Tranexamic Acid Mouthwash Versus Autologous Fibrin Glue in Patients Taking Warfarin Undergoing Dental Extractions: A Randomized Prospective Clinical Study

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Purpose: The aim of this prospective study was to compare the effectiveness of a 4.8% tranexamic acid mouthwash versus an autologous fibrin glue preparation to control hemostasis in patients therapeutically anticoagulated with warfarin who required dental extractions without interruption of their treatment.

Patients and Methods: The 49 patients who underwent 152 dental extractions were randomly allocated to 2 groups: Group A were required to rinse with 10 mL of a 4.8% tranexamic acid solution 4 times a day for 7 days postoperatively. Group B received autologous fibrin glue intraoperatively. The international normalized ratio was measured on the day of the procedure. All procedures were performed on an ambulatory basis by the same surgeon.

Results: Of the 49 patients, 2 presented with postoperative bleeding (4%). Both patients were from the autologous fibrin glue group and were found to have grossly elevated international normalized ratios on the day of the bleeding that was unaccounted for.

Conclusions: This study supports the consensus that dental extractions can be performed without modification of oral anticoagulant treatment. Local hemostasis with an absorbable oxidized cellulose mesh, tranexamic acid, and sutures is the more cost efficient of the 2 methods compared; however, autologous fibrin glue has an important role in patients unable to use a mouthwash effectively.
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Patients receiving oral anticoagulant therapy who undergo minor oral surgical procedures may have prolonged and excessive hemorrhage. 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.[1] Various protocols have been suggested for treating these patients, including substituting heparin for warfarin,[2] decreasing the level of anticoagulation preoperatively,[3] temporarily stopping the warfarin,[4] and not altering the anticoagulant regimen at all.[5-13] 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.

The purpose of this study was to compare 2 local agents that aid hemostasis, following minor oral surgery in patients therapeutically anticoagulated with warfarin. The alternative regimens will, we hope, eliminate the need to interfere with anticoagulation regimes, minimize associated risks, and decrease hospital admissions along with their associated physical and social inconveniences.

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Materials and Methods

A group of 49 patients (31 men and 18 women; age range, 24 to 85 years; mean age, 65 years) underwent 152 dental extractions. All patients were therapeutically anticoagulated with warfarin, and no modification in dosage was undertaken. The indications for anticoagulation included atrial fibrillation (12 patients), valvular heart disease (19 patients), arterial thromboembolism (2 patients), venous thromboembolism (8 patients), recurrent transient ischemic attacks (3 patients), and ischemic heart disease (5 patients). Patients were randomized to receive either a 4.8% tranexamic acid mouthwash or an autologous fibrin glue (AFG) preparation to aid with local hemostasis. All patients were treated on an ambulatory basis in the Oral and Maxillofacial Surgery Unit of the Adelaide Dental Hospital. The procedures were all performed under local anesthetic (2% lignocaine with 1:80,000 epinephrine) by the same surgeon. Blood samples were taken on the day of surgery to evaluate the anticoagulant activity by calculating the international normalized ratio (INR). Only patients with an INR of $\geq$2.0 and $\leq$4.0 were included in the study. Patients with cardiac valvular disease received antibiotic coverage according to the institutional protocol. At surgery, the number of extracted teeth, number of surgically treated teeth, duration of surgery, and complications in connection with the procedure were recorded. The analgesic drugs used in this study were paracetamol or paracetamol/codeine. Patients who 1) had not given informed consent, 2) ingested acetylsalicylic acid or nonsteroidal agents within 14 days before surgery, 3) had a known hemorrhagic diathesis, 4) had a known hypersensitivity to products of bovine origin, or 5) had a known hypersensitivity to all proposed local anesthetic agents were excluded from the study.

GROUP A: TRANEXAMIC ACID MOUTHWASH

An active, 4.8% tranexamic acid (Cyclokapron; Pharmacia, New York, NY) mouthwash solution was produced by the Royal Adelaide Hospital Pharmacy Department. Immediately after tooth extraction, the sockets were irrigated with 10 mL of the tranexamic acid solution. An absorbable oxidized cellulose mesh (Surgicel; Johnson & Johnson, New Brunswick, NJ) was soaked in the solution and then placed in the apical third of each socket before placement of a resorbable suture (4.0 Vicryl; Ethicon, Cornelia, GA). Before leaving the department, the patients received 27 containers, each containing 10 mL of tranexamic acid solution (7-day course), written information regarding its correct use, a supply of analgesics, and gauze pads. Patients were instructed to use the mouthwash by rinsing for 2 minutes 4 times daily, expectorating after use, until all containers were used.

