Chapter

Bleeding in Dental Surgery

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Abstract

Excessive bleeding complicates surgery and may result in a higher risk of morbidity in dentistry. Although multiple evidence-based clinical guidelines regard dental interventions as minor procedures, with low risk of bleeding, patients on anticoagulation therapy are at elevated risk of bleeding complications, during and following dental surgeries. In many instances, discontinuation or altering of anticoagulation can be avoided through the use of local hemostatic agents during or after the procedure (or both), while patients are therapeutically continued on their prescribed anticoagulant doses. In addition, patients with diagnosis of hereditary bleeding disorders, such as von Willebrand disease and hemophilia, and individuals without any history of bleeding complications can present the need for the use of topical hemostatic agents. In this chapter, we discuss the mechanisms of action, practical applications, effectiveness, and potential negative effects of biosurgical topical hemostatic agents, such as gelatin sponges, collagen, oxidized regenerated cellulose (ORC) and oxidized cellulose, fibrin sealants, flowables, adhesives, and topical thrombin in dental surgery.

Keywords: bleeding, antiplatelet, hemostasis, biosurgical agents, topical agents, dental surgery

1. Introduction

All surgical procedures, including dental surgery, present risk of complications, which may include pain, nerve injury, swelling, infections, and hemorrhage. Dental surgery is defined as any dental intervention including an incision in the oral mucosa or gingiva, including anything from a simple dental extraction to alveoloplasties [1]. Bleeding control is an important step during dental surgery procedures [2] because excessive bleeding complicates surgery and increases the risk of morbidity. To avoid such complications when long-lasting bleeding occurs, despite the proper use of traditional techniques for hemorrhage control, a broad range of hemostatic agents are available, as adjunctive measures to enhance hemostasis in the course of dental surgeries [3]. Despite the expressive rise in the amount and types of topical hemostats in the past decade, high-level evidence regarding the management of these agents during bleeding in dental surgery is still lacking.

The periprocedual management of patients receiving therapeutic anticoagulation represents a challenge for dental practitioners, as the risk of bleeding must be counterbalanced against the risk of systemic or local thromboembolic phenomena. Recommendations for dental interventions in individuals receiving anticoagulation therapy remain quite unclear, in spite of practice guidelines from both dental [4] and medical [5] fields.

This chapter aims to discuss the effective ways of managing bleeding complications in dental surgery, mainly in high-risk patients. The role of biosurgical materials to prevent or solve these complications, during and after dental surgery procedures, will also be addressed, as well as their modes of action, practical applications, adverse effects, and effectiveness.

2. Normal hemostasis

The physiological mechanism that prevents and hinders bleeding at the area of an injury while preserving regular blood flow everywhere else in the circulation is called hemostasis [6]. The hemostasis process has two major components. Primary hemostasis initiates promptly after vascular injury, and it can be divided into four consecutive and superposed stages: (A) vasoconstriction, (B) platelet adhesion, (C) platelet activation, and (D) platelet aggregation [7–10]. Primary hemostasis results in the formation of a platelet plug [10]. Secondary hemostasis comprises a sequence of serine protease zymogens and their cofactors, which interact successively on phospholipid surfaces (damaged endothelial cells or platelets), leading to the development of covalently cross-linked fibrin [10–12]. This cross-linked fibrin mesh is then incorporated into and around the platelet plug. It strengthens and stabilizes the blood clot. These two processes are intertwined and occur at the same time [6]. These systems are regulated by multiple anticoagulant mechanisms, which are responsible for maintaining blood fluidity in the absence of injury, generating a clot that is consistent with the trauma. Hemostasis and the avoidance of bleeding or thrombosis are directly related to the adequate balance between procoagulant and anticoagulant systems [6].

3. Bleeding diathesis in dental surgery: acquired, autoimmune, or genetic

Hemorrhage in dental surgery can be categorized as:

1. Primary hemorrhage: bleeding occurs during surgery

2. Reactionary hemorrhage: bleeding occurs 2–3 hours after surgery

3. Secondary hemorrhage: bleeding occurs until 14 days after surgery, probably due to an infection

Hemorrhage can also be categorized according to the area injured: vascular, bone, and soft tissue [13, 14]. Bleeding diathesis is an unusual susceptibility to bleeding and may be genetic, autoimmune, or acquired (**Table 1**) [15, 17]. Selected bleeding disorders will be covered in this chapter.

