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CASE REPORT

Usefulness of platelet-rich fibrin as a hemostatic agent after dental extractions in patients receiving anticoagulant therapy with factor Xa inhibitors: a case series

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Abstract

Purpose To evaluate the clinical outcomes of platelet-rich fibrin (PRF) application for hemostasis after dental extraction in patients receiving anticoagulant therapy with factor Xa inhibitors.

Methods In total, 25 patients receiving anticoagulant therapy with rivaroxaban or apixaban who required routine dental extraction were evaluated. In all patients, PRF was used for hemostasis in addition to adapting sutures. Bleeding was subjectively assessed using a sterilize gauze pad at 24, 48, and 72 h after the procedure.

Results All invited participants (n = 25) consented to participate. The PRF clots successfully arrested bleeding after extraction in all patients, with no complications at any time point after the procedure. Favorable soft tissue healing was observed during suture removal at 10 days after the procedure in all patients, with no signs of infection or late healing.

Conclusions The results of this case series indicate that PRF is a promising natural hemostatic agent for the management of bleeding after dental extraction in patients receiving factor Xa inhibitor therapy. Further controlled clinical studies with larger patient samples are necessary to clarify the findings of this case series.

Keywords Platelet-rich fibrin · Anticoagulant therapy · Clot stability · Hemostasis · Dental extraction

Introduction

Several patients routinely require anticoagulant drugs for the prevention and treatment of thromboembolic complications associated with various medical conditions such as pulmonary embolism, venous thrombosis, atrial fibrillation (AF), prosthetic heart valves, and acute myocardial infarction. These drugs may even be administered before orthopedic surgeries [1, 2]. Drugs such as coumarin and its derivatives (warfarin), which belong to the class of vitamin K antagonists, have been extensively used via the oral route over the past few decades [1, 2]. These drugs act by inhibiting various factors of the coagulation cascade and are sensitive to the influence of food and other drugs, particularly non-steroidal anti-inflammatory drugs and certain antibiotics, which consequently require dose adjustments [1, 3]. Patients receiving these drugs also require constant laboratory monitoring of the prothrombin time (PT) and the international normalized ratio (INR), with an INR value of 2.0–3.0 considered appropriate for effective anticoagulation in most conditions [1–3].

Recently, a new class of anticoagulants, also known as new oral anticoagulants (NOAs), was introduced. The drugs are direct inhibitors of coagulation factors II (thrombin) and Xa and include dabigatran etexilate (factor II inhibitor) and rivaroxaban and apixaban (inhibitors of factor Xa). These

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NOAs provide adequate anticoagulation and exhibit minimal interference with food and interactions with other drugs [1, 4–6].

Surgical procedures in patients receiving anticoagulant therapy remain a challenge because of the increased risk of perioperative hemorrhage. While the continued use of anticoagulants increases the risk of bleeding, their withdrawal increases the risk of thromboembolic complications. In such cases, clinical management should be based on the risk of bleeding due to the proposed procedure and the risk of thromboembolic complications due to an underlying medical condition [1, 4, 7]. In patients receiving treatment with vitamin K antagonists, oral procedures with a low risk of bleeding, such as simple tooth extraction, small biopsies, and simple periodontal procedures, can be performed without withdrawal of the anticoagulant drug, provided the INR values are at therapeutic levels [8, 9]. Previous studies have suggested that minor procedures can be safely performed without a risk of major hemorrhagic complications in patients with INR values of up to 4.0, although local bleeding control measures such as the use of hemostatic sponges, fibrin glue, oxidized cellulose, and topical antifibrinolytics, are necessary [7, 10, 11]. However, there is insufficient evidence on the safety of invasive oral surgical procedures in patients receiving NOAs [2, 4].

In a recent study, platelet-rich fibrin (PRF) was proposed as a hemostatic agent for use during oral surgical procedures [12]. It was found that hemostasis was successfully induced by an autologous fibrin mesh, with favorable clot stability. Moreover, Sammartino et al. [13] provided evidence of the potential effectiveness of PRF in the prevention of hemorrhagic events after dental extractions in patients receiving anticoagulant therapy with warfarin. However, to our knowledge, no study has evaluated the usefulness of PRF for bleeding management in patients receiving factor Xa inhibitor treatment.

