

REVIEW OF USING HEMOSTATIC AGENTS IN ORAL CAVITY/Review Paper

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Abstract

Background Hemostatic agents (Ha) are essential for controlling oral hemorrhage, particularly during surgical procedures, trauma, and certain medical conditions that predispose individuals to bleeding. This review examines the various types of hemostatic agents, including absorbable and non-absorbable materials, topical agents, and biological products, highlighting their mechanisms of action, efficacy, and safety profiles. The review categorizes these agents based on their mode of action, such as platelet aggregation, clot formation enhancement, and vasoconstriction. Additionally, we discuss the clinical applications of (Ha) in dentistry, including tooth extractions, periodontal surgeries, and management of oral hemorrhaging. A comparative analysis of commonly used hemostatic products, including gelatin sponges, collagen-based agents, and fibrin sealants, is provided to assist clinicians in selecting appropriate options tailored to specific clinical scenarios. Furthermore, the review addresses potential complications and contraindications associated with the use of hemostatic agents, emphasizing the importance of individualized patient assessment. Ultimately, the effective use of (Ha) can significantly improve patient outcomes by minimizing bleeding, reducing operative time, and enhancing recovery in various dental practices. Future research directions are proposed to explore innovative hemostatic technologies and their application in oral and maxillofacial surgery; the purpose of this study is to assess the safety and effectiveness of different (Ha) used in oral surgery.

Keywords: Hemostatic agents, tooth extractions, oral surgeries, oral hemorrhaging, clinical applications

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Introduction

Pain, nerve damage, swelling, infections, and bleeding are all possible side effects of any surgical operation, including dental surgery. From a straightforward tooth extraction to an alveoloplasty, dental surgery is any dental procedure that involves an incision in the gingiva or oral mucosa controlling bleeding is a crucial stage [1] in dental surgical operations [2]. As severe bleeding raises the risk of morbidity and makes operation more difficult and bleeding or oozing frequently

happens right after a tooth extraction, a wide variety of hemostatic medications are available as supplemental measures to improve hemostasis during dental surgeries in order to prevent such consequences when prolonged bleeding occurs, even when typical approaches for hemorrhage control are used appropriately.[3]

Most of the time, this bleeding is easily controllable [4]. Then, within eight hours of extraction, it virtually stops. But occasionally, it might go on, posing a hazard

to life. Suture ligatures and electrocautery are the most common methods used in major oral and maxillofacial surgical procedures to stop bleeding from both major and small vessels. However, using electrosurgical instruments could jeopardise teeth and nerves when there is widespread leakage and pressure is ineffective. In these cases, topical hemostasis medicines can be required [5].

Through a variety of mechanical techniques or physical interactions between the agent and blood, local Ha improve the natural clotting process and reduce external bleeding. In this review study we collected the information from many of references about fifteen to twenty years ago to compare between hemostatic agents by the different experience along years studies .

Aim of study

The purpose of the study is to assess the effectiveness and safety of various Ha used in oral surgeries and to compare their effectiveness in achieving hemostasis.

Review of literature

1.1 Normal hemostasis

Hemostasis is the physiological process that stops and restricts hemorrhaging at the locus of hurt while maintaining normal systemic circulation throughout the body [6]. There are two main parts to the hemostasis process: hemostasis, both primary and secondary.

1.1.1 Primary hemostasis the importance of platelets' participation in hemostasis has been well-established in the literature for the past century. For normal hemostasis to occur, platelets must function and be present in sufficient numbers. The relationships

between the injured vasculature and platelets, as well as their reactions, are highlighted in primary hemostasis. An initial hemostatic plug that momentarily stops blood flow at the site of injury is one of its components. [7]. Vasoconstriction, platelet adhesion, platelet activation, and platelet aggregation are the four successive and superposed steps that it begins with as soon as vascular damage occurs [8].

