 2.5% or 5% tranexamic acid solution for 2 minutes, care being taken not to suck this out of the socket. The socket wall was compressed using finger pressure over a swab soaked in tranexamic acid solution. At the completion of surgery, the patient was asked to bite on a pressure pad soaked in tranexamic acid solution. After 10 minutes

the pack was removed and the wound observed. After achieving haemostasis, patient was discharged.

All the patients received postoperative instructions. Patients were prescribed appropriate antibiotics (Tab. Cephadroxyl – 500 mg) and analgesic drugs (Tab. Paracetamol – 500mg). They were given tranexamic acid tablets (500mg), 30 tablets, for the preparation of tranexamic acid mouthwash for oral rinsing for 2 minutes, dissolving one tablet, in the 10 ml of distilled water for 5% solution or dissolving one tablet, in the 20 ml of distilled water for 2.5% solution, 4 times a day for 7 days. The patients were instructed to enter the degree of bleeding in given recording form for post-operative 7 days on a daily basis according to given visual analogical scale [VAS]reference values. Table I shows the reference values given to patients for bleeding, and the corresponding clinical situations.

For a test of compliance of the mouthwash protocol, the patients were asked to come for follow up on 7th day and to obtain data and number of tranexamic acid tablets used.

Grading Score

"0" No Bleeding - The patient does not detect any blood in saliva

"1" Oozing - The patient detects a slight blood but it is not very noticeable

"2" Accidental Low Bleeding - The patient has low bleeding sometimes

"3" Continues Low Bleeding - The patient has low bleeding often

"4" Massive Bleeding - Continues high bleeding

Statistical analysis

The results obtained were entered in Microsoft excel and further statistical analysis was done by using SPSS version 21.

Results

A total of 120 patients, who were on oral anticoagulant therapy (warfarin) &required extractions (single or multiple) enrolled in the study. From which, 86 patients had undergone extraction in single visit & 17 patients had undergone extraction in multiple visits. 20 patients who failed for postoperative follow-up were excluded from the study.

Reasons for taking oral anticoagulant therapy (warfarin) included prosthetic valvular replacement (45), atrial fibrillation (13), deep venous thrombosis (21), transient ischemic attack (7), & left ventricular thrombus (14).

Patients' INR were obtained on the day of extraction. Amongst all, 65 had INR between 1.5 – 2.0, 17 had INR between 2.1- 2.5 & 18 had INR ranging between 2.6-3.0.

1. The Age distribution of patients

The age ranged between 43 to 86 years. Mean age of patients in group I is 62.62 years with standard deviation of 8.02 years (Table I, Graph I), and in group II is 64.82 years with standard deviation of 9.05 years (Table II, Graph II).

2. The sex distribution of patients

Out of 100 patients, 57 were male & 43 were female (Table III, Graph III)

Total 169 teeth were extracted, which included11 maxillary incisors, 3 maxillary canines, 19 maxillary premolars, 24 maxillary molars, 26 mandibular incisors, 4 mandibular canine, 14 mandibular premolars & 68 mandibular molars.

After extraction, patients of both groups (Group 1: patients who were given 5% tranexamic acid mouthwash after extraction and Group 2: patients who were given 2.5% tranexamic acid mouthwash after extraction) were evaluated for postoperative bleeding consecutively for 7 days. For bleeding score patients were given values from

0 to 4 to rate it accordingly (0: no bleeding; 1: oozing; 2: accidental low bleeding; 3: continuous low bleeding; 4: massive bleeding). Patients were recalled on seventh post-operative day for follow-up data collection & returning unused tablets.

3. Bleeding assessment of patients in Group I

Postoperatively on day of extraction, out of 50 patients 35 patients in Group I had no bleeding and 15 had oozing, from day 1 to day 7 postoperatively all patients had no bleeding (Table IV, Graph IV).

4. Bleeding assessment of patients in Group II

While in group II out of 50 patients on the day of extraction 14 patients had no bleeding, 31 patients had oozing and 5 patients had accidental low bleeding, post-operatively on day one 27 had no bleeding and 23 had oozing, postoperatively on day two, 48 had no bleeding and 2 had oozing, on day 3,4,5,6 and 7 no patients had any complain of bleeding (Table V, Graph V).