3.1 von Willebrand disease and hemophilia

The most prevalent hereditary bleeding disorders are von Willebrand disease and hemophilia, affecting 1% of the population and 20,000 people in the USA, respectively [18–22]. Dental patients presenting inherited bleeding present a significantly higher risk of perioperative bleeding. The frequency and severity of bleeding are related to disease-related factors, such as the severity of the hemophilia. Factors related to the patient include the level of periodontal disease, vasculopathy or

Disorders of Platelets	Thrombocytopenias: immune thrombocytopenia; drug-induced thrombocytopenia (heparin-induced and chemotherapy); hypersplenism; myelodysplasia/aplastic anemia
	Platelet function alterations: adhesion disorders (genetic); von Willebrand disease; therapeutic platelet inhibitors [$P2Y_{12}$ inhibitors (clopidrogel and prasurgel), cyclo-oxygenase inhibitors (aspirin), phosphodiesterase inhibitors (cilostazol), GP IIB/IIIA inhibitors, adenosine reuptake inhibitors (persantine)]; uraemia; cirrhosis
Disorders of coagulation	Hemophilia: factor VII (classic/A), IX (B), and XI (C), and others; factor antibody syndromes; hepatic dysfunction
	Therapeutic anticoagulants: vitamin K antagonists (ex: warfarin, acenocoumarol); low-molecular-weight heparins (tinzaparin, dalteparin, enoxaparin); direct dental anticoagulants [factor II inhibitor (dabigatran); factor X inhibitors (apixaban and rivaroxaban)]
	Diffuse intravascular coagulopathy
	Massive transfusion states
Vascular Disorders	Scurvy Hereditary hemorrhagic telangiectasia Ehlers-Danlos syndrome
Fibrinolytic Defects	Streptokinase therapy Disseminated intravascular coagulation

Table 1.
Hemorrhagic diatheses–adapted from Vezeau [15] and Goswami et al. [16].

platelet dysfunction, and procedure-related factors (teeth extracted—type and the number—or the size of the wound area) [23].

3.2 Immune thrombocytopenia

One example of autoimmune bleeding diathesis is the immune thrombocytopenic purpura (ITP), an idiopathic thrombocytopenic purpura condition, characterized by isolated thrombocytopenia without a clinically apparent cause [24].

3.3 Common hemostasis-altering medications

The most common acquired bleeding diathesis is the one related to hemostasis-altering medications. Anticoagulant agents are among the most prescribed medications in the USA [25]. For decades, anticoagulants have been prescribed to prevent arterial and venous thromboembolism [1]. Prolonged bleeding and bruising are some of the adverse events related with these medications [4]. The most frequently used drugs are therapeutic platelet inhibitors, vitamin K antagonists, or direct oral anticoagulants. Patients susceptible to hemorrhage may present severe bleeding resulting from dental surgery procedures. The use of biosurgical hemostatic agents to decrease or control bleeding may be beneficial for patients at risk for bleeding diathesis.

4. Biosurgical topical hemostatic agents in dental surgery

Bleeding complications can occur either in healthy or systemically compromised patients. Some patients tend to bleed excessively during or after dental surgery, due to different factors, such as anticoagulant therapy, inherited bleeding disorders, uncontrolled hypertension, extreme trauma to soft tissues, and non-compliance to postoperative recommendations. In these cases, the use of an effective hemostatic agent enhances hemostasis, providing a wide spectrum of benefits, such as superior management of the anticoagulated patient, shorter operation time, as well as smaller wound exposure and shorter recovery time.

The ideal topical hemostatic agent should be biocompatible, affordable, and effective [14, 26, 27]. In recent years, the number of different topical hemostatic agents has increased significantly (**Table 2**). Knowledge and familiarity with the wide range of topical hemostatic agents available are essential for dental practitioners, including their effectiveness, mode of action, and adverse effects. A well-informed professional will be able to opt for the most effective and practical agent for each situation. In

Topical hemostatic		Commercial name
Passive or Mechanical Agents	Gelatins	Surgifoam®, Gelfoam®, Gelfilm®, Gelitaspon®, Geli putty®
	Collagen	Instat®, Helitene®, Helistat®
	Cellulose-based products: oxidized regenerated cellulose	Surgicel Original®, Surgicel Nu-Knit®, Oxycel®, Surgicel Fibrillar®, Interceed®, Gelitacel®
	Cellulose-based products: oxidized cellulose	ActCel®, Gelitacel®
	Polyssacharide hemospheres	Arista™AH
	Adhesives	BioGlue®
Active Agents	Topical thrombin	Thrombin-JMI®, Evithrom®, Recothrom®
	Fibrin sealants	Tisseel®, Evicel®, Crosseal™
Flowable agents	Porcine gelatin + thrombin Bovine collagen + thrombin	Surgiflo®, Floseal®

Table 2.
Types and trade name of some biosurgical agents–adapted from Pereira et al. [28].

relation to the use of local hemostatic in dental procedures, available scientific data is not homogenous. Most publications use one or more local hemostatic agents to compensate for the anticoagulant effect and prevent postoperative bleeding [29]. The most common local biosurgical hemostatic agents used in dentistry and approved by the Food and Drug Administration (FDA) are listed in **Table 2**.