1.1.2 Secondary hemostasis

As shown in (Figure1-1), secondary hemostasis is conventionally divided into the intrinsic and extrinsic pathways, which are the two basic pathways. Collagen is the primary activator of the intrinsic route; it binds clotting factor XII (Hagman factor) to start this cascade when it is exposed. Damage to the tissue reveals tissue factor, which activates the extrinsic pathway. This process is initiated by the activation of Factor V11. When fibrinogen is transformed into fibrin by thrombin, the final clot, these two pathways eventually merge in a unified pathway [5].

1.2. Investigations for bleeding disorders

1.2.1. Bleeding time (BT)

Is frequently used to look into primary hemostasis [9]. Prior to surgery, the bleeding time is most commonly used to check for possibly dangerous platelet abnormalities. BT is considered very extended if it lasts longer than 15 minutes. BT normally lasts between one and six minutes. Given that surgery poses a substantial challenge to hemostasis and that hemostatic abnormalities could have catastrophic consequences, it makes reasonable to seek preoperative screening for potentially dangerous bleeding [10].

1.2.2 Platelets Counts (PLT)

A laboratory test called platelet count test counts the platelets in your blood. Platelets typically range from 150000 to 450000/mm³. Thrombocytes, another name for platelets, are small, spherical cell fragments that move through the bloodstream and are crucial for blood clot formation. A lump of blood that the body creates to halt bleeding is called a blood clot [11].

1.2.3 Prothrombin time (PT) and international normalized ratio (INR)

In laboratory equipment and point-of-care (POC) devices, the PT calculates the amount of time needed for coagulation to transpire subsequent to the introduction of a tissue factor source to recalcified citrated plasma, as shown in Table 2-1. The typical Prothrombin time count is between 11 and 13 seconds. According to the World Health Organization (WHO), To test PT and assess clot formation, a patient's citrated plasma sample is mixed with thromboplastin, a mixture of tissue factor, calcium, and phospholipid. In order to adjust their VKA dosages, patients using oral anticoagulants need to keep an eye on their INR because they vary from patient to patient. Between 2.0 and 3.0 is the score for the dimensionless INR value [12].

1.2.4 Partial Thromboplastin Time (PTT)

The intrinsic coagulation pathway is screened by partial thromboplastin time, which also assesses the sufficiency of factors I, II, and V of the common pathway and factors VIII, IX, X, XI, and XII of the intrinsic system. In hemophiliacs, it lasts longer [13]. PTT typically ranges from 25 to 35.

1.3 Hemostasis process

Various processes involved in hemostasis process are:

Vasoconstriction,

- Formation of a platelet plug, and
- Blood (secondary hemostasis).

Step 1. Vasoconstriction:

Immediate constriction of damaged blood vessels is caused by vasoconstrictive paracrine released by the endothelium cells which results in a temporary decrease in blood flow within the injured vessel.

Step 2. Formation of a platelet plug:

The defect is then mechanically blocked by a plug that develops when platelets adhere to the exposed collagen at the site of endothelial damage (platelet adhesion) and become activated, releasing cytokines (endothelin 1, thromboxane A₂, and serotonin) into the surrounding area. The vasoconstriction process is strengthened by released platelet factors (adenosine diphosphate, fibronectin, thrombospondin, fibrinogen, and platelet-derived growth factor), which also encourage platelets to adhere to one another (platelet aggregation) and form the platelet plug at the site of damage [14].

Step 3. Coagulation (Secondary hemostasis):

When collagen and tissue factor are exposed, a sequence of events known as the coagulation cascade is started, which culminates in the creation of fibrin polymer. In order to stabilize the platelet, plug and assist it form a blood clot, fibrin protein fiber mesh is used. Traditionally, the clotting cascade (secondary hemostasis) is divided into two fundamental mechanisms.

