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Tranexamic acid mouthwash—A prospective randomized study of a 2-day regimen *vs* 5-day regimen to prevent postoperative bleeding in anticoagulated patients requiring dental extractions

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Abstract. This prospective randomized study analyses the use of a prescribed 4.8% tranexamic acid post-operative mouthwash over 2 days *vs* 5 days to prevent bleeding in patients taking warfarin who require dental extractions. Eighty-five patients therapeutically anticoagulated with warfarin for various conditions, ranging in age from 21 to 86 years and requiring dental extractions, were randomly divided into two groups. Group A postoperatively received a 4.8% tranexamic acid mouthwash to be used over a 2-day period. Group B received the same mouthwash and instructions postoperatively, to be taken over 5 days. All procedures were performed on an ambulatory basis under local anaesthetic by the same surgeon. Patients were reviewed 1, 3, and 7 days postoperatively to assess bleeding. Eighty-two of the 85 patients encountered no postoperative problems. Two patients in group A and one in group B had minor postoperative bleeds that required minor ambulatory intervention to control. This study shows that a 2-day postoperative course of a 4.8% tranexamic acid mouthwash is as equally effective as a 5-day course in controlling haemostasis post-dental extractions in patient's anticoagulated with warfarin.

Key words: tranexamic acid; warfarin; dental extractions.

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Warfarin, the most commonly prescribed oral anticoagulant, is a vitamin K antagonist that impairs the synthesis of coagulation factors II, VII, IX, and X and endogenous proteins C and S in the liver, resulting in impaired fibrin formation. This coagulation defect is used to prevent thromboembolism in various recognized conditions[7]

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such as atrial fibrillation and valvular heart disease. Its effects are at the same time however, associated with an increased risk of haemorrhage.

There remains no general consensus on the appropriate peri-operative management of anticoagulation for patients who have been receiving long-term warfarin therapy[10]. In recent years, continuation of anticoagulant therapy in minor oral surgical procedures has gained more attention in the literature, emphasizing the role of local haemostasis[1–4,6,8,9,11].

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. The significant haemostatic effect of local fibrinolysis inhibition in the oral cavity has been demonstrated by utilizing a 4.8% tranexamic acid solution as a postoperative mouthwash[8]. Classically the mouthwash has been prescribed over a 7-day period postoperatively yet some authors have used shorter duration regimens[9]. The shorter course has the benefit of increased compliance and decreased cost.

In this single-blind, prospective randomized study, the effect of a 2-day *vs* 5-day regimen of a 4.8% tranexamic acid mouthrinse on patients who were therapeutically anticoagulated with warfarin and requiring dental extractions were evaluated.

Materials and methods

Patients older than 18 years of age, therapeutically anticoagulated with warfarin in the range of 2.0 to 4.0 according to the International Normalized Ratio (INR), who were referred for simple tooth extraction (single or multiple), or surgical removal of a retained tooth (single or multiple), were included in the study. Each patient gave signed informed consent as required by the institutional ethical clearance for this study. The patients were treated on an ambulatory basis with exodontia performed under local anaesthetic in the out-patient clinic. They were randomly allocated through the Royal Adelaide Hospital Pharmacy Unit by a computer-generated randomization chart to receive either a 2-day or 5-day course of a 4.8% tranexamic acid (Cyclokapron®, Pharmacia) solution to aid with haemostasis post-dental extraction. The following patients were excluded from the study:

1. Those that did not give informed consent
2. Those that were unable to comprehend the English language
3. Those that were psychiatrically or mentally impaired to give consent
4. Those who had taken aspirin or non-steroidal anti-inflammatory agents within 14 days before surgery
5. Those who had a known haemorrhagic diathesis
6. Those with a known hypersensitivity to the proposed medications including local anaesthetics used in the study

Any patient who consented to participate in the trial had the right to withdraw at any stage and was excluded from the statistical analysis.

