

# Randomized Clinical Trial Comparing Three Local Hemostatic Agents for Dental Extractions in Patients under Chronic Anticoagulant Therapy - A Comparative Study

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## Abstract

**Introduction:** Oral anticoagulants are widely used worldwide for many systemic diseases. Recent oral surgical protocols suggest that therapeutic levels of the anticoagulant drug should be maintained for simple dental extractions because bleeding complications could be managed with proper local hemostasis. The aim of the present study was to compare bleeding complication of three different local hemostatic agents for dental extractions without interrupting drug administration in patients undergoing oral Vitamin K antagonist chronic anticoagulant therapy. **Material and Methods:** Randomized control trial of three hemostatic agents for dental extractions, in patients under oral anticoagulant therapy without drug interruption. The present study included 240 patients with international normalized ratio between 1.5 and 3.5. Patients took their anticoagulation drug normally. A single surgeon performed calibrated simple dental extractions and applied a plug of bismuth subgallate (BS), fibrin tissue adhesive (FTA) or microfibrillar collagen (MC), assigned randomly. Statistical analysis of bleeding between the groups was performed using the Chi-square test. **Results:** There was no hemorrhagic complication in the BS group, and only one in the FTA group. However, in the MC group, 10 patients (12.5%) suffered postoperative bleeding. Data analysis showed statistical differences between the MC group and the other two groups ( $P < 0.05$ ). **Discussion:** BS and FTA showed similar clinical effectiveness and were more effective than MC for the control of postoperative bleeding in oral anticoagulated patients.

**Keywords:** Bismuth subgallate, chronic anticoagulant therapy, dental extraction, fibrin tissue adhesive, hemorrhage, hemostatic agent, microfibrillar collagen

## INTRODUCTION

Secondary bleeding after dental surgeries can lead to emergency presentation, occurring most often in anticoagulated patients.<sup>[1,2]</sup> Vitamin K antagonists are oral anticoagulant agents derived from 4-hydroxy-coumarin that reduce plasma concentration of coagulation factors II, VII, IX a and X.<sup>[3]</sup> These drugs reduce the risk of thromboembolism, but increase the risk of hemorrhage. They are used on patients with deep-vein thrombosis, pulmonary embolism, mitral valve prolapse with regurgitation, atrial fibrillation, rheumatic heart disease, or mechanical cardiac valve prosthesis, as well as after cerebrovascular occlusions or myocardial infarction.<sup>[3]</sup> Dental extraction is often performed on patients who take different oral anticoagulant treatments. Conventionally, treatment protocol included discontinuation of the oral anticoagulant drug for several days immediately before the surgery, bridging it with

heparin.<sup>[4,5]</sup> The management of dental extraction in patients receiving oral anticoagulation has changed in recent years because of the risk: benefit ratio of a postextraction hemorrhage or a potentially deadly thromboembolic episode.<sup>[6]</sup> Therefore, the current trend for patients who take oral anticoagulants and need minor oral surgery is to maintain the anticoagulation therapy and improve the hemostatic process by using local hemostatic agents.<sup>[3,7]</sup> Several local hemostatic agents have

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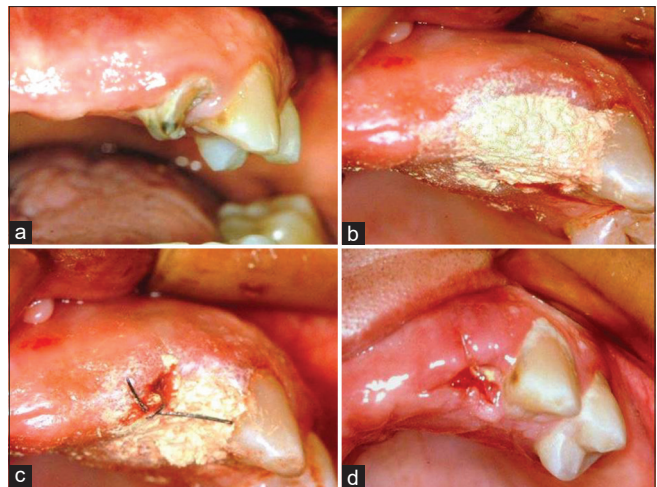
been used after tooth extractions in patients under sustained anticoagulation therapy, such as tranexamic acid, fibrin tissue adhesive (FTA), microfibrillar collagen (MC), or gelatin sponge.<sup>[5,7]</sup> However, no data exist in the literature on the clinical use of bismuth subgallate (BS) as a local anticoagulant agent in dental extractions.