- Intrinsic pathway: Also known as contact activation pathway, is primarily activated by collagen, which is exposed at the site of injury and binds Factor XII to initiate this coagulation cascade.
- Extrinsic pathway: Also known as tissue factor pathway, is stimulated by tissue factor, which is exposed by the tissue injury and through Factor VII activation initiates this pathway [15].

1.4 In dental surgery, bleeding diathesis can be classified as: either acquired, autoimmune, or hereditary hemorrhage.

1. Primary bleeding: bleeding that occurs in the course of operation
2. Reactive hemorrhage: bleeding occurring between two and three hours after surgery.
3. Secondary hemorrhage: bleeding occurring 14 days or more after surgery, usually due to an underlying condition.

Another way to classify hemorrhage is by the area that was damaged: soft tissue, bone, and vascular [14]. An uncommon propensity to bleed, bleeding diathesis can be acquired, autoimmune, or hereditary. (Table 1-1) [16]

1.5. Bleeding disorders Types: According to Table 1-1, bleeding disorders can be categorized as coagulation factor deficiencies, platelet disorders, vascular disorders, or fibrinolytic defects.

Although there are a number of bleeding diseases, the most prevalent ones are:

1.5.1 von Willebrand disease (VWD):

The most common hereditary bleeding problem is, as shown in Table 1-2, and is caused by either qualitative

(Type 2) or quantitative (Type 1 and Type 3) abnormalities in von Willebrand factor (VWF) As a carrier protein for Factor VIII, Von Willebrand factor prolongs its half-life by protecting it from proteolytic degradation. Furthermore, it promotes platelet aggregation and helps platelets adhere to injured vascular endothelium [20]. Considering how important VWF is for hemostasis and perioperative bleeding, patients with VWD are more vulnerable to bleeding [18], and wound healing [19]

The type of surgery or operation being performed and the severity of the patient's bleeding characteristics determine this risk. When undergoing surgery, patients with VWD may benefit from adjunctive antifibrinolytic therapy, such as tranexamic acid (TXA), desmopressin, which causes the vascular endothelium to release stored endogenous VWF, and the administration of concentrates containing VWF (both recombinant and plasma derived). [20]. Endothelial cells and megakaryocytes produce von Willebrand factor (vWF), which is mostly a big, glycosylated protein, which are platelet progenitors. The fact that there are three main subtypes of VWD makes diagnosis more challenging.

Management

Three essential components will guide the safe administration of dental treatment for patients whose diagnosed with vWD: examining the patient's hematologic history, determining the patient's dental needs and the expected risks of bleeding during the procedure, and coordinating and communicating with the patient's hematologist [21].

Suturing, cautious soft tissue handling, and precise surgical techniques all contribute to reduce local bleeding in all patients [22]. Furthermore, It has also been shown that using one or more of the prohemostatic treatments below can help vWD patients.

: the mainstay of local treatments for vWD includes the use of tissue adhesives, hemostatic wound dressings, and antifibrinolytic oral rinses. As with other wound bleeding situations, a thorough evaluation of the efficacy of local interventions is required [21]

1.5.2 Hemophilia A and B

Hemophilia A is the most prevalent type of this disorder, impacting roughly 1 in 5,000 males. In contrast, Hemophilia B occurs less frequently, affecting about 1 in 30,000 males. (Table 1-3) [23] .

A factor IX deficiency causes hemophilia B, also referred to as Christmas disease, which is clinically identical to hemophilia A [26]. According to Miller and Bean (2021), hemophilia A and B are both X-linked recessive diseases. Males are more likely than females to have hemophilia A and B due to the X-linked inheritance pattern [28] .There are three forms of hemophilia A based on the amount of factor VIII in the plasma: mild, moderate, and severe [24].

Laboratory analysis

To determine the possible source of bleeding in hemophilia, screening tests such platelet function tests or prothrombin time (PT) and activated partial thromboplastin time (APTT) are used [25] . (Table 1-4)

4) Interpretation of screening Tests

Management

Coagulation factor replacement is typically not necessary for patients with mild hemophilia who do not have inhibitors and can be treated as outpatients [26]. For less invasive treatments, patients with mild hemophilia who are not taking inhibitors might need factor replacement; for more they will require factor replacement following invasive oral surgical treatments.