Therefore, the aim of the present study was to evaluate the clinical outcomes of PRF application for hemostasis after dental extractions in patients receiving anticoagulant therapy with factor Xa inhibitors.

Materials and methods

Study design

This case series is in accordance with the CARE case report guidelines [14] for ensuring the accuracy and transparency of the evidence.

Patient selection

This case series included 25 patients who required routine dental extraction under anticoagulant therapy with rivaroxaban or apixaban. A total of 44 dental extractions were performed after each patient signed a free informed consent form at a private clinic in Brazil. The inclusion of participants was based on their screening at the surgery clinic between 2017 and 2018.

PRF preparation

From each patient, a blood sample was collected using a 21G needle (BD®, Brazil) in a 10-mL glass collection tube (BD®, Brazil) without additional chemicals. After collection, the blood was immediately centrifuged in a vertical rotor centrifuge (FibrinFuge25®, Montserrat, São Paulo, Brazil) at 708*g* for 12 min [15]. At the end of the procedure, the samples were removed from the collection tubes and directly placed in the extraction sockets.

Extraction procedures

All extraction procedures were performed by a single experienced oral surgeon in the presence of a second professional in charge of data collection. The following information was gathered: age, sex, systemic condition, extraction site, and the amount of postoperative bleeding at 24, 48, and 72 h after extraction and PRF placement. All patients were placed under the same preoperative treatment protocol based on the characteristics inherent to each procedure. Local anesthesia was induced with 2% lidocaine with 1:100,000 epinephrine (3.6 mL for each patient; DFL®, Brazil), and tooth extraction was performed using the appropriate technique. Sutures were placed using catgut threads in a 4–0 needle (*Johnson & Johnson*®, Brazil). The number of PRF clots was selected as per the surgeon's judgment and the size of the defect. The clots were adequately packed into the extraction sockets, followed by the placement of a final cross suture overlaying the clots.

Bleeding evaluation

After the procedure, the patients remained under the care of the oral surgeon for 2 h, following which bleeding was subjectively assessed by placing a sterile dry gauze pad at the extraction site and evaluating the presence of the blood on the pad. All patients returned to the dental office at 24, 48, and 72 h after the procedure for subjective bleeding assessments, and they reported slight bleeding for a few hours during the first 24 h.

Results

Ten men and 14 women with a mean age of 72.44 ± 14.90 years (range, 34–91 years) were included in this study. Most of the extraction procedures involved the mandibular teeth (24 mandibular tooth extractions and 20 maxillary tooth

extractions). The data collected for all patients are presented in Tables 1 and 2, in chronological order of treatment. The mean duration of anticoagulant therapy was 9.6 ± 3.18 months (range, 5–15 months).

The PRF clots successfully arrested bleeding after extraction in all patients, with no complications at any time point after the procedure. Table 1 shows that no bleeding was observed at 24 and 48 h after the procedure in all patients. Moreover, there was no postoperative infection at 7 days after the procedure, and favorable soft tissue healing was observed during suture removal at 10 days. Figures 1, 2, 3, and 4 illustrate a representative case (patient no. 2) involving a mandibular second molar with a combined periodontal–endodontic lesion identified on a radiograph (Fig. 1). The surgeon proceeded with tooth extraction, following which there was severe bleeding (Fig. 2). Two PRF clots were inserted into the extraction socket, followed by suture placement (Fig. 3). Postoperative adaptation of the PRF clots within the extraction socket resulted in arrested bleeding (Fig. 3). Favorable healing was observed at 10 days after the procedure (Fig. 4).