The aim of the present study was to perform a clinical evaluation of the effectiveness of three hemostatic agents—BS, FTA, and MC in dental extractions in patients undergoing chronic oral anticoagulant therapy, without drug interruption.

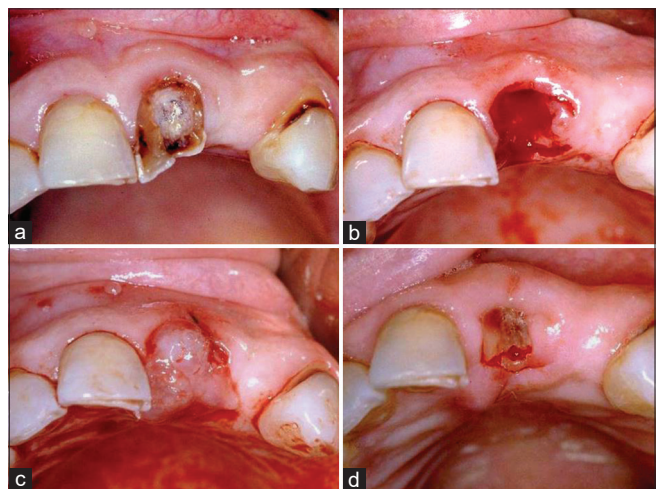
## PATIENTS AND METHODS

Patients under chronic oral Vitamin K antagonist anticoagulant therapy that presented to the Oral Surgery Department in Buenos Aires, Argentina, from March 2014 to December 2018, were included in the study. The study design was approved by the Ethical Committee of the University of Buenos Aires (Research Ethics Committee No. 006 CD48607), in accordance with its ethical guidelines of declaration of Helsinki. Written informed consent was obtained before the study. The inclusion criteria for this study were: age >18 years, patients under chronic oral Vitamin K antagonist treatment, simple dental extractions, and signature of informed consent form. The exclusion criteria were: medical conditions contraindicating surgery (such as uncontrolled systemic diseases), patients under chronic new oral anticoagulant drugs (such as rivaroxaban, apixaban, or endoxaban), patients unable to receive any standard medications, third molar surgeries, patients with an international normalized ratio (INR) value lower than 1.5 or higher than 3.5, patients with hepatic disease or taking drugs able to affect hepatic functions.