. Additionally, DDAVP (desmopressin) and EACA (epsilon-aminocaproic acid) or tranexamic acid can be used to treat patients with moderate hemophilia [26] Hospitalization and therapy using tranexamic acid, DDAVP, EACA, or factor replacement are necessary for patients with severe hemophilia [27]. Both the patient and the healthcare professional may have concerns about the surgical treatment of hemophiliacs. However, careful preoperative planning, collaboration with the patient's hematologist, and comprehensive preoperative evaluation enable safe and efficient surgical management of hemophiliac patients [26].

It's important to plan for surgical operations, such a simple tooth extraction, to reduce the chance of hematoma formation, severe bruising, or bleeding. An urgent surgery is rarely required in dentistry since pain may often be controlled without the need for an unexpected treatment. It is necessary to consult the hemophilia unit about any treatment plans that need the use of prophylactic cover [28].

1.5.3 Vitamin k deficiency

In order to avoid vitamin K-deficient bleeding, which could otherwise occur because vitamin K cannot pass through the placenta, newborns are administered vitamin K at delivery. Deficiency in vitamin K is uncommon after the neonatal stage. According to recent research of the 2011–2012 NHANES, vitamin K intakes have generally decreased over the past 20 years, and more than half of persons over 70 do not consume enough vitamin K in their diets [29]. Cardiovascular disease is one of the age-related comorbidities that have been linked to low vitamin K intake and status, even if this does not show up as an obvious vitamin K deficiency. However, vitamin K supplementation research has yielded conflicting results [29].

The patient has melena, mucous membrane bleeding, bruises easily, and blood clots under their nails [30].

Lab investigations

To determine whether a vitamin K shortage is the cause of the symptoms, your doctor will probably do a coagulation test known as the prothrombin time (PT). This blood test calculates the time it takes for your blood to form a clot. [31].

Managements

In the event of postoperative bleeding, surgery is required. Following local anesthetic, the wound should be reopened, checked, and the local hemostasis techniques should be repeated. Additionally, postoperative instructions should be highlighted. The study of hemostasis should involve platelet counts and INR measurements, and the patient should be admitted to the hospital if the bleeding persists after hemostasis has been recapitulated [38]. In the 24 hours before surgery, the biological status sheet should be completed, including the INR number [32].

1.5.4 Liver disease

Nodule formation and fibrous tissue replacing the hepatic parenchyma are hallmarks of liver cirrhosis [33]. Several cirrhotic consequences and impairment of other organs and systems, such as the kidneys, lungs, cardiovascular system, etc., are caused by physiological damage to the liver [34]. Because they can raise patient morbidity and mortality rates, hemorrhagic processes are of special interest. Insufficient clotting factor production, vessel wall dilatation and relaxation brought on by nitrogen compound accumulation (especially nitric oxide, or NO), a decrease in circulating platelets (due to hypersplenic sequestration and a decrease in the liver's production of thrombopoietin), and alterations in platelet function (adhesion) brought on by the action of NO and ammonia are some of the mechanisms underlying bleeding events.

Furthermore, endogenous heparinoids may also be released as a result of bacterial infections [35].

Prothrombin time (PT), international normalized ratio (INR), and platelet count should be ordered in order to predict bleeding events during dental procedures. According to published research, patients who have a platelet count of fewer than 40,000 or 50,000 and/or an INR higher than three should not have surgery; instead, they should have preventative transfusions to prevent bleeding during or after surgery [36].