When chi square test was applied to compare 5% & 2.5% concentration of TXA, the p-value found to be statically not significant, [for 5% TXA it is 7.75 & for 2.5% TXA it is 1.92]

Discussion

Cardiovascular conditions represent a main cause of death in the world population and are related to an increased risk for thromboembolic complications. Patients affected by cardiovascular conditions may be treated, when indicated, by an oral anticoagulant drug that interfere with the process of hemostasis, therefore leading to an increased tendency to bleed after trauma.[8] Continuation of anticoagulants can be extremely important for patients at high risk of thromboembolic events, such as those who have mechanical heart valve prostheses and those who have recurrent or recent thromboembolic events. When planning dentoalveolar surgery in such patients, the possible consequences of postoperative bleeding in those on continuous treatment with anticoagulants must be weighed against the possible consequences of a thromboembolic event.

The agents most commonly used to control and prevent thromboembolic events are thrombocyte aggregation inhibitors (such as acetylsalicylic acid and clopidogrel) and vitamin K antagonists (such as warfarin, acenocoumarol, and fenprocoumon) [9]. Despite of certain limitations, warfarin is the most commonly used oral anticoagulant worldwide [2], because of its predictable onset, duration of action and its excellent bioavailability with an elimination half-life of 36 hours due to its slow rate of biotransformation and high amount of plasma protein binding.[10]

Tranexamic acid is the material which is safe, convenient and overcomes the disadvantages of previously described methods & also does not cause any systemic effects if it is used as a topical application as mouthwash.

This study was undertaken to observe that using tranexamic acid, ‘the antifibrinolytic agent’ mouth rinse is a safe, effective, and acceptable method of managing anticoagulated patients. A technique that broadly meets these requirements was first described by Sindet-Pedersen et al. [11] and subsequently verified by Ram Strom et al [12], they used, tranexamic acid as a mouth rinse to prevent post extraction bleeding. A novel aspect of this investigation was the evaluation of potential risk factors associated with the removal of the teeth and the identification risk factors for bleeding.

All previous studies have used 10 ml of 4.8% tranexamic acid mouth rinse. [2,12,13,14,15] This study used 10ml of 5%[4]or2.5% [5]tranexamic acid mouth rinse. The reason for this decision was that pre-manufactured 5% or 2.5%

tranexamic acid mouthwash are not available in India, so freshly prepared [16] 5% or 2.5% tranexamic acid mouthwash was used by dissolving 500mg tranexamic acid tablet into 10 ml or 20ml of distilled water. The other reason was that 5% is relatively closer to 4.8% concentration and 2.5% was chosen to because it was half of the previous study concentration so that evaluation of tranxemic acid concentration can be done.

A particular benefit of this technique is its simplicity. Provided the patient has an INR below 3.0 at the time of surgery and has not taken aspirin or NSAIDs within the preceding 7 days, teeth maybe removed without significant risk. Surgery can be confidently scheduled with a definite date that avoids loss of operating time due to cancellations resulting from variable INR correction enabling tooth removal to proceed with minimum delay and inconvenience. The procedure can be undertaken with parenteral antibiotic support and any difficulty in reestablishing a stable post extraction warfarin level is avoided.

All the patients were advised for TXA mouthwash rinsing for post-operative 7 days[3,10,12,13,15 4,17.18,19,] as the majority of postoperative bleeding episodes in anticoagulated patients, who have undergone oral surgery, tend to occur 2 or 3 days after the initial surgery, presumably secondary to increased concentrations of plasminogen and plasminogen activators in the external oral environment with subsequent fibrinolysis, though some authors have experienced same beneficial effect of TXA mouthwash in 2 days regimen[2,20] & 5 days.[2]

Because tranexamic acid mouth rinse has minimal systemic absorption and was spit out after 2 minutes [3], it was very safe. If accidentally swallowed it does not have any significant adverse effect.

Amoxicillin as a postoperative antibiotic and Aspirin or Diclofenac Sodium as analgesics were avoided, as reported in the literature, they interrupt the effect of warfarin & increase the risk of post-operative bleeding.[21]

The major risks associated with removal of teeth in these anticoagulated patients were either uncontrolled bleeding or a thromboembolic event. Only minor bleeding occurred and this was controlled at home with pressure. No bleeding required systemic therapy or admission to hospital. No thromboembolism occurred. No medical emergencies occurred to patients during the period of the study.

In our study, Very few incidence (0 in group-I &23 in group-II) of accidental minor bleeding was reported on the 1st day after extraction, which is suggestive of antifibrinolytic activity of tranexamic acid.