The patient's medical history was obtained at the first visit and a standardized form was completed for each patient to record the relevant clinical data. Blood samples were taken on the day of surgery for analysis of the vitamin K-dependent coagulation factors (II+VII+IX+X), calculating the INR utilizing thromboplastin with a known international sensitivity index. The same surgeon treated all of the patients. Patients with cardiac valvular disease received prophylactic antibiotic cover according to the institutional protocol[12].

At surgery, the number of extracted teeth, number of surgically treated teeth, and type of surgery performed were recorded, as well as the duration of surgery and any complications in connection with the procedure. The analgesic drugs used in this study were paracetamol or paracetamol/codeine. All patients received local anaesthetic (2% lignocaine with epinephrine 1/80 000).

Immediately after tooth extraction, but before suturing, the surgically treated region was irrigated with an active 4.8% tranexamic acid mouthwash solution produced by the Royal Adelaide Hospital Pharmacy Department. An oxidized cellulose mesh (Surgicel®, Johnson & Johnson) was soaked in the tranexamic acid solution and then placed in the base of each tooth socket. Resorbable (4.0 Vicryl®, Ethicon) sutures were then placed over the individual sockets.

Before leaving the facility, the patients received a bag containing either 8 or 20 plastic containers each containing 10 ml of the tranexamic acid solution, a supply of analgesics, and gauze pads, postoperative instructions and a list of review appointments (1, 3 and 7 days after surgery). The patients were instructed to use the mouthwash by rinsing for 2 min four times daily, expectorating after use until all containers supplied to them were finished. They were asked not to eat or drink during the first hour after using the mouthwash, and to maintain a liquid diet on the first day after surgery.

Efficacy was monitored by: the recording of subjective bleeding; the need for further intervention to control haemostasis (e.g. alternative haemostatic agents, pharmacological control); other complications; and patient acceptance to the regimen. The monitoring of safety involved ensuring all patients fit the selection criteria, reporting any adverse side effects immediately to the Oral and Maxillofacial Surgery Unit or on-call resident. If postoperative bleeding developed that could not be controlled by compression with a gauze pad for a 20 min period with the patient sitting upright, the patient was reviewed and irrigation of the bleeding surgical site with a 4.8% tranexamic acid solution for 2 min and application of a gauze pad soaked in the solution with compressive biting force for a period of 20 min was instituted.

At the final review visit, all patients were asked whether any discomfort had developed in connection with the mouthwash. The occurrence of haematoma, oedema, and pain was recorded, as well as the ingestion of any drug not previously recorded. For a test of compliance of the mouthwash protocol, the patients were asked to return unused containers of the tranexamic acid solution.

Differences in the treatment groups with respect to postoperative bleeding necessitating intervention were analysed by the χ^2 test.

Results

Eighty-five patients, 54 males and 31 females ranging from 21 to 86 years of age, underwent a total of 152 dental extractions without cessation or dose modification of their warfarin therapy. The reasons for anticoagulation are presented in Table 1. The patient's demographics and results are presented in Table 2.

Statistically there was no significant difference at the 5% probability level in

Table 1. Indications for anticoagulant therapy in the present group of patients ($n=85$)

Diagnosis	No.	%
Atrial fibrillation	14	16
Valvular disease	33	39
Arterial thromboembolism	1	1
Venous thromboembolism	20	24
Cerebrovascular disease	10	12

postoperative bleeding between the two groups in our trial ($P=0.57$). The observed postoperative bleeding incidence of 4% in our trial is in keeping with that recorded in non-medically compromised patients undergoing routine dental extractions. The postoperative bleeding noted in three cases in our study were all associated with the presence of severe localized bone loss consistent with adult periodontitis in maxillary teeth. All patients tolerated the procedures under local anaesthetic as an outpatient. Post-surgical complications were minimal with only three cases of delayed bleeding occurring, two in group A and one in group B. All cases occurred in the first 48 hours after surgery whilst the patients were still using the mouth rinse, and involved solitary posterior maxillary tooth sockets, in teeth that were routinely delivered with forceps extraction. The common factor in all three cases was severe periodontitis as the indication for extraction, and it is possible the infection in the surrounding soft tissues and local inflammation may have contributed to these bleeds. In all three cases, the bleeding was a persistent ooze of venous origin and haemostasis was achieved by irrigating the sockets with tranexamic acid for 2 min and applying compressive biting pressure for 20 min with a gauze pack soaked in the solution. No case required resuturing, vitamin K or the infusion of fresh frozen plasma. The INR recorded on the day of the bleed was within the therapeutic range for all three patients (3.4, 2.4, 3.7).