Discussion

The treatment of patients receiving anticoagulant therapy is perceived as a challenge by oral surgeons, because such patients present an increased risk of bleeding during and after surgical procedures [16–18]. For many years, even minor surgical procedures were contraindicated in such patients unless their medication regimens were modified for a certain period before/after surgery in order to avoid excessive bleeding [16, 18, 19]. To our knowledge, no study has assessed the actual risk of bleeding in patients receiving treatment with NOAs such as rivaroxaban and apixaban who require surgical dental procedures. Furthermore, no established treatment protocol is available for such patients, although evidence suggests that good maintenance of anticoagulant therapy (proper INR values) and the implementation of local hemostatic measures in patients with normal renal function are adequate for performing routine dental extractions [4]. Thus, the present study is the first to investigate the usefulness of PRF as a natural fibrin mesh favoring clot formation/stability after dental extractions in patients receiving factor Xa inhibitor therapy.

Table 1 Data collected from the participants

Patients	Age	Sex	Systemic condition	Extraction site	Membranes per site	Bleeding 2 h	Bleeding 24 h	Bleeding 48 h
No. 1	84	M	Non-valvular atrial fibrillation	26	2	+	–	–
No. 2	34	M	Venous thromboembolism prophylaxis	47	2	+	–	–
No. 3	67	F	Deep vein thrombosis	28	2	+	–	–
No. 4	78	M	Venous thromboembolism prophylaxis	41/42	3	+	–	–
No. 5	68	F	Deep vein thrombosis	23	2	+	–	–
No. 6	55	F	Deep vein thrombosis	26/27	2	+	–	–
No. 7	84	M	Venous thromboembolism prophylaxis	17	2	+	–	–
No. 8	87	M	Non-valvular atrial fibrillation	33/34	3	+	–	–
No. 9	79	M	Venous thromboembolism prophylaxis	14/16	2	+	–	–
No. 10	76	F	Venous thromboembolism prophylaxis	38	2	+	–	–
No. 11	49	F	Deep vein thrombosis	46	2	+	–	–
No. 12	64	F	Venous thromboembolism prophylaxis	16	2	+	–	–
No. 13	75	F	Venous thromboembolism prophylaxis	22/23	3	+	–	–
No. 14	66	M	Venous thromboembolism prophylaxis	27	2	+	–	–
No. 15	84	F	Venous thromboembolism prophylaxis	41	1	+	–	–
No. 16	67	F	Venous thromboembolism prophylaxis	32/31/42/42	3	+	–	–
No. 17	76	F	Venous thromboembolism prophylaxis	46/47	3	+	–	–
No. 18	75	M	Venous thromboembolism prophylaxis	27/28	3	+	–	–
No. 19	78	F	Venous thromboembolism prophylaxis	33/34	2	+	–	–
No. 20	91	M	Venous thromboembolism prophylaxis	44/45	2	+	–	–
No. 21	67	F	Deep vein thrombosis	23/24	2	+	–	–
No. 22	84	F	Venous thromboembolism prophylaxis	26/27	3	+	–	–
No. 23	86	M	Venous thromboembolism prophylaxis	31/32/41/42	3	+	–	–
No. 24	64	F	Venous thromboembolism prophylaxis	44/45	3	+	–	–
No. 25	73	F	Venous thromboembolism prophylaxis	27/28	3	+	–	–

Table 2 The reason for dental extractions and the type and time of use of the medicine per patients

Patient	Dental extraction reason	Medicine	Anticoagulant therapy (months)
No. 1	Root fracture	Rivoroxaban	8
No. 2	Endo-perio lesion	Apixaban	6
No. 3	Extension of caries lesion	Rivoroxaban	12
No. 4	Extension of caries lesion	Rivoroxaban	11
No. 5	Endo-perio lesion	Rivoroxaban	5
No. 6	Extension of caries lesion	Apixaban	11
No. 7	Root Fracture	Rivoroxaban	12
No. 8	Extension of caries lesion	Rivoroxaban	14
No. 9	Endo-perio lesion	Rivoroxaban	8
No. 10	Extension of caries lesion	Rivoroxaban	7
No. 11	Extension of caries lesion	Apixaban	6
No. 12	Root fracture	Rivoroxaban	15
No. 13	Extension of caries lesion	Rivoroxaban	13
No. 14	Extension of caries lesion	Rivoroxaban	7
No. 15	Endo-perio lesion	Rivoroxaban	9
No. 16	Endo-perio lesion	Apixaban	6
No. 17	Extension of caries lesion	Rivoroxaban	11
No. 18	Endo-perio lesion	Rivoroxaban	9
No. 19	Extension of caries lesion	Rivoroxaban	8
No. 20	Extension of caries lesion	Rivoroxaban	13
No. 21	Endo-perio lesion	Rivoroxaban	8
No. 22	Endo-perio lesion	Rivoroxaban	14
No. 23	Extension of caries lesion	Rivoroxaban	12
No. 24	Extension of caries lesion	Rivoroxaban	6
No. 25	Endo-perio lesion	Rivoroxaban	9