Local biosurgical hemostatic agents can be classified into (A) passive or mechanical, (B) active, and (C) flowables [30].

4.1 Passive or mechanical agents

Considered as the most effective agents for small amounts of bleeding, passive or mechanical agents provide platelet activation and aggregation. This results in a matrix formation in the bleeding area that works as a barrier to stop bleeding, by activating the extrinsic clotting pathway and providing a surface that will allow coagulation to occur faster [30]. As these agents are biologically inactive, they rely on the individual's own fibrin production to attain hemostasis. Passive hemostats are only indicated for individuals with an unscathed coagulation cascade [27]. They are generally applied as frontline agents, since they are readily available, do not require special storage or handling, and are relatively affordable [14, 27, 31].

4.1.1 Gelatin (Gelfoam®, Surgifoam®, Gelfilm®, Gelita-Spon®, Geli Putty®)

Gelatin is a hydrocolloid derived from acid partial hydrolysis of purified animal collagen. It is presented as a gelatin sponge, powder (mixed to form a paste), or film. Gelatin can be placed dry or after moistening it with saline [14, 28, 32, 33]. Gelatin-based products adapt effortlessly to wounds making it appropriate for application into irregular surfaces [27]. Although their mode of action is not completely understood, gelatin-based products likely act more physically than chemically in the coagulation cascade [28, 34]. Affordability, ease of use and good hemostatic activity make topical hemostats with gelatin matrix a popular tool for reducing the morbidity caused by hemorrhage [27, 28] after dental extractions and periodontal surgeries.

The most popular absorbable gelatin sponge in dentistry is Gelfoam®. It is a hemostatic compressed sponge obtained from purified porcine skin gelatin. Gelfoam® is capable of absorbing many times its weight of whole blood [35]. Generally, when applied in soft tissues, its complete absorption occurs within 4–6 weeks.

4.1.2 Collagen (Helistat®, Instat®, Helitene®)

Collagen absorbable products are nontoxic and non-pyrogenic. They are sourced from either bovine dermal collagen or bovine tendon. Collagen hemostats provide a matrix for clot formation and consolidation. These products also improve clotting factor release and platelet aggregation and degranulation, thereby breaking up clot formation. Their presentation in sheets and flours allows for easy adaptation and adhesion to irregular surfaces. Although they are commercialized at a higher price than gelatin-based hemostats, hemostasis can usually be accomplished relatively quicker (1–5 min). Collagen absorbable products are easily removed, reducing the risks of rebleeding and the need for various applications. They are absorbed in 8–10 weeks if remained in place. Adverse effects linked to bovine collagen products might include swelling and allergic reaction [30].

Helistat® is a collagen-based product originated from purified and freeze-dried bovine flexor tendon and is available as a spongelike structure [14, 27]. Helistat® can hold many times its own weight of fluid, as it is highly absorbent. Collagen

induces platelet agglomeration when in contact with blood. In order to achieve hemostasis, Helistat® must be kept at the site (approximately 2–5 minutes). Subsequently, it can be removed, replaced, or left in place. It is easily manipulated, and it must be handled dry, and any excess must be removed. Complete reabsorption occurs within 14–56 days [14, 27, 36]. Helistat® may foster bacterial growth, acting as a nidus for abscess formation [14, 27, 37]; therefore, it should not be placed in wounds with any kind of contamination or infection. Possible adverse reactions of Helistat® or similar products are allergic reaction, foreign body reaction, and adhesion formation [27, 38].