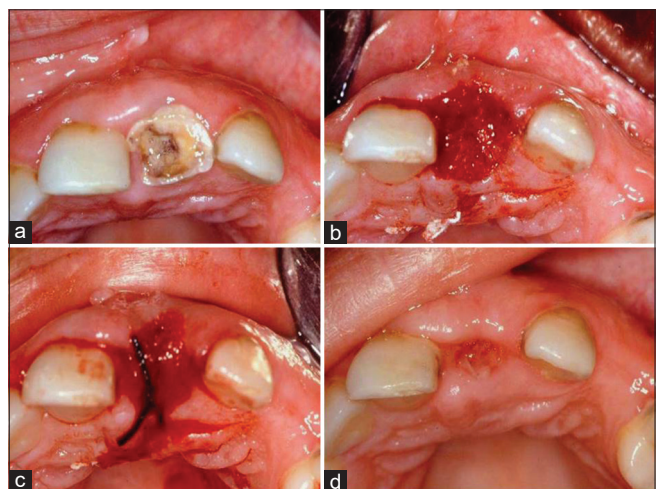
A clinical research comparing three treatment groups, with randomly allocation was designed. The patients underwent clinical and radiographic examination and their systemic coagulant situation was evaluated. The etiologies of extractions were advanced dental caries or periodontal disease. None of the patients interrupted their systemic anticoagulant therapy. INR values at the time of surgery were recorded. Prophylactic antibiotic treatment was applied if patients were at risk of bacterial endocarditis according to the standardized guideline of the American Heart Association.<sup>[8]</sup> Patients were randomly allocated to one of three groups ( $n = 80$ ) by using a random numbers function in Microsoft Office Excel software, and their identifications kept inside envelopes numbered according to the order in which they presented for surgery. Group 1 was treated with BS [Figure 1], Group 2 with FTA [Figure 2], and Group 3 with MC [Figure 3]. A single professional, trained in dealing with patients with bleeding disorders, performed the extractions. Surgeries consisted of applying local anesthesia (4% articaine chlorhydrate and 1:100,000 adrenaline), intracrevicular incision, gentle dissection of the gingiva, no surgical flap, no ostectomy, using elevator and forceps. After extraction, wound toilette was performed, and the local hemostatic plug was placed in the socket. BS powder



**Figure 1:** Bismuth subgallate. (a) Presurgical; (b) Bismuth subgallate; (c) Simple suture; (d) 7 days postoperative



**Figure 2:** Fibrin tissue adhesive. (a) Presurgical; (b) Surgical lodge; (c) Fibrin tissue adhesive and a simple suture; (d) 7 days postoperative



**Figure 3:** Microfibrillar collagen. (a) Presurgical; (b) Microfibrillar collagen; (c) A simple suture; (d) 7 days postoperative



was mixed with physiological solution in a ratio of 0.5 g of BS every 0.3 ml of liquid, making a paste to completely filling the socket. FTA was placed with a mixer disposable syringe; applied from the apical to the coronal portion of the socket completely filling it. MC pellets were embedded in blood, and packed in the socket. Finally, the wound was sutured. All patients received the same postoperative indications, which included cold soft diet for 48 h, intermittent local application of cold, and no use of mouth rinses, aspirin or nonsteroid anti-inflammatory drugs. Paracetamol was administered for pain relief. Patients were instructed to contact the service immediately if a hemorrhagic episode developed. Patients were checked 30 min after the surgery to evaluate the presence of immediate hemorrhages, and a compressive pack was applied for 4 h. A different professional, who was not involved in the surgery, checked patients during the whole week, evaluating the presence of mediate hemorrhages. At 7<sup>th</sup> day after the surgery, sutures were removed.

A previously established standard protocol was used to compile the following data for all patients: age, gender, reason for anticoagulant therapy (secondary variables), INR, Quick test (confounder variables), immediate hemorrhage, and mediate hemorrhage (primary variables). There was no dropout. Statistical analysis included descriptive statistics of numerical variables, including arithmetic mean, standard deviation, minimum and maximum (range). INR and quick values were compared between groups with Kruskal–Wallis test. The association between the categorical variables was examined using the Pearson’s Chi-square. Statistical analysis was performed with the SPSS software (SPSS version 12.0, Chicago, IL, USA). The level of statistical significance was set at 0.05. The sample size was estimated with the data analysis of the first 60 patients.