We found that PRF was a promising natural hemostatic agent for patients receiving anticoagulant therapy with factor Xa inhibitors, consistent with the initial findings of Sammartino et al. (2011) [13]. All extraction sockets in our study showed no signs of bleeding at 24 h after the procedure, which is normally observed in individuals who are not receiving anticoagulant therapy [20]. Moreover, clinical evaluation immediately after tooth extraction (Figs. 2 and 3) showed reduced bleeding that was maintained throughout the healing process.

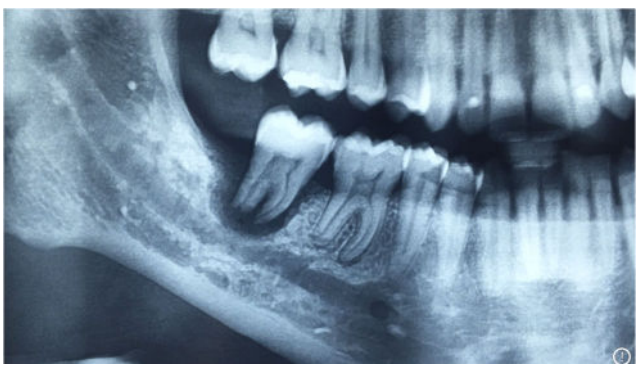

Fig. 1 A radiograph showing a combined periodontal–endodontic lesion involving the second mandibular molar in a patient receiving anticoagulant therapy with a factor Xa inhibitor

Because clot formation is essential for wound healing, PRF application initiates the process and favors the further clotting of whole-blood oozing from the extraction site. Various other studies found that PRF could be similarly utilized for the management of bleeding after extraction of the mandibular third

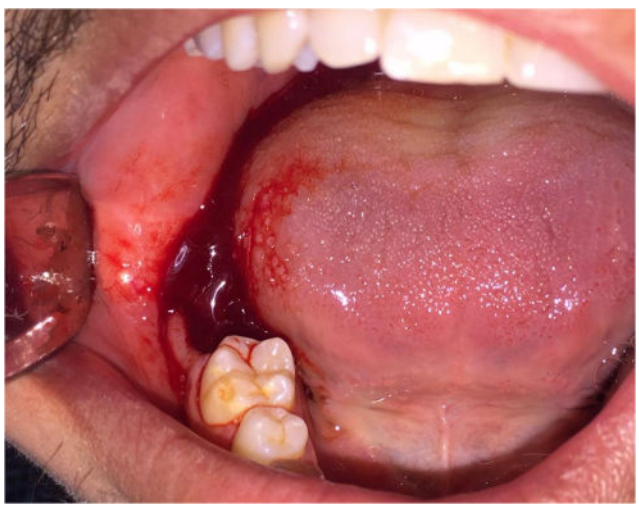

Fig. 2 Severe bleeding after extraction of the second mandibular molar in a patient receiving anticoagulant therapy with a factor Xa inhibitor

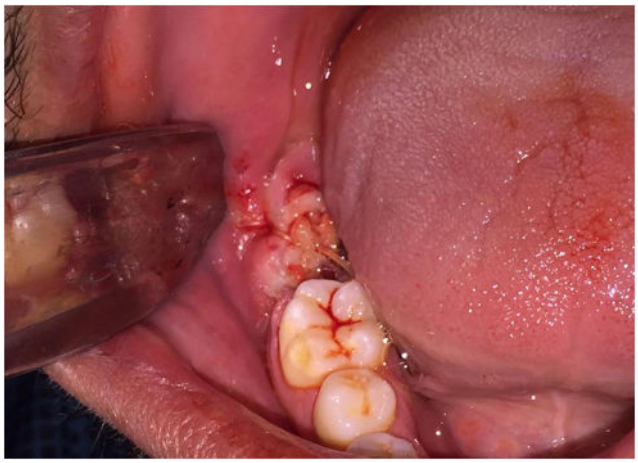

Fig. 3 Placement and suturing of platelet-rich fibrin (PRF) clots in the socket for the management of severe bleeding after extraction of the second mandibular molar in a patient receiving anticoagulant therapy with a factor Xa inhibitor