4.1.3 Cellulose-based products

4.1.3.1 Oxidized regenerated cellulose (Surgicel®, Oxycel®, Surgicel Nu-Knit®, Surgicel Original®, Surgicel Fibrillar®, Interceed®, Gelita-Cel®)

Simple oxidized cellulose was first introduced in the early 1940s in the USA. In the 1960s, a new topical hemostatic-oxidized regenerated cellulose (ORC) was launched as a meshwork made from treated and sterilized cellulose—Surgicel®. ORC products are originated from vegetal-based alpha cellulose, available in absorbable knitted fabrics (low or high density), and prepared as sterile fabric meshworks. They are ready-to-use products that may be kept at room temperature and absorb 7–10 times its own weight [27, 30]. ORC cause contact activation and platelet activation, and, when absorbed, a gelatinous mass is created, assisting in the establishment of the clot formation [30]. Thrombin is ineffective with these agents due to low-pH factors. ORC are utilized in the management of capillary, venous, and small arterial bleeding, and they require dry application, without addition of saline or thrombin [27, 39] and are absorbed within 4–8 weeks, depending on the volume applied, the tissue bed, and the magnitude of blood saturation [27, 40–42]. To prevent delayed healing, excessive volumes should be removed [27]. ORC should not be used in osseous defects as it may intervene with bone regeneration [14, 27, 31]. Adverse effects also include reactions related to the acidic nature of ORC. This characteristic may induce necrosis and inflammation of the surrounding tissue and makes thrombin inefficient with these agents. When left in the wound, they may lead to fluid encapsulation and foreign body reaction [14, 27].

The most common commercial products in this category are Surgicel®, Oxycel®, and Surgicel Nu-Knit®. Surgicel® and Surgicel Nu-Knit® come in knit, solid fiber form, whereas Oxycel® comes in knit, hollow fiber form; however, they function basically in a similar manner [30].

4.1.3.2 Oxidized cellulose (ActCel®, Gelita-Cel®)

Oxidized cellulose (OC) agents are produced from sterilized and treated cellulose, presented as a meshwork. In the presence of blood, they present a three- to fourfold increase in volume and are converted into gel. OC dissolve completely in 1–2 weeks into biodegradable end products glucose and water, and they do not interfere with wound healing [14, 27].

ActCel® binds to calcium ions, resulting in more calcium available for the coagulation cascade [14, 27, 37]. Biochemically, it intensifies the coagulation process by increasing platelet aggregation and physically by 3D clot stabilization. ActCel® is especially indicated in third molar extractions, to avoid the occurrence of dry sockets, and in orthognathic and periodontal surgeries [27]. ActCel® is hypoallergenic, as it does not contain collagen, thrombin, or chemical additives. It also has important bacteriostatic properties [27, 43], which are particularity relevant in infected wounds [27].

Gelita-Cel® is a relatively quick acting, oxidized resorbable cellulose hemostatic gauze of natural origin. It presents a decreased risk for encapsulation, as it resorbs as fast as 96 hours [14, 27, 37].

4.1.4 Polysaccharide hemospheres (Arista™AH)

Polysaccharide hemospheres are a fairly new class of topical biosurgical hemostatic agents, produced from vegetable starch, and they contain no animal or human elements. They are commercially presented in powder form. Polysaccharide hemospheres increase barrier formation by creating a hydrophilic effect, dehydrating the blood, and concentrating its solid components [14, 27]. Due to their 3D scaffold, they are devised to enhance clot formation and organization, even in the absence of intrinsic coagulation activity [14, 44, 45]. Polysaccharide hemospheres should be used with caution in diabetic patients, as they consist of sugars [27].

Arista™AH is the only FDA-approved product in the polysaccharide hemosphere category. It is used in dental surgery as an adjunctive hemostatic agent, when conventional mechanical procedures, such as pressure and ligature, are not effective or practical.

4.1.5 Adhesives (BioGlue®)

Hemostatic adhesives are often used as adjuncts to standard hemostatic procedures to control bleeding from surgical areas [30]. One of the most well-known products in this category is BioGlue®. It consists of a solution of 10% glutaraldehyde and 45% bovine albumin solution purified by precipitation, heat, and chromatography radiation [28, 46]. BioGlue® has been extensively used for its sealants and hemostatic characteristics. The risk of leaking through the suture tracks is the main disadvantage of BiolGue® [27]. In the search for newly created adhesives with the chemical features and the safe reabsorptive profile required to benefit dental surgery patients, several clinical trials are currently in process.

4.2 Active agents

Active hemostatic agents are biologically active, as they play a direct role in the coagulation cascade, inducing the formation of a fibrin clot [26, 27].