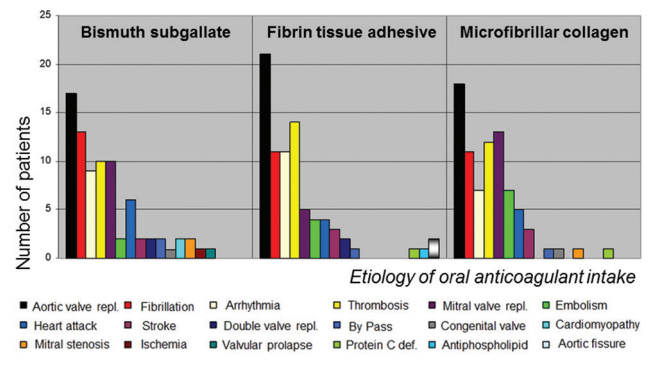
**RESULTS**

Two hundred and sixty-seven extractions were performed on 240 patients (94 males and 146 females) aged 36–94 years (mean 60.5 ± 14.5 years). The most frequent reason for being under anticoagulant therapy was aortic valve replacement in all groups [Table 1]. Mean INR value was 2.62, and mean quick test value was 26.80%. No patient from any of the three groups (BS, FTA or MC) experienced immediate postoperative bleeding, but 11 patients suffered mediate postoperative bleeding complications [Table 2].

In group BS (mean INR 2.56 ± 0.6, mean quick test 27.5% ± 9.7), no bleeding complication was observed during the whole week (0%).

In group FTA (mean INR 2.71 ± 0.5, mean quick test 25.1% ± 7.3), a single postoperative bleeding complication was observed (1.25%) 24 h after 4 teeth were extracted in a 62-year-old man (INR 3.02) who was taking acenocoumarol to treat a mitral and aortic valve replacement. Hemorrhage was controlled through clinical maneuvers which consisted of BS pack replacement and local compressive pack soaked in antifibrinolytic drug.

**Table 1: Etiology of oral anticoagulant therapy in three groups**



**Table 2: Dental surgeries per group**

GROUPS	NUMBER OF EXTRACTIONS	INR MEAN (SD)	IMMEDIATE BLEEDING	MEDIATE BLEEDING
Bismuth subgallate n = 80	91	2.56 (±0.6)	0	0
Fibrin tissue adhesive n = 80	91	2.71 (±0.5)	0	1 -1.25%
Microfibrillar collagen n = 80	85	2.59 (±0.54)	0	10 -12.50%

\* P < 0.05

In group MC (mean INR 2.59 ± 0.54, mean quick test 27.8% ± 8.6), 10 postoperative bleeding complications were observed (12.5%) (mean INR 2.6 ± 0.57). Three bleeding complications were observed during the first 24 h, six during the second postoperative day, and one during the 3<sup>rd</sup> day. Three bleeding complications occurred in the maxilla and seven in the mandible; four were in anterior teeth and six in posterior teeth. The etiologies of extraction were caries in six patients and periodontal disease in four patients. Three bleeding complications were controlled through local pressure with gauze soaked in antifibrinolytic for 3 h, and seven complications were controlled through wound curettage and replacement of a hemostatic plug and suture.

None of the mediate postoperative bleeding required hospitalization, blood transfusion or any further local clinical maneuvers to stop the bleeding. No thromboembolic complication or infectious endocarditis was observed.

INR and quick test values did not differ statistically among groups (P > 0.05). Postoperative bleeding complication in groups SB and FTA differed statistically (P < 0.05) from group MC, which presented significantly more bleeding complications.

**DISCUSSION**

Patients under chronic oral anticoagulant therapy who require dental extraction pose a problem for dental surgeons because there is no international consensus for their surgical

management. Conventionally, the anticoagulant therapy was either suppressed from 2 to 6 days before surgery or the dose of the anticoagulant was reduced to obtain sub-therapeutic levels in plasma, or even replaced by heparin.<sup>[4,5]</sup> These protocols have changed, mainly due to the fact that they often require hospitalization and even worse, because of the enhanced risk of thromboembolism. In recent years, the continuation of the oral anticoagulant regime during the course of oral surgery procedures has gained more attention in the literature, which emphasizes the role of local hemostasis.<sup>[3,6,7,9]</sup> Several local hemostatic agents have been used after tooth extractions in patients under sustained anticoagulation therapy,<sup>[9-12]</sup> however, no data exist in the literature on the clinical use of BS as a local anticoagulant agent for the use in dental extractions.