molar [21–24], which is situated in an area often prone to several complications. A considerable decrease in the rate of complications was also observed after the use of PRF [22, 23]. Previous systematic reviews evaluated the effects of PRF in third molars socket post-extraction on promoting bone and soft tissue healing [25], pain relief [26–28], swelling, trismus, and reducing the incidence of alveolar osteitis [27, 29] after tooth extraction when compared with dental socket without filling, but none of them had evaluated the use of PRF as a potential hemostatic agent.

The primary mechanism of action of PRF is possibly related to its ability to act as a functional physical barrier [12, 13]. The use of autologous fibrin material facilitates the activation of the coagulation cascade [12, 13], leading to the establishment of a stable clot at the surgical site. However, there is a possibility that the quality of the final fibrin mesh produced using the standard protocol could be altered by the anticoagulant drug being taken by the patient. Nevertheless, a recent study comparing the quality of concentrated blood-derived growth factors between healthy patients and those taking anticoagulant therapy showed no qualitative differences between the two groups [30]. This indicates that the action of basal prothrombin, along with the silica in the collection tubes and the mechanical action of the centrifuge, may be sufficient for the formation of a good-quality clot in patients receiving anticoagulants. Oxygen is involved in the coagulation cascade of prothrombin and fibrinogen [31]; therefore, in cases where a full-thickness fibrin clot is not formed, removal of the centrifugation tube caps is recommended for adequate oxygenation within the centrifugation tubes, which leads to appropriate fibrin clot formation.

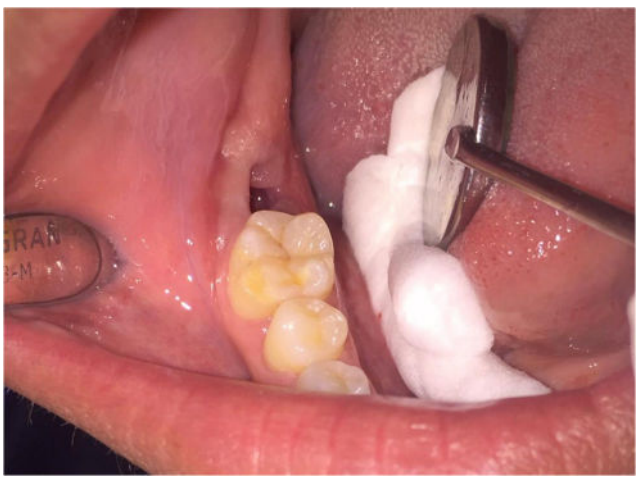

Fig. 4 Image showing the healing process 10 days after platelet-rich fibrin (PRF) application for the management of severe bleeding after extraction of the second mandibular molar in a patient receiving anticoagulant therapy with a factor Xa inhibitor

Although further studies are necessary to compare the efficacy of PRF with that of other clinically available hemostatic agents, this case series introduces a promising alternative approach for patients receiving factor Xa inhibitor therapy, with the findings creating a foundation for further controlled clinical studies with larger patient samples are necessary to clarify the findings of this case series, involving not only patients receiving anticoagulants but also healthy patients. Even though the risk of bleeding after dental extractions is consistenly lower in patients receiving factor Xa inhibitors than in those receiving warfarin [32], PRF may serve as an alternative low-cost autologous hemostatic agent with regenerative properties for these patients.

Conclusions

Within the study limitations, the findings suggest that PRF is a promising natural hemostatic agent for the management of bleeding after dental extraction in patients receiving factor Xa inhibitor therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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