4.2.1 Topical thrombin (Thrombin-JMI®, Evithrom®, Recothrom®)

Thrombin is key to hemostasis, as well as to the inflammatory and cell signaling processes. It is the base of the fibrin clot, fostering the transformation of fibrinogen to fibrin [28]. Topical thrombin hemostats are originated from either bovine or human plasma, and they can also be produced through recombinant DNA techniques [14, 27]. In the past, the only thrombin hemostat available was composed of bovine plasma (Thrombin-JMI). Although it has proven to be efficient in terminating bleeding, bovine thrombin induces an important immune response [28, 47]. Individuals on hemodialysis, with increased levels of antibodies against topical bovine thrombin, had higher incidence of vascular access thrombosis, severe coagulopathy, and bleeding after exposure to bovine thrombin [28, 48]. As an attempt to avoid these hazardous effects, thrombin derived from human plasma (Evithrom®) and recombinant human thrombin (Recothrom®) were developed. In 2010, Browman et al. [49] demonstrated, in a comparative study between recombinant human thrombin and bovine thrombin, that human recombinant thrombin showed the same efficacy in surgical hemostasis, a comparable safety profile, and

a remarkably lower immune response than bovine thrombin. Thrombin may be applied topically, as a solution combined with gelatin sponges mixed with a gelatin matrix, as a dry powder, or as a spray [14, 27]. It is commonly used in conjunction with Gelfoam® to stop moderate to severe bleeding.

4.2.2 Fibrin sealants (Tisseel®, Evicel®, Crosseal™)

Fibrin sealant or fibrin glue originates from bovine and/or human blood components and simulates the last phases of the coagulation cascade, generating a fibrin clot [30]. These agents control local, as well as diffuse, bleeding from the surgical area. Nevertheless, they are ineffective in controlling intense bleeding. Its use in dentistry includes tooth extraction sites, bone grafting, and periodontal surgery [14].

Tisseel® was the first fibrin sealant approved by the FDA. It has in its composition human thrombin and fibrinogen, intermixed with aprotinin and $CaCl_2$. Because aprotinin is a bovine protein, it is a potential allergen. Multiple exposures may cause allergic reactions, as well as anaphylactic reaction approaching lethality [30, 50]. As for its ideal application, a dry operating field is required; Tisseel® is particularly effective when applied prior to bleeding. In this situation, fibrinogen may polymerize before blood pressure increases local microcirculation flow. When used after the onset of bleeding, one should apply local pressure over the wound to allow polymerization [28, 51]. Tisseel® is available in a pre-filled syringe, allowing for effective application using the EasySpray and DuploSpray MIS systems.

Another option for fibrin sealants, Evicel®, originates from pooled human plasma. It is available as two separate vials of fibrinogen and human thrombin. Prior to use, the two deep frozen solutions must be thawed and mixed after defrosting and heating up (20–30°C) [30].

Crosseal™ is a virally inactivated, second-generation surgical sealant. It is produced from concentrated human clottable proteins, namely, biological active component (BAC), which contains the active component fibrinogen, and human α-thrombin (1000 IU/ml) [52]. This fibrin sealant is applied using an application device which drips/sprays Crosseal™ onto the bleeding site.

4.3 Flowables (Surgiflo®, Floseal®)

There are two main categories of flowable biosurgicals: products containing porcine gelatin, which can be combined with thrombins (bovine, human-pooled plasma thrombin, or rhThrombin), and bovine collagen-based agents, packed with human-pooled plasma thrombin. The flowable agents are deemed the most effective of all the local hemostatic agents [30, 53].

Surgiflo® is an absorbable, sterile, hemostatic porcine gelatin matrix, combined with Thrombin-JMI, a topical bovine-derived thrombin. It should be placed directly to the bleeding areas to activate the hemostatic process [30]. A compression period is required for polymerization of the sealant components [28].

Floseal® consists of a bovine gelatin matrix, plasma-extracted human thrombin, and $CaCl_2$. Its gelatin granules expand (10–20%), as it comes in contact with blood, producing a seal when the product is applied to a bleeding area [27, 30]. The thrombin fraction of the product triggers the regular pathway of the coagulation cascade, converting fibrinogen to a fibrin polymer and creating a clot around the firm matrix [27], which is reabsorbed within the expected period of standard wound healing (6–8 weeks) [14, 27, 33, 42, 54]. A distinctive feature of Floseal® is the need for the presence of blood for activation [30, 55]. Neither compression, nor a dry surgical field is required for its application [28].

Because of this biosurgical flowability, they can easily adapt to irregular wounds. Flowables have been utilized as frontline topical hemostats in major dental surgeries, in patients where conventional procedures are ineffective. They can be utilized as an adjunct to hemostasis in practically all dental surgical interventions. Flowables are effective on both hard and soft tissues [27, 30]. They have a risk of transmitting infectious agents and are contraindicated in patients who are allergic to materials of bovine origin [27].

5. Effectiveness of different biosurgical hemostatic agents in dentistry

Although traditional methods, such as ligature and manual pressure, can promote hemostasis, they are not an effective approach of bleeding control in less accessible sites and complex injuries. Furthermore, bleeding control is especially challenging in patients presenting acquired or congenital coagulation disorders.

