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Intra-alveolar epsilon-aminocaproic acid for the control of post-extraction bleeding in anticoagulated patients: randomized clinical trial

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Abstract. The aim of this study was to compare the effectiveness of the intra-alveolar administration of epsilon-aminocaproic acid (EACA) and daily gentle rinsing with EACA mouthwash with that of routine postoperative procedures for the control of bleeding after tooth extraction in anticoagulated patients. A randomized clinical trial was conducted involving 52 patients submitted to 140 tooth extractions, assigned randomly to two groups. The intervention group was treated with intra-alveolar administration of EACA immediately after surgery and gentle rinsing with EACA mouthwash during the postoperative period. The control group received routine postoperative recommendations. A single episode of immediate bleeding occurred in the intervention group. Late bleeding episodes occurred in 23 procedures (16.4%): 11 (15.7%) in the intervention group and 12 (17.1%) in the control group. Among the patients with late bleeding, 18 (78.3%) events were classified as moderate and were controlled by the patient applying pressure to a gauze pack placed over the extraction socket. The remaining five cases (21.7%) required re-intervention. No statistically significant difference in the frequency of postoperative bleeding was observed between the groups. Thus, routine measures were as effective for the control of bleeding after simple tooth extractions in anticoagulated patients as the topical administration of EACA.

Key words: epsilon-aminocaproic acid; anticoagulated patients; tooth extractions.

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Among the candidates for oral surgical procedures, anticoagulated patients are at greater risk of intraoperative and postoperative bleeding. However, although the maintenance of anticoagulation therapy poses a high risk of bleeding, its discontinuation increases the risk of thromboembolic complications[1]. Therefore, the management of these patients should be based on the probability of bleeding after a procedure and on the risk of thromboembolic complications, particularly among high-risk patients (e.g., those with prosthetic heart valves or high venous thrombotic risk)[2,3].

Warfarin sodium is an oral anticoagulant used widely to reduce the risk of thrombotic events. This drug is a vitamin K antagonist and, therefore, interferes with haemostasis by inhibiting factors II, VII, IX, and X and anticoagulation proteins C and S. Since the effect of warfarin sodium is influenced by the intake of certain foods and by other drugs (mainly non-steroidal anti-inflammatory drugs, antibiotics, and antifungals), it is sometimes necessary to adjust the dose to ensure proper anticoagulation. Routine laboratory follow-up to assess the prothrombin time (PT) and the international normalized ratio (INR) should also be conducted. Most medical conditions should have an INR between 2.0 and 3.0 for effective anticoagulation[4,5].

Recent studies have demonstrated a low risk of bleeding in warfarin-treated patients with INR in the therapeutic range undergoing certain dental procedures, including simple extractions (up to three teeth), small biopsies, crown lengthening, and root planing and scaling. When bleeding occurs, it is easily controlled with local haemostatic measures, so it is important that a minimally invasive surgical technique is chosen and that postoperative care is optimized[6–8]. Several studies advocate this practice and claim that an INR of up to 4.0 is sufficiently safe to treat these patients[9–11]. In patients with an INR <3.0, bleeding can be controlled by merely applying local pressure, with no need for additional haemostatic measures[12].

In the case of bleeding complications, different measures are proposed to stop the bleeding, including fibrin glue, oxidized cellulose, haemostatic sponges, sutures, and compression of the surgical wound with gauze with or without the addition of an antifibrinolytic agent (e.g., tranexamic acid (TXA) or epsilon-aminocaproic acid (EACA))[7,12–15].

Haemostatic mouthwashes have been proven efficacious in the control of postoperative bleeding in anticoagulated patients, even among those for whom anticoagulant therapy was not modified or discontinued[9,16]. TXA is the most widely used antifibrinolytic agent and also the one whose use as a mouthwash has been investigated most extensively. While several treatment regimens and different concentrations have been proposed, the use of this drug within the first 2 days after surgery has proven efficient in the control of bleeding[17]. There is little evidence of the use of EACA as a local haemostatic agent in these patients; however, it could be administered as an antifibrinolytic agent in countries where TXA is not readily available[14,18].

Antifibrinolytics act by competitively inhibiting the activation of plasminogen and by inhibiting plasmin, which reduces the fibrinolytic activity of the latter, increasing the blood clotting efficiency. In addition to mouthwashes, crushed tablets applied as a paste (mixed with sterile saline or anaesthetic solution) can be used directly on the surgical wound[19,20].

Antifibrinolytic agents, such as EACA and TXA, have been used either systemically or locally for the control of bleeding in patients with haematological diseases submitted to tooth extractions[21,22]. These drugs reduce the fibrinolytic activity in the saliva, which allows improved clot stability in patients with coagulation disorders. The local administration of antifibrinolytics, especially TXA, has been proposed for the prevention and treatment of bleeding complications in anticoagulated patients[23]. This drug remains at high concentrations in the saliva and its action lasts up to 8 hours. On the other hand, the serum concentration of TXA is nearly undetectable when this agent is used as a mouthwash, thus it poses a negligible risk of systemic effects. When used as a mouthwash in the postoperative period for anticoagulated patients submitted to oral surgeries, severe bleeding complications are not observed; this includes patients who have maintained oral therapy and in whom the INR is within the therapeutic range[17,23]. The same benefits are reported when a gauze pad soaked in TXA is applied firmly over the dental alveolus[15] or when an intra-alveolar gel is used[24].

The use of oral and topical EACA is recommended for tooth extractions in patients with bleeding disorders[20–22]. Although the use of topical EACA has been described in anticoagulated patients submitted to tooth extractions, no methodologically robust clinical trials have assessed its efficacy as a local haemostatic agent in these patients[14]. The aim of this study was to compare the effectiveness of intra-alveolar EACA combined with gentle daily EACA mouthwashes with the effectiveness of routine postoperative procedures for the control of bleeding after tooth extraction in anticoagulated patients.

Patients and methods

Patients

The patients included in this study were on regular anticoagulant therapy and had been referred from the anticoagulation clinic to the outpatient clinic of the oral health programme for tooth extraction. Patients older than 18 years of age treated regularly with warfarin sodium combined or not with antiplatelet agents, referred for simple tooth extractions and with an INR between 2.0 and 4.0 on the day of surgery, were included in the study. Patients with a platelet count $<50 \times 10^9$/l, pregnant or lactating women, patients with sensitivity to EACA components, patients with hereditary coagulation disorders, and patients presenting ankylosed, partially embedded or embedded teeth, or an abnormal root morphology that could compromise the procedure were excluded.

Fifty-two patients were enrolled, of whom 29 underwent more than one surgical procedure. A total of 140 simple tooth extractions were performed. Patients were allocated randomly to one of two groups, with patients from both groups receiving routine postoperative recommendations and those in the intervention group receiving additional intra-alveolar EACA. Each tooth extraction was performed at a different appointment, and patients could be allocated to a different group at each intervention.

The extracted teeth were those with pulpal or periodontal involvement that could not be spared, either because of the tooth structure or because the patient could not afford to pay for the conservative dental treatment. Those patients who met the inclusion criteria were assigned randomly to one of the two groups in accordance with the order established by Random Allocation Software 1.0 (Isfahan, Iran, 2004). The patients assigned to the intervention group received intra-alveolar EACA (Ipsilon; Nikkho do Brasil, Rio de Janeiro, RJ, Brazil) post-extraction and used this drug as a mouthwash to gently rinse the mouth during the postoperative period, as well as receiving routine postoperative recommendations. The control group received only routine postoperative recommendations.

All patients agreed to participate in the study and signed a free informed consent agreement. This study was approved by

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