1.5.5. Scurvy

Collagen synthesis is disturbed when vitamin C is deficient in the diet, leading to deformity and the lack of mature collagen. It is challenging to diagnose scurvy in its early stages, which occur about three to six months when the daily dosage falls below 10 mg due to nonspecific symptoms such as arthralgia, weakness, fatigue, irritability, weight loss, and vague myalgia. Tissue bleeding with nonpalpable purpura is the most distinctive sign of scurvy. Utecht and Stephen Later on, more typical symptoms like bone fragility, hemarthroses, Dystrophic hair lesions, purpura, petechiae, and delayed wound healing manifest [37]. Significant gingival hyperplastic lesions were present in the patient, as shown in Figure 1-2

The production of collagen, which is necessary for the blood vessels to be firm, requires vitamin C. Scurvy sufferers have abnormal bleeding, weakening of the arteries, and leakage. Scurvy typically manifests as weariness, bruises, tight joints, and malaise, primarily on the upper thighs and legs. It is common to experience easy bleeding of spongy gums. The following phase includes open wounds, fever, jaundice, tooth loss, and death [38].

1.5.6 Thrombocytopenia

Platelet counts less than 150×10^9 are known as thrombocytopenia, can be brought on by peripheral platelet destruction, increased sequestration, or decreased platelet synthesis. Dental care for these medically impaired patients is significantly impacted by a low platelet count since it may be linked to potentially fatal bleeding [39].

When handling a patient who is at risk for postoperative bleeding, precise surgical technique is essential. To reduce soft tissue damage, it is realistic to avoid making large flaps or releasing incisions. To lessen bleeding in hard tissues, conservative bone removal and teeth sectioning are recommended. [40] Granulation tissue may be the cause of postoperative bleeding, so it should be carefully removed and curetted [41]. Several medications that have been shown in numerous studies to cause Table 1-5 lists thrombocytopenia caused by drugs.

Laboratory tests

Complete blood count (CBC), thromboelastography (TEG), bleeding time (BT), and coagulation tests including prothrombin time (PT) and platelet function analysis (PFA)-100 are all considered first-line bloodwork [41].

Management

Those with a platelet count of more than $30,000/\mu\text{L}$ can safely undergo low-risk bleeding treatments in a dentist's practice. [39] For patients undergoing invasive procedures like tooth extractions or in need of platelet prophylactic transfusions, a hospital outpatient facility is the ideal choice since it facilitates care coordination and gives the dentist additional resources to address surgical issues [38].

1.6 Patient assessment

1.6.1 Preoperative assessment and risk of bleeding:

Prior to surgery, the dentist should evaluate the patient's risk of bleeding as well as the risk of bleeding from the surgical procedure. The expert can then develop an intraoperative and postoperative plan after evaluating both bleeding risks. Patients who report an increased risk of bleeding should have their international normalized ratio (INR) assessed. Hirsh [42] states that the therapeutic range is between 2.0 and 3.5, whereas the standard coagulation criterion has an INR of 1. In this case, local hemostatic measures, either by themselves or in combination with more conventional methods, are recommended. Before, during, and after dental operations, these chemicals can be applied.

A thorough medical history that includes all of the patient's prescriptions in order to detect any possible bleeding problems before surgery [43]. Patients on anticoagulant therapy would require more exodontia treatments to reduce surgical bleeding [44]. For people with compromised immune systems, laboratory results such as platelet count, INR, and prothrombin time are crucial [43]. Risk factors for demographics (older age and female sex) [45] According to Verma and Collet et al. other risk factors for patients include diabetes mellitus, hypertension, obesity, hemostatic diseases, renal impairment, and other major organ system failures. Timing of the appointment: early morning visits allowing patients to return to the dental office in case of postsurgical hemorrhage [45]