Topical biosurgical hemostatic agents comprise a wide range of products aiming at minimizing the risk of bleeding. In recent years, several clinical trials have analyzed the effectiveness, advantages, and limitations of biosurgicals, as well as performed comparisons among the different types of biosurgicals and other non-biologic agents. Despite the beneficial effect of these local hemostatic agents in preventing bleeding in dental surgery, available data comparing their effectiveness and efficiency is still scarce and inconclusive. Methodological heterogeneities, such as the lack of a standard therapy and comparable treatment regimens, are noticeable among studies, as well as the reduced number of randomized controlled trials [2, 56–70].

In summary, local hemostatic agents are very distinct products with diverse indications. Presently, there is no definite evidence-based approach to guide the dental practitioner when selecting a local hemostatic agent. They must be aware of the characteristics of each single hemostatic agent, to elect the most suitable product for every particular clinical situation. In addition, current available data shows that no topical agent can be regarded as superior or more effective than the others [2]. Further experimental research and controlled clinical trials are warranted to define the most cost-effective biosurgical hemostatic agents in dentistry.

6. Preoperative assessment and risk of bleeding

The dental practitioner should assess the bleeding risk of the patient, as well as the bleeding risk of the surgical intervention, preoperatively. After assessing both bleeding risks, the professional can then conceive an intraoperative and postoperative plan. The international normalized ratio (INR) must be evaluated in patients reporting an elevated risk of bleeding. While a standard parameter of coagulation has an INR of 1 [71], the therapeutic range runs from 2.0 to 3.5. In this case, it is recommended to use local hemostatic measures independently or in combination with conventional methods. These agents can be used before, during, and after dental surgeries.

6.1 Preoperative assessment

- Comprehensive medical history, including all medications in the patient's regimen, to identify potential bleeding issues prior to the surgery [26].

- In order to decrease surgical bleeding, patients receiving anticoagulant therapy may need to break up exodontia into multiple appointments [26, 72].

- Laboratory values such as platelet count, INR, and prothrombin time are of critical value in medically compromised patients [26].

- Demographic risk factors (female sex and older age) [73].

- Supplemental patient-related risk determinants: diabetes mellitus, hypertension, obesity, hemostatic disorders, renal impairment, and other major organ system failures [73–75].

- Timing of the appointment: early morning visits allowing patients to return to the dental office in case of postsurgical hemorrhage [26].

6.2 Identifying patients at risk of bleeding

Patients at a higher bleeding risk are those reporting family history of bleeding and previous bleeding problems after dental surgery or trauma and individuals using medications, such as aspirin, anticoagulants, and/or long-term antibiotics. Any illnesses associated with bleeding problems, such as leukemia, congenital heart disease, liver disease, or hemophilia, present a higher risk of bleeding. The dental professional needs to be aware and prepared for any intercurrence, during or after a surgical procedure. Individuals presenting advanced periodontal disease are also considered as having a higher risk of perioperative bleeding. In such cases, the surgical plan should include a preoperative phase, consisting of scaling and root planning and a proper chlorhexidine gluconate mouth rinse regimen, 2 weeks before an elective procedure [26].

The risk of bleeding of a dental intervention may be ranked as high, moderate, and low [25, 76–78]. In most patients, antithrombotic therapy is not interrupted before dental interventions with low bleeding risk, due to the disastrous complications of thrombosis (**Table 3**) [25, 76–78]. Moderate and high bleeding potential interventions might need the temporary discontinuation of the antithrombotic therapy [25, 76–78].

Dental interventions that are unlikely to cause bleeding	Dental interventions that are likely to cause bleeding (low risk)
Local anesthesia	Ordinary extractions (1-3)
Basic periodontal clinical examination	Incision and drainage of intradental abscess
Supragingival cleaning	Periodontal probing
Supragingival indirect or direct restorations	Subgingival scaling
Endodontics	Subgingival margins of direct or indirect restorations
Impressions and other prosthetic procedures	Implant surgery
Fitting and adjustment of orthodontic appliances	Soft-tissue biopsies

*For vitamin K antagonist therapy (INR values should always be within the therapeutic range when possible)

Table 3.
Dental interventions that do not require anticoagulation therapy interruption–adapted from Kaplovitch and Dounaevskaia [25].*

7. Bleeding in dental surgery: clinical implications

Dental surgical interventions are considered by most recommendations, as minor procedures presenting self-limited blood loss and low bleeding risk. Bleeding, in most cases, can be managed with local hemostatic agents [79, 80].