GROUP B: AUTOLOGOUS FIBRIN GLUE

AFG was prepared by the Royal Adelaide Hospital Transfusion Medicine Unit. Patients randomly allocated to this group were required to present 1 to 2 weeks before surgery to have approximately 80 mL of blood collected at the Haematology Day Centre. When the AFG was required for surgery, component 1 (autologous fibrinogen, factor XIII, and fibronectin dissolved in a sterile calcium chloride solution that had been stored in the frozen state at $-70°C$) was thawed and then transferred with component 2 (bovine thrombin and ϵ-aminocaproic acid) into separate sterile vials and issued. A specialized fibrin glue applicator kit (Fibrijet; Micromedics, Eagan, MN) comprising a twin-syringe assembly was used to apply the AFG to the wound site, where a fibrin mass resulted on mixing. Immediately after extraction of a tooth, the socket was curetted and then suctioned to keep the site as dry as possible. Surgicel was placed in the apical third of each socket. Fibrin glue was applied to the socket walls, followed by the placement of a suture. A final application of the glue was then placed over each socket to seal any gingival bleeding.

All patients in both groups were asked not to eat or drink in the first hour after surgery and advised of a liquid diet on the first day after surgery. Patients were given a list of postoperative instructions and were reviewed at 1, 3, and 7 days postsurgery. At the final visit, all patients were asked whether any discomfort had developed in connection with the mouthwash or fibrin glue. The occurrence of hematoma, edema, and pain was recorded as well as the ingestion of any drug not previously recorded. Patients were instructed to contact the department or on-call oral and maxillofacial surgery resident if they experienced any adverse event or postoperative bleeding that could not be controlled by compression with a gauze pad for 20 minutes with the patient sitting upright.

Differences in the treatment groups with respect to postoperative bleeding necessitating intervention were analyzed by the chi-squared test.

Results

The results of the trial are presented in Table 1. In group A (tranexamic acid), 26 patients with INRs ranging between 2.3 and 4.0 underwent 71 dental extractions. The causes for extraction were severe periodontitis in 33 teeth and deep caries in 38 teeth. There were no postoperative bleeding complications reported in this group.

In group B (AFG), 23 patients with INRs ranging between 2.1 and 4.0 underwent 81 dental extrac-

Table 1. PATIENTS THERAPEUTICALLY ANTICOAGULATED WITH WARFARIN UNDERGOING DENTAL EXTRACTIONS (N = 49 PATIENTS)

	Group A (Tranexamic Acid)	Group B (Autologous Fibrin Glue)	Total
Gender			
Male	16	15	31
Female	10	8	18
Age range (yr)	24-85	40-83	
No. of extractions			
Mandible	46	32	78
Maxilla	25	49	74
Range	1-13	1-18	
Reason			
Periodontal disease	33	27	60
Caries	38	54	92
INR			
Mean	3.0	3.1	
Range	2.3-4.0	2.1-4.0	
Postoperative bleed (n)*			
Mandible	0	0	0
Maxilla	0	2	2
INR mean for postoperative bleed		6.7 (range, 5.9-7.6)	

*χ^2, df = 1.0, 2.36.

tions. The causes for extraction were severe periodontitis in 27 teeth and deep caries in 54 teeth. Two cases of light bleeding, both occurring on the second day postsurgery, necessitated intervention. Both cases involved maxillary molar teeth that had severe periodontal involvement. Successful hemostasis was achieved with biting pressure and gauze packs followed by reapplication of the patient's own stored AFG. Interestingly both of these patients were found to have grossly elevated INRs on postoperative presentation for bleeding (5.9 and 7.6), necessitating warfarin dosage adjustment after consultation with their local medical officer.

Statistically there was no significant difference at the 5% probability level in postoperative bleeding between the 2 groups in our trial (P = .12).

Discussion

In recent years, continuation of anticoagulant therapy in oral surgical procedures has gained more attention in the international literature, emphasizing the role of local hemostasis.[5-13] There remains, however, a lack in consensus of treatment methods to secure this local hemostasis. Hemostasis in the oral cavity is dependent on the dynamic balance between fibrin formation and resolution and is influenced by the external environment, which contains both plasminogen and plasminogen activators.[14]

Tranexamic acid impedes the proteolytic degradation of fibrin by preventing the attachment of plasminogen and plasmin. A 4.8% solution has been proven to be very effective in reducing bleeding complications with negligible systemic absorption.[7] Fibrin sealant, on the other hand, simulates the last stages of the coagulation cascade, that is, the conversion of fibrinogen to fibrin.[15] The 2-component system often has an antifibrinolytic agent (eg, tranexamic acid), added to impede fibrinolysis following surgery. Despite the appealing attributes of this system, and the fact that it has been used for local hemostasis enhancement after dental extractions for over 2 decades,[15-19] it has failed to gain widespread acceptance.

The obvious advantage of local inhibition of fibrinolysis in anticoagulated patients is the simplicity and effectiveness of the treatment combined with the lack of severe side effects. Because the anticoagulant therapy is not discontinued, the patient is not exposed to potential complications such as thromboembolism and its consequences.[1] Hemostasis can be achieved quickly and safely with no greater complication risk than that observed in routine cases.

In all the cases in our study there was no need for hospitalization before surgery. Hence, patients did not need to be subjected to multiple venipunctures, nosocomial infection risks, or the social issues that arise when they are separated from their usual familiar environment. Moreover, the exodontia could be performed over several appointments if required, reducing the need to expose these medically compromised patients to the stress of multiple extractions.