In only 2 of the group-II patients were reported oozing at home on the 2nd day after extraction, who required pressure for control. This oozing was readily controlled at our department after infiltration of the adjacent mucosa with 2% lignocaine solution containing 1:80,000 adrenaline, removal of the clot, irrigation of the wound with 2.5% tranexamic acid solution, application of pressure with a swab soaked in tranexamic acid solution. No patients required hospital admission for systemic management of bleeding. (Table V)

None of 100 patients of both the groups reported bleeding episode from the 3rd day.

Other techniques for managing patients on warfarin requiring tooth extraction are potentially more complicated. An INR reduction below 2.0 cannot be guaranteed 2 days after stopping warfarin [15] and often takes 3 days. This delays treatment, increases the risk of thromboembolism, involves the patient's medical

practitioner in reducing warfarin and necessitates extra tests to re-establish the INR following surgery. If the INR on the planned day of surgery is still above 2.0, surgery maybe further delayed and requires rescheduling the operation. Removal of teeth with an INR greater than 2.0, without using antifibrinolytic mouth rinses is associated with increased bleeding and this has the potential to cause further inconvenience. Heparin substitution of warfarin requires 4- or 5-days hospitalisation (Roser and Rosenbloom, 1975). This is both expensive and inconvenient. [15]

With our study, it is suggestive that Tranexamic acid mouthwash is useful as a hemostatic agent due to its localized antifibrinolytic activity in patients on oral anticoagulant therapy & in 2.5% TXA mouthwash adverse comments like bad taste, nausea are less with few but less significant episodes of bleeding, it is be better to use low concentration (2.5%) of mouthwash when INR is low, i.e. less than 2.

Tables

Table 1: Reference values given to patients to evaluate bleeding

	Bleeding perceived				
	No bleeding	Oozing	Accidental low bleeding	Continuous low bleeding	Massive bleeding
Day- 0					
Day- 1					
Day- 2					
Day- 3					
Day- 4					
Day- 5					
Day- 6					
Day- 7					

"0" No Bleeding - The patient does not detect any blood in saliva

"1" Oozing - The patient detects a slight blood but it is not very noticeable

"2" Accidental Low Bleeding - The patient has low bleeding sometimes

"3" Continues Low Bleeding - The patient has low bleeding often

"4" Massive Bleeding - Continues high bleeding

Table 2: mean age of the patients using 5% concentration of tranexamic acid mouthwash

No. Of participants	Mean age	Std. Dev.
50	62.62	8.02

Table 3: mean age of the patients using 2.5% concentration of tranexamic acid mouthwash

No. Of participants	Mean age	Std. Dev.
50	64.82	9.05

Table 4: gender distribution of patients

Gender	No of patients
Male	57
Female	43
Total no of patients	100

Table 5: bleeding scores of patients using 5% concentration of tranexamic acid mouthwash

	Bleeding Score-0	Bleeding Score-1	Bleeding Score-2
Day-0	15	35	0
Day-1	50	0	0
Day-2	50	0	0
Day-3	50	0	0
Day-4	50	0	0
Day-5	50	0	0
Day-6	50	0	0
Day-7	50	0	0

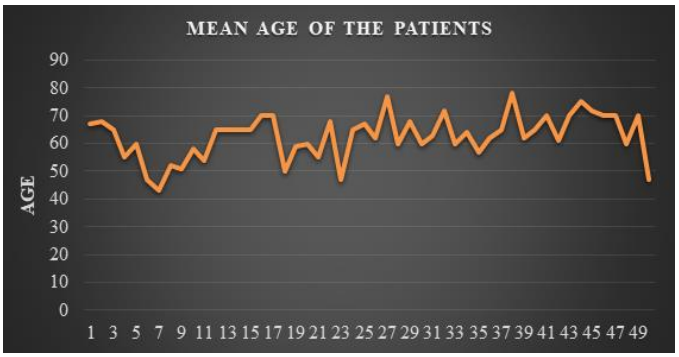
Table 6: bleeding scores of patients using 2.5% concentration of tranexamic acid mouthwash

	Bleeding Score-0	Bleeding Score-1	Bleeding Score-2
Day-0	14	31	5
Day-1	24	26	0
Day-2	48	2	0
Day-3	50	0	0
Day-4	50	0	0
Day-5	50	0	0
Day-6	50	0	0
Day-7	50	0	0