7.1 Should anticoagulants, antiplatelets, or direct oral anticoagulants be discontinued for minor dental surgeries?

The dental care of individuals receiving therapeutic anticoagulation becomes critical when invasive procedures are needed. At this time, the clinician must decide either to maintain the anticoagulation therapy and risk bleeding complications or withdraw the anticoagulation medication and risk developing systemic thrombosis [1]. After decades of controversial data, there is currently a nearly unanimous consensus that anticoagulation therapy, for most dental surgeries, should not be discontinued. The higher risk of bleeding complications is compensated by the elevated risk of developing thromboembolic complications [1, 81–84].

National dental and medical group statements and multiple evidence-based clinical guidelines have considered the issue independently and support the maintenance, for most dental patients, of anticoagulation therapy (American Dental Association; American Academy of Dental Sleep Medicine; American Heart Association; American College of Cardiology; American Academy of Neurology; American Society of Anesthesiologists; Society for Neuroscience in Anesthesiology and Critical Care; American College of Chest Physicians (ACCP)) [1]. In a 2012 statement [76], the ACCP recommended continuing anticoagulation therapy with warfarin, with the additional utilization of a local hemostatic. The ACCP advised a 2–3-day anticoagulation therapy suspension, in order to lower the INR levels to a range of 1.6 and 1.9 [76, 85].

Lately, the dental care of patients receiving anticoagulant treatment has been the focus of expressive scientific interest, in both dental and medical fields. A recent literature review showed that only 31 (0.6%) of more than 5400 patients receiving over 11,300 dental surgical interventions while continuing to take vitamin K antagonist anticoagulants (warfarin in most cases) demanded more than local maneuvers for hemostasis. No cases of fatal hemorrhage were reported. In over 2600 individuals whose anticoagulation was discontinued for dental interventions, 22 thromboembolic complications (0.8% of medication withheld), including 6 fatal events (0.2% of medication withheld), were observed [83]. Similar results have been shown in a literature review of dental surgery and antiplatelet medications. Of more than 1200 patients receiving over 2300 dental surgical procedures while continuing their antiplatelet medications (aspirin in most cases), only 2 (0.2%) needed more than local measures for hemostasis. Conversely, in over 320 individuals undergoing 370 antiplatelet interruptions for dental procedures, 17 (5.3%) suffered thromboembolic complications [86].

Available data shows that the majority of dental interventions can be safely conducted in patients receiving anticoagulation treatment, when considering older medications [4]. However, there are fewer studies reporting the provision of dental care in individuals using newer direct oral anticoagulants. The clinical implications of these newer anticoagulant and antiplatelet therapies have only been recently investigated [80, 87]. The protocol followed by the dental practitioner when managing these patients varies significantly and shows inconsistencies reflecting the lack of large-scale studies and evidence-based clinical guidelines [80, 88, 89]. The risk

of postoperative bleeding after invasive periodontal treatment in individuals using different anticoagulation therapies was assessed, retrospectively, in 456 individuals receiving an antiplatelet and/or anticoagulant therapy [90]. Data was collected after 484 invasive periodontal interventions, with 99.6% of patients continuing their medications during the procedures. Postoperative bleeding was reported only following three interventions (0.35%), and it was controlled with local hemostatic maneuvers. Although the authors did not specify which type of local hemostatic procedure was used, this retrospective study showed a very low risk of bleeding in patients receiving an invasive periodontal intervention while using an anticoagulant or antiplatelet medication [90]. These results support the recommendation that such medications do not need to be discontinued in anticipation to invasive periodontal interventions.

Extended inter- or postoperative bleeding following dental surgery is infrequent, seldom demanding anything more than the use of local hemostatic biosurgicals. The judgment of whether or not to interrupt anticoagulation treatment can be both intricate and dynamic, and it should be based on the indication for pharmacological therapy, as well as previous thromboembolic history. The discontinuation of anticoagulant therapy may be required in dental interventions with moderate and high bleeding risk [25, 76–78]. Currently, most clinicians dealing with anticoagulant management tend to personalize the periprocedural management of the bleeding potential, according to the individual risk of each procedure—low, moderate, or high—following the current clinical practice recommendations based on best evidence and maintaining the anticoagulant therapy. Thereby, the patient anticoagulant regimen should be continued in specific low-risk dental procedures, without consultation or fear of disproportionate bleeding demanding additional intervention (**Table 3**) [25].