1.6.2 Identifying patients at risk of bleeding

Patients are more likely to bleed if they have a family history of bleeding, have had bleeding problems after oral surgery or trauma, or are taking aspirin, anticoagulants. The risk of bleeding is increased by any conditions linked to bleeding issues, including

hemophilia, liver disease, and leukemia. During or after a surgical treatment, the dentist must be alert and ready for any unforeseen circumstances. Patients with severe periodontal disease are also thought to have a higher risk of perioperative bleeding. In these cases, the surgical plan should include a preoperative phase that includes scaling and root planing, along with an appropriate chlorhexidine gluconate mouthwash regimen, two weeks before an elective procedure. [43]

There are three levels of risk for bleeding during a dental procedure: high, moderate, and low. [44] Due to the severe consequences of thrombosis, antithrombotic medication is typically not stopped before dental procedures with minimal bleeding risk in the majority of patients [45]. It may be necessary to temporarily stop taking antithrombotic medication for interventions with moderate to high bleeding potential [47].

1.7 Hemostatic agents

A hemostatic agent (antihemorrhagic) is a substance that promotes hemostasis (stops bleeding)

The acquired bleeding diathesis associated with hemostasis-altering drugs is the most prevalent. According to Kaplovitch and Dounaevskaia, anticoagulant medications are among the most often prescribed medications in the United States [46]. Anticoagulants have been used for decades to prevent venous and arterial thromboembolism. Bruising and prolonged bleeding are among the side effects associated with these drugs. Vitamin K antagonists, oral anticoagulants, and therapeutic platelet inhibitors are the most commonly utilized medications. Dental surgical techniques can cause substantial bleeding in those who are prone to hemorrhage. Patients at risk for bleeding diathesis may benefit from the use of biosurgical agents to reduce or control bleeding [1].

1.7.1. Using of the Biosurgical topical hemostatic agents in dental surgery:

Both healthy patients and those with systemic impairment may experience bleeding problems. A number of variables, including anticoagulant medication, congenital bleeding disorders, uncontrolled hypertension, severe soft tissue damage, and noncompliance with postoperative instructions, might cause certain patients to bleed significantly during or after dental surgery. In these situations, using an efficient hemostatic agent improves hemostasis and offers a number of advantages, including better anticoagulated patient care, a faster recovery period, and less exposure to the wound.

Effective, economical, and biocompatible topical (Ha) are desirable [48]. The variety of topical hemostatic drugs has grown dramatically in the last several years (Table 1-6). Dental professionals must be knowledgeable about the several topical hemostatic medications that are available, including their effectiveness, mechanism of action, and adverse effects. A skilled expert can select the most beneficial and effective agent in any situation. The scientific evidence that is now available about the application of local hemostatic in dental operations is not consistent. To counteract the anticoagulant effect and control bleeding after surgery, the majority of publications employ one or more local hemostatic drugs [49]. The most common local biosurgical (Ha) used in dentistry and approved by the Food and Drug Administration (FDA) are listed in Table 1-6.

1.7.2 Passive or mechanical agents

Passive or mechanical agents are thought to be the most effective for mild bleeding because they activate and aggregate platelets. By triggering the extrinsic clotting pathway and creating a surface that will facilitate faster coagulation, this causes a matrix to form in the bleeding location, which acts as a barrier to stop bleeding [50]. These agents depend on the person's own fibrin production to achieve hemostasis

because they are physiologically inactive. Passive hemostats should only be used by people whose coagulation cascade is unharmed [51]. Since they are widely accessible, don't need to be handled or stored specifically, and are reasonably priced, they are typically used as frontline agents [52].

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

Porcine cutaneous collagen is the source of the hydrocolloid gelatin. It comes in powder and sponge form and can be applied dry or wet with saline. It offers a porous matrix that promotes the development of fibrin clots and platelet aggregation. It can absorb 40 times its weight in moisture, making it very hygroscopic and perhaps contributing to surrounding wound pressure. In 4-6 weeks, hydrolysis fully resorbs the gelatin matrix. Kim et al. (2017) observed that the use of absorbable gelatin sponge after extraction of the third molar dramatically reduced postoperative edema, mucosal petechiae, and cutaneous ecchymosis [53].

