Efficacy of topical tranexamic acid soaked absorbable Gelfoam in relieving post-extraction pain in warfarin patients: A randomized, triple-blinded, multicenter, split-mouth, active-controlled clinical trial

Background

Dental extraction is one of the most common procedures in dental practice. However, the dental extraction process is not without complications, such as pain, inflammation, and infection, which the dentist is responsible for avoiding. Pain following an extraction is the most common complication due to trauma to the bone and surrounding structures, which in turn affects the patient's quality of life (QoL), especially in the first days following the extraction. Therefore, it is mandatory to look for factors that help relieve pain and improve the patient's QoL in the post-extraction period. Blood clot formation is crucial for wound healing because it evokes the requested immune response for physiological bony healing. If the blood clot is dislodged, healing may be delayed and extremely painful, especially in the first hours after the extraction. Gelatin-based hemostatic agents were first introduced as Gelfoam® (Pfizer, USA) in 1945, which achieved excellent clot formation. Tranexamic acid (TXA) is one of the most famous antifibrinolytic agents, as it works to prevent the conversion of plasminogen into plasmin by inhibiting tissue-type plasminogen activator (tPA), which leads to the prevention of fibrinolysis. Thus, a more stable blood clot is formed that fills the alveolar cavity. Topical application of tranexamic acid can inhibit local fibrinolysis at the extraction site with minimal systemic effects since there is less systemic absorption after topical application.

Warfarin is an anticoagulant drug that is used as treatment and prophylaxis of thromboembolic events. Warfarin patients who need dental extraction face the problem of bleeding, which may be difficult to control, and no sufficient hemostasis results in dry socket and postoperative pain. This study aimed to evaluate and compare the efficacy of the topical application of TXA-soaked absorbable Gelfoam (TXA-Gel) and Gelfoam sponge soaked in sterile saline solution in relieving postoperative pain following simple extraction of mandibular teeth in warfarin patients.

Materials and methods

Study Design and Ethical Considerations

This was a randomized, triple-blinded, multicenter, split-mouth, active-controlled clinical trial, which was conducted in full accordance with the Declaration of Helsinki and CONSORT statement. It was performed at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Damascus University, between November 2021 and October 2023. Ethical approval was provided by the Biomedical Research Ethics Committee (N4041). The treatment plan was clarified in detail, and participation was confidential and optional. Patients signed written informed consent before enrollment.

Sample size calculation

Sample size calculation was performed using G*Power version 3.1.9.4 (G*Power 3.1.9, Heinrich Hein Universität Düsseldorf, Düsseldorf, Germany). A sample size of n = 60 achieved a medium effect size f (0.36), 80% Power (1 - β err prob), and a significance level of 0.05. A pilot study on 10 samples was conducted to calculate the effect size.

Eligibility criteria and sampling

The inclusion criteria were as follows:

1. Patients taking warfarin.
2. International Normalized Ratio (INR) ranges between 2.0 to 3.5.
3. Patients aged 45-70 years.
4. Patients requiring bilateral simple extraction of mandibular teeth.

The exclusion criteria were as follows:

1. Smoking patients.
2. Patients with coagulopathies.
3. Patients with uncontrolled diabetes mellitus.
4. Patients are allergic to any anesthetic agent.
5. Patients with temporomandibular joint disorders.

The CONSORT flow diagram is illustrated in Figure 1. 35 patients who were referred to the Department of Oral and Maxillofacial Surgery were assessed for eligibility by a surgeon. Based on the inclusion criteria, 30 patients were recruited. 60 bilateral mandibular teeth which were indicated for simple extraction in 30 patients randomly assigned into two groups according to the topical hemostatic agents after extraction used:

Group 1: control group, Gelfoam sponge (SURGISPON®, Aegis Lifesciences, Gujarat, India) soaked in sterile saline solution (SODIUM CHLORIDE 0.9% MIAMED, Miamed Pharmaceutical Industry, Damascus, Syria) (n = 30)

Group 2: TXA-soaked absorbable Gelfoam (TXA-Gel) (Trenekop, Kopran Ltd, Haryana, India) (n = 30)

Blinding and randomization

This was a triple-blinded trial, where the investigator, the study participants, and the outcome assessor were blinded to the treatment allocation. A simple randomization method was performed by flipping a coin.

Procedure

The patient's baseline demographic data and their medical and dental history were recorded. The clinical and radiological examination was performed, and the level of the INR was determined before dental extraction using a self-testing instrument (CoaguChek® XS system, Roche Diagnostics, Indiana, USA) to ensure that it is at the appropriate level for minor surgery. Local anesthesia was administered at the site of extraction by depositing

2% lidocaine with epinephrine 1:80,000 solution (2% Lidocaine HCL Injection, Huons Co., Ltd, Seongnam, Korea) using a dental carpule syringe (Dental carpule syringe, Dental Laboratorio, Guangdong, China) and a 27-gauge x ¾ inch needle (Disposable Dental Needles, J Morita, Connecticut, United States). Bilateral extraction was carried out with the least possible trauma by a single experienced surgeon at the same appointment. Extraction was performed according to asepsis and antisepsis rules. The sockets were thoroughly irrigated and rinsed to remove follicular tissue and debris after extraction. A Gelfoam sponge sized (10x10x10 mm) was soaked in tranexamic acid (500mg/5mL) and then applied immediately after extraction in the sockets of the study group. A Gelfoam sponge soaked in sterile saline solution was also applied immediately after extraction in the sockets of the control group. Sockets closed by performing figure-of-8 suturing technique using 3.0 silk sutures (TUDOR® DVR-4942, Champion Biotech & Pharma Corp., Manila, Philippines).

Primary outcome measure

Visual Analogue Scale (VAS)

The intensity of pain was evaluated on the 1st (t1), 2nd (t2), 3rd (t3), 4th (t4), 5th (t5), 6th (t6), and 7th (t7) day following extraction and hemostatic agents application. VAS scores were as follows:

1. 0 = No pain.
2. 1-3 = Mild pain.
3. 4-6 = Moderate pain.
4. 7-9 = Severe pain.
5. 10 = Worst pain possible.

The Kappa coefficient of intra-examiner reliability was > 0.8.

Statistical analysis

IBM SPSS software version 24 (IBM SPSS Statistics® version 24, IBM Corp., New York, USA) was used to perform statistical analysis. Descriptive statistics were presented as mean, standard deviation, standard error, minimum, and maximum. Kolmogorov–Smirnov test was applied to check the normality of data, followed by performing a Mann-Whitney U test to compare VAS scores at different time points in two groups. The level of significance was set at 0.05 ($p < 0.05$).