FTA (also referred to as fibrin glue or fibrin sealant adhesive) is composed of fibrinogen, thrombin, factor XIII and anti-fibrinolytics, including aprotinin or tranexamic acid. When these components are combined, they mimic the final stages of the physiological process that cleaves fibrinogen and transforms it into fibrin polymers under the action of thrombin. Factor XIII, activated by thrombin in the presence of Ca<sup>2+</sup>, cross-links the fibrin polymers into a stable, insoluble fibrin clot.<sup>[10]</sup> For patients treated with FTA, some studies report bleeding incidence in approximately 4%,<sup>[13,14]</sup> while another reports 8.7%.<sup>[15]</sup> In the current study, bleeding incidence was 1.25%, as only one patient presented bleeding 24 h after the surgery. The disadvantages of FTA are the possibility of an anaphylactic reaction or the onset of acquired bleeding diathesis secondary to exposure to bovine factor V.<sup>[16]</sup> These complications were not observed in the present study. Furthermore, its high price considerably increases the cost of dental extraction.

MC (or textured collagen), either porcine or bovine, has a reticular arrangement that enables the entrapment and subsequent aggregation of circulating platelets, activation of coagulation factor XII (Hageman Factor), and stabilization of fibrin filaments. Moreover, the micro fibrils swell in contact with the water fraction of blood, thus adhering to the affected area and creating effective vascular cement that physically obstructs the capillary vessels, decreasing postoperative pain and improving the clinical aspects of the wound.<sup>[17]</sup> Bublitz *et al.*<sup>[9]</sup> have reported 19% incidence of postoperative bleeding in patients under an anticoagulant regime treated locally with MC, and similar incidence was observed in the present study, at 12.5%.

Another commonly used antifibrinolytic drug is tranexamic acid, which is a synthetic derivative of lysine that reversibly binds to lysine receptors on plasminogen and plasmin molecules, thus interfering with the fibrinolytic process. Some studies have demonstrated its effectiveness in the control of postoperative bleeding when used in the form of mouthwash.<sup>[12,18]</sup>

BS is an insoluble compound that has been extensively used in the past in the treatment of a range of disorders such as Vincent's angina and syphilis, reducing colostomy odor, and cleaning open

wounds. BS has hemostatic properties, acting on coagulation factor XII (Hageman factor), thus leading to the activation of the coagulation cascade and improving early formation of the fibrin clot. It behaves as a light astringent, precipitating vascular proteins that may obliterate the small capillary vessels. Previous studies in rats showed that BS does not interfere with the wound-healing process<sup>[19,20]</sup> or postextraction bone healing.<sup>[21]</sup> Good hemostasis has been achieved by using the drug as local hemostatic in tonsillectomy<sup>[22]</sup> and in dentistry as topical hemostatic agent at palatal donor sites.<sup>[23]</sup> One of its main advantages, particularly in underdeveloped or developing countries, is its low cost. BS appears to be as effective as FTA in preventing postextraction hemorrhage. Both BS and FTA are more effective than MC for controlling postoperative bleeding in anticoagulated patients, as the results of this clinical trial have shown. BS could be considered an alternative to FTA as a local anticoagulant agent for the prevention of bleeding complication after simple dental extractions in orally anticoagulated patients.

In cases of multiple dental extractions, it is prudent to realize single tooth extraction surgeries, to reduce the chances of bleeding complications.<sup>[24]</sup> The single postoperative bleeding complication in FTA group observed in this study corresponded after the extraction of four teeth in the same surgery.

Our findings support previously published studies in that severe postoperative hemorrhage does not generally constitute a problem after dental extraction in patients receiving anticoagulant drugs, and who are treated under local analgesia on an outpatient basis with local maneuvers.<sup>[3,7]</sup> Simple dental extractions in orally anticoagulated patients can be performed without interrupting their anticoagulation drug by applying local hemostatic maneuvers. Future researches will explore the influence of INR values on postsurgical bleeding.

## CONCLUSION

This clinical trial showed significantly lower postoperative bleeding complication when BS or FTA plugs were used than when MC plugs were used.

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## Conflicts of interest

There are no conflicts of interest.

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