7.2 Common anticoagulants and potential interactions with dental medications

Undoubtedly, anticoagulant agents are effective in preventing thromboembolism. Nevertheless, their potential for critical adverse effects cannot be ignored. The use of antithrombotic medications is the most frequent cause of an adverse drug event requiring individuals to seek out emergency care [25, 91]. The majority of drug interactions with anticoagulants lead to elevated risk of bleeding. The nature of the interactions cannot be predicted, as they are expressed through both pharmacodynamic mechanisms and pharmacokinetic properties [25].

Regarding patient safety, potential risk for interaction, as well as knowledge of appropriate prescribing and monitoring, is crucial. Equally decisive is selecting the appropriate anticoagulant agent and monitoring the potential for drug–drug interaction [10–15, 17, 25]. Common anticoagulants and their interaction with the most common medications prescribed for dental patients are described in **Table 4** [25, 92–98].

7.3 What is the difference in the risk of bleeding between patients ongoing anticoagulant therapy and patients not treated?

Most studies evaluating the occurrence of peri- and postoperative bleeding show anticoagulation therapy can be maintained when adequate local hemostatic maneuvers are used.

As an example, a controlled clinical trial compared the occurrence of bleeding following dental extractions in individuals receiving oral anticoagulants (experimental group) versus patients that had never received oral anticoagulant therapy (control group). Tooth extractions were performed, and a piece of oxidized cellulose was placed only into the sockets in the experimental group. The wound borders were sutured, and a gauze saturated with tranexamic for 30–60 minutes

Anticoagulant medication	Drug interactions with anticoagulants*
Vitamin K Antagonists Warfarin Acenocoumarol	Antibiotics[a][92,93]: Clindamycin; Amoxicillin; Amoxicillin Clavulanate; Cephalexin; Doxycycline; Macrolides; Metronidazole Azole antifungals [92] Analgesics [94-96] Carbamazepine Oxcarbazepine Nonsteroidal anti-inflammatory drug
Direct Dental Anticoagulants Apixaban Rivaroxaban Dabigatran Edoxaban	Antibiotics [97]: Clarithromycin; Erythromycin[b] Azole antifungals [97] Analgesics [97] Carbamazepine Nonsteroidal anti-inflammatory drug
Low-Molecular-Weight Heparins Tinzaparin Dalteparin Enoxaparin	Analgesics [98] Nonsteroidal anti-inflammatory drug

* "This list is not exhaustive. [a]Single doses of antibiotics are unlikely to modify anticoagulation effect in a clinically significant manner. Consider increased monitoring for 2 or more days of treatment. [b]Erythromycin predominantly interacts with Dabigatran and Edoxaban"

Table 4.
Common anticoagulants and potential interactions with dental medications–adapted from Kaplovitch and Dounaevskaia [25].

was applied with pressure in the wound. Both groups presented similar bleeding complications [99]. In a similar clinical trial [100], 161 tooth extractions were performed in patients undertaking warfarin. After tooth extraction, an oxidized cellulose gauze was placed in the socket, and the wound was sutured. Patients were assigned to four groups, according to their INR range (INR was 1.5–1.99 in group 1; 2.0–2.49 in group 2; 2.5–2.99 in group 3; and 3.0–3.7 in group 4). No significant differences were found in the postoperative bleeding among groups.

8. Conclusions

Based on the latest evidence and clinical practice recommendations on the perioperative management of dental patients receiving direct oral anticoagulants, on single or dual antiplatelet therapy or vitamin K antagonists, as well as on the current scientific knowledge on biosurgical hemostatic agents, the following conclusions can be made:

- The majority of dental procedures can be securely executed without the withholding of anticoagulants, using only local hemostatic therapy. In fact, current recommendations and consensus support the continuation of antiplatelet or anticoagulant therapy. Discontinuing these drugs can increase the risk of thromboembolism, at the cost of minor bleeding, which can be restrained without difficulty. The appropriate use of local hemostatic measures, such as topical biosurgical hemostatic agents, should always be considered whenever indicated.

- In order to safely treat a patient receiving anticoagulant therapy, familiarity with anticoagulants and with the potential for drug–drug interactions is required, in addition to knowledge about the topical hemostatic options available.

- Topical biosurgical hemostatic agents are diverse agents with distinct indications. The dental practitioner must be aware of the properties of each single agent, in order to properly select the product needed in each different clinical condition.

- Based on current available data, no topical hemostatic agent can be regarded as superior or more effective than the others. Further experimental research and controlled clinical trials are warranted to define the most cost-effective biosurgical hemostatic agents in dentistry.

- A definite protocol for excessive bleeding is still required for dental surgery in patients with hemorrhagic diathesis. The most effective local hemostatic agent with lesser complications should be determined in future research, considering their availability and cost-effectiveness.

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Conflict of interest

The authors declare no conflict of interest.

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