Microfibrillar collagen

Because Collagen provides a lot of surface area for the generation of clotting factors including thromboxane A2 and platelet activation and aggregation, it aids in hyalinization but is less effective in patients with severe thrombocytopenia. Microfibrillar collagen comes in powder, nonwoven sheets, sponge, and pad forms and is made from the skin or tendon of cows. It is often absorbed in less than eight weeks and does not swell considerably. In their split-mouth RCT, Kim et al (2020). showed that collagen improved the 31 patients with bilateral mandibular impacted third molars showed reduced discomfort (VAS score), reduced probing depth, and initial healing of soft tissues and periodontal abnormalities [54].

Huang has been shown in various studies to be effective in periodontal surgery, particularly in the palatal tissue autograft donor site. The blood flow rate

was significantly reduced by 51% ($p < 0.01$) after 10 minutes of treatment, and the bleeding time was shortened by 1 minute as opposed to approximately 20 minutes in the control group, according to the investigators. However, patients did not perceive any variations in the rate or quality of healing or the level of pain [55].

Oxidized Regenerated Cellulose (Surgicel®, Oxycel®, Gelita-Cel®)

Oxidised cellulose is made from cellulose and comes in sheets of absorbable fibres. It is classified as either non-regenerated (ONRC, having unorganized fibres before oxidation) or regenerated (ORC, organized fibres are created before oxidation). Though unhandy20, the ONRC appears to be more effective. It is antibacterial, produces hemolysis, and is incompatible with topical thrombin due to its acidic pH. It should be removed because, although it is absorbed in roughly eight weeks, the acidic pH may cause issues such granulation formation and the diagnosis of a clinical abscess by delaying resorption [56].

Acrylate monomers, which make up this substance, polymerise when they come into touch with bodily fluids. According to the length of their side chains, cyanoacrylates are categorised as long-chain products like Dermabond® and Surgiseal® and intermediates like Tissu-Glu®. [57], treated 30 patients with sutures and 130 patients with adhesive following various procedures (molar extraction, mucogingival grafting, and apicectomy). When Tisuacryl was applied to donor sites and mucosal ulcerations, the authors experienced instantaneous hemostasis, typical incision healing, and pain alleviation. In 120 patients with impacted mandibular third molars, Escobar et al. evaluated cyanoacrylates with silk sutures. There was no discernible difference in postoperative discomfort, oedema, wound dehiscence, or infection, however

there was a statistically significant difference in postoperative bleeding (day 1) between the control group and the cyanoacrylate tissue adhesive group [58].

The soft, malleable substance known as bone wax, which was developed by Sir Victor Horsley in 1886 and is composed of beeswax, salicylic acid, and almond oil, is used to stop bleeding and locate its cause. It just obliterates the vascular gaps in cancellous bone without encouraging coagulation. It is not absorbed due to its insolubility, which also inhibits bone repair and increases the risk of infection, inflammation, and foreign body reaction. These factors make it important to use it sparingly and to get rid of any excess. Bone wax is a safe and effective way to stop bleeding after tooth extractions, including in patients on the medication without stopping or changing the treatment, according to Scarano et al., who used it to stop the bleeding in 176 patients on chronic anticoagulant therapy after tooth extractions or surgical extraction of a retained tooth. Other author reported bone wax-induced inferior alveolar nerve damage after third molar surgery [59]. The patient complained 2 months of paraesthesia of the cutaneous distribution of the right mental nerve for two months after having the lower third molar extracted eleven years prior. The CT scan showed a focused spherical expansion of the right inferior alveolar canal with a diameter of 9 mm. After excising the lesion and grafting the nerve (sural nerve donor site), a sizable portion of bone wax was taken from the specimen during dissection [60]. The patient was pain-free and had regained sensitivity after a year of follow-up. In this instance, brain tissue was crushed and invaded by foreign body reactions to bone wax [61].