Discussion

This study shows a similar low bleeding rate for a 2-day postoperative course of a 4.8% tranexamic acid mouthrinse as compared to the 5-day regimen.

In Sindet–Pedersen's original article[8], anti-coagulant-treated patients undergoing oral surgery, were prescribed a 4.8% aqueous solution of tranexamic acid for seven days post-surgery to prevent re-bleeding secondary to fibrinolysis of the wound clot. Indeed, the same protocol has been employed in our unit for several years and the significant haemostatic effectiveness of the mouthwash has been confirmed. Interestingly, in a study reported by SOUTO et al.[9], patients rinsed postoperatively for a period of only two days with a similar low incidence of bleeding. This study however, included small numbers of patients, reducing the possibilities of drawing useful conclusions from the data. The results of the present study confirm that anticoagulation treatment with warfarin need not be withdrawn prior to dental extractions, provided that the patients do not have a preoperative INR value greater than 4.0, and local measures including antifibrinolytic therapy is instituted.

Recently some authors have recommended that most anticoagulated patients are capable of withstanding routine, limited, oral surgery procedures without additional medical intervention such as an antifibrinolytic mouthwash provided a good surgical technique is employed[4]. However, they limit acceptable INR values for this proposal to 3.0 or less when clearly there are patients with therapeutic levels higher than 3.0 and this group tends to comprise those most at risk of serious thromboembolic events if their anticoagulation is temporarily discontinued or decreased such as prosthetic mitral valve replacement.

All patients in our study had INR measurements performed by the hospital laboratory prior to treatment, a process that required planning to avoid delays in management. The use of point-of-care-assays to monitor warfarin therapy has received attention recently, claiming several advantages over standard hospital laboratory testing[9].

We chose to use Surgicel® in this study because it is widely available, easy to handle, inexpensive and acts as a good delivery vehicle for the tranexamic acid deep into the base of the tooth sockets and subsequent blood clot after surgery. Surgicel is an oxidized regenerated cellulose preparation whose local haemostatic action depends on the binding of haemoglobin to oxycellulose, allowing the dressing to expand into a gelatinous mass, which in turn acts both as a scaffolding for clot formation and a clot stabilizer[6,7]. The material is completely absorbable and does not interfere with healing or bone regeneration.

The common factor in the three recorded cases of postoperative bleeding in our study was severe periodontitis as the indication for extraction, and it is possible the infection in the surrounding soft tissues and local inflammation may have contributed to these bleeds. Similar findings have been noted in a recent previous study[2] confirming that severe local infection with its increased vascularity is a predominant risk factor for bleeding most likely by enhancing local fibrinolysis.

A 4.8% tranexamic acid mouthwash is effective in controlling local haemostasis in anticoagulated patients undergoing dental extractions. Statistically there appears to be no difference between a prescribed two-day *vs* a five-day course.

Table 2. Demographics and statistical results of tranexamic acid mouthwash (TAMW) study 2 days *vs* 5 days

	TAMW 2 days—Group A	TAMW 5 days—Group B	Total
Gender			
Male	22	32	54
Female	21	10	31
Age range	21–77	24–86	
Median age	65.2	65.7	
No extractions			
Mandible	49	62	111
Maxilla	48	42	90
Range	1–13	1–16	
Reason for exodontia			
Periodontal disease	47	41	88
Caries	48	61	109
Other	3	1	4
INR Mean	2.7	2.8	
Postop bleed*			
Mandible	0	0	0
Maxilla	2	1	3

*Statistical method=χ^2, df=1.0, 0.32.

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