In the present study, postoperative bleeding was observed in the AFG group only. However, both of these patients had significantly elevated INRs of uncertain etiology accounting for this bleeding. The first patient had an initial INR of 3.6 on the day of surgery and commenced bleeding on the seventh day postsurgery with a minimal ooze of approximately 12 hours' duration and a repeat INR recorded at 5.9. The second patient had an initial INR on the day of surgery of 2.2 and experienced a minor postoperative bleed on the third day postsurgery of approximately 8 hours' duration with a recorded INR of 7.9. Interestingly, both patients had multiple teeth extracted at the initial surgery, yet only 1 socket site was responsible for the postoperative bleed. Both cases involved maxillary teeth that were periodontally involved and routinely removed with forceps. The patients denied ingestion of postoperative antibiotics, over-the-counter medications, or herbal products that may have potentially interacted with warfarin. Although compliance with regular warfarin dosaging is the most likely explanation for the anticoagulation, both patients denied changes in their usual warfarin dose or dietary modifications. Because the amount of bleeding was minimal with nonnecessity for fluid replacement, control with simple local measures and bleeding from only 1 extraction site in patients who had multiple teeth

extracted at the same appointment, the existence of a consumption coagulopathy was deemed unlikely.

From a cost-evaluation perspective, the elimination of the need for hospitalization dramatically reduces the financial cost of the procedure. In Australia the average cost of a 200-mL bottle of tranexamic acid mouthwash is Aus $15, whereas AFG costs approximately Aus $300. When compared with the previously used protocol of heparinization and inpatient hospitalization costing on average Aus $2500, the savings are very significant.

In conclusion, both tranexamic acid mouthwash and AFG can be used successfully to control postoperative bleeding in patients therapeutically anticoagulated with warfarin requiring dental extractions. Both techniques are safe, cost effective, and clinically proven methods of providing hemostasis. Overall, tranexamic acid mouthwash has several advantages over AFG for simple dental extractions, namely: low cost and ready availability and therefore we recommend this treatment modality unless compliance is an issue, in which case, AFG should be used.

References

1. Kearon C, Hirsch J: Management of anticoagulation before and after elective surgery. N Engl J Med 336:1506, 1997
2. Roser SM, Rosenbloom B: Continued anticoagulant in oral surgery procedures. Oral Surg Oral Med Oral Pathol 40:448, 1975
3. Johnson WT, Leary JM: Management of dental patients with bleeding disorders: Review and update. Oral Surg Oral Med Oral Pathol 66:297, 1988
4. Mulligan R, Weitzel KG: Pretreatment management of patients receiving anticoagulant drugs. J Am Dent Assoc 117:297, 1988
5. Blinder D, Manor Y, Martinowitz U, et al: Dental extractions in patients maintained on continued oral anticoagulant: Comparison of local haemostatic modalities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88:137, 1999
6. Wahl M: Dental surgery in anti-coagulated patients. Arch Intern Med 158:1610, 1998
7. Sindet-Pedersen S, Ramstrom G, Bernvil S, et al: Haemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 320:840, 1989
8. Borea G, Montebugnoli L, Capuzzi P, et al: Tranexamic acid as a mouthwash in anticoagulant-treated patients undergoing oral surgery. An alternative method to discontinuing anticoagulant therapy. Oral Surg Oral Med Oral Pathol 75:29, 1993
9. Devani P, Lavery K, Howell C: Dental extractions in patients on warfarin: Is alteration of anticoagulant regime necessary? Br J Oral Maxillofac Surg 36:107, 1998
10. Beirne O, Koehler J: Surgical management of patients on warfarin sodium. J Oral Maxillofacial Surg 54:1115, 1996
11. Souto JC, Oliver A, Zuazu-Jausoro I, et al: Oral surgery in anti-coagulated patients without reducing the dose of oral anticoagulant: A prospective randomised study. J Oral Maxillofac Surg 54:27, 1996
12. Webster K, Wilde J: Management of anticoagulation in patients with prosthetic heart valves undergoing oral and maxillofacial operations. Br J Oral Maxillofac Surg 38:124, 2000
13. Campbell J, Alvarado F, Murray R: Anticoagulation and minor oral surgery: Should the anticoagulation regimen be altered? J Oral Maxillofacial Surg 58:131, 2000
14. Sindet-Pedersen S: Haemostasis in oral surgery—The possible pathogenetic implications of oral fibrinolysis on bleeding. Dan Med Bull 38:427, 1991
15. Matras H: Fibrin seal: The state of the art. J Oral Maxillofac Surg 43:605, 1985
16. Wepner F, Fries R, Platz H: The use of the fibrin adhesion system for local haemostasis in oral surgery. J Oral Maxillofac Surg 40:555, 1982
17. Zusman S, Lustig J, Baston I: Postextraction haemostasis in patients on anticoagulant therapy: The use of a fibrin sealant. Quintessence Int 23:713, 1992
18. Rakocz M, Mazar A, Varon D, et al: Dental extractions in patients with bleeding disorders: The use of fibrin glue. Oral Surg Oral Med Oral Pathol 75:280, 1993
19. Davis B, Sandor G: Use of fibrin glue in maxillofacial surgery. J Otolaryngol 27:107, 1998