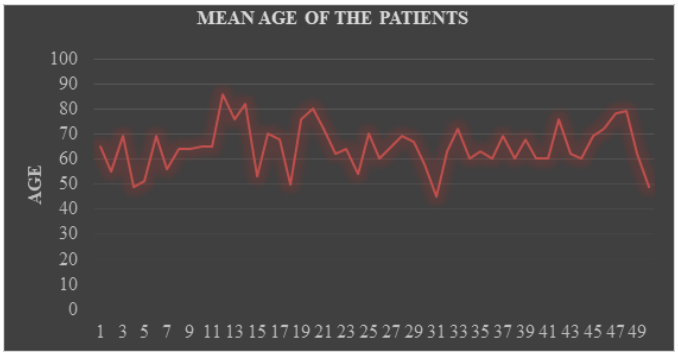
Table 7: comparison using chi-square test between 2.5 %concentration and 5% concentration of tranexamic acid mouthwash

	5 % conc. Of tranexamic acid		2.5 % conc. Of tranexamic acid	
	Observed	Expected	Observed	Expected
Bleeding score 0	365	133.33	336	133.33
Bleeding score 1	35	133.33	59	133.33
Bleeding score 2	0	133.33	5	133.33
p- value	7.75		1.92	

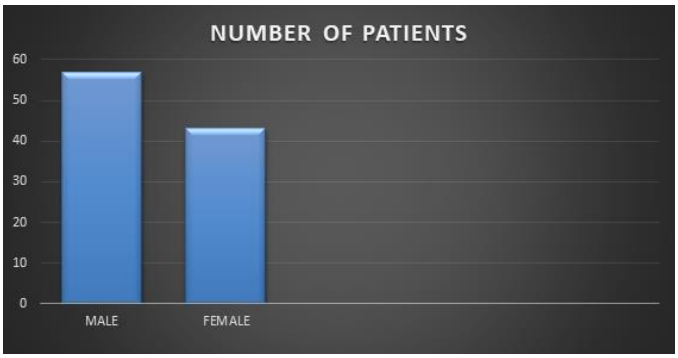
Graphs 1: mean age of the patients using 5% concentration of tranexamic acid mouthwash



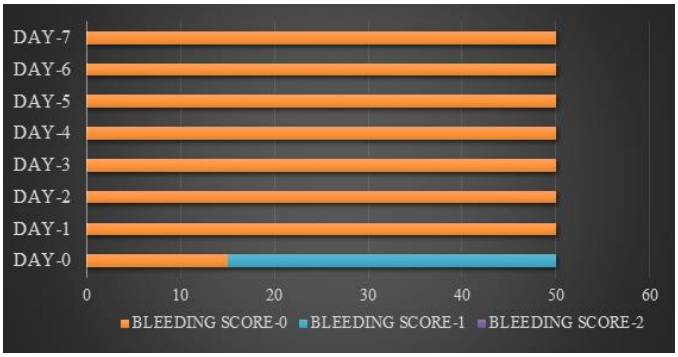
Graphs 2: mean age of the patients using 2.5% concentration of tranexamic acid mouthwash.



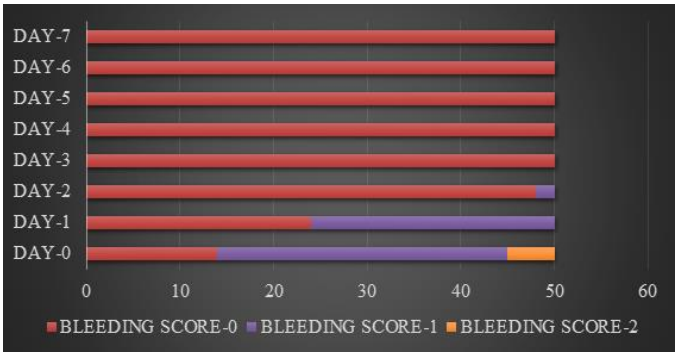
Graph 3: gender distribution of patient



Graph 4: bleeding scores of patients using 5% concentration of tranexamic acid mouthwash



Graph 5: bleeding scores of patients using 2.5% concentration of tranexamic acid mouthwash



Conclusion

We conclude by our study that in spite of continuing oral anticoagulation therapy bleeding events were significantly less in both the groups when different concentrations of tranexamic acid mouthwash are used.

This method is safe, cost effective, and clinically proven to provide hemostasis. In comparison with 5% mouthwash, in 2.5% mouthwash patients have less complains about bad taste of mouthwash, nausea, slight burning sensation, so lower concentration can be beneficial to provide hemostasis when the INR is low (i.e below 2.5) in patients with oral anticoagulation therapy.

When INR is above the therapeutic level (above 4.0), tranexamic acid mouthwash can be used in conjunction of other substitutional therapies to achieve hemostasis when oral anticoagulants therapies are continued.

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