Aluminum Chloride (AlCl₃)

In order to increase visibility and employ materials for root canal obturation, other chemical agents may be used during endodontic surgery to halt bleeding. Blood flow from the arteries is stopped by a barrier made of coagulated blood proteins created by Aluminum chloride (AlCl₃). It is frequently utilized due to its commercial availability, affordability, and ease of application. A bone curette or a tiny round bur should be used to clean the bone defect because when applied as a paste, It may adhere to the bony crypt's walls, and any remaining particles may cause localized foreign body reactions and impede healing [62].

Ferric Sulfate

Although ferric sulfate (FS) interacts with blood proteins and causes coagulation, it is cytotoxic and has a very low pH (0.8–1.6), which can result in bone damage, severe foreign body reactions, and the formation of abscesses.

Calcium Sulfate

Calcium sulfate (CaS) is inexpensive, rapidly setting, and easily removable characteristic agent. According to experimental studies, CaS has a high biocompatibility and produces outstanding outcomes without causing inflammation or adverse effects on the outcome. It can be removed or left in place because it serves as a physical barrier. If some CaS particles are left around the tooth after surgery, there shouldn't be any issues because this material is completely biocompatible and restorable. In clinical practice, it has been effectively utilized to control bleeding during endodontic surgery. Additionally, it has been used to decrease bleeding in surgical-orthodontic treatment of impacted teeth and as a (Ha) following tooth extraction in patients receiving anticoagulant therapy [63].

1.7.3 Active Hemostatic Agents

They directly contribute to the coagulation cascade and have biological activity, which causes a clot to form. Examples of active agents include thrombin and product formulations that incorporate thrombin with a passive agent to produce an active product. Thrombin is a suitable choice for those on antiplatelet or anticoagulant medications. Gelatin foam is typically used with it. Many hemostatic medications shouldn't be used on polluted wounds [71] .

Flowables (Surgiflo, Floseal)

Another type is flowable, which has a thrombin-containing animal gelatin matrix and is easily able to conform to uneven wounds. Since FloSeal (Baxter, Deerfield, IL, USA) has no fibrinogen but mixes thrombin with a microgranular gelatin flowable matrix made from cows, contact with the patient's fibrinogen—that is, exposure to the patient's blood—is required for clotting. Surgiflo is made up of a bovine-derived thrombin and a porcine gelatin matrix.

The Floseal procedure was shown by Ali et al. (2022) to be effective in preventing post-dental extraction bleeding in individuals with inherited bleeding disorders, as well as in patients who already had clotting factor inhibitors or allergy to clotting concentrates [70]. Compared to the conventional perioperative factor replacement approach, the floseal protocol is more cost-effective and equipotent.

Surgiflo

Is a topical bovine-derived thrombin called Thrombin-JMI mixed with an absorbable, sterile, hemostatic porcine gelatin matrix. To initiate the hemostatic process, it must be applied directly to the areas that are bleeding for the components of the sealant to polymerize, a compression period is necessary. [50]

Floseal

Consists of CaCl_2 , human thrombin isolated from plasma, and a bovine gelatin matrix. When the product is placed on a bleeding region, the gelatin granules expand (10–20%) when they come into contact with blood, creating a seal [50] .The product's thrombin fraction starts the usual pathway of the coagulation cascade, turning fibrinogen into a fibrin polymer and creating a clot around the solid matrix [14,60 and 61] The clot is reabsorbed within 6–8 week, which corresponds to the normal wound-healing period. The requirement for blood to activate Floseal is one of its unique characteristics [62]. Neither compression, nor a dry surgical field is required for its application.

This bio surgical flowability allows them to readily conform to uneven wounds. In major dental surgery, For patients for whom conventional treatments have not worked, flowable hemostats have been utilized as first-line topical treatments. They can be added to hemostasis in practically all dental surgical procedures. Both soft and hard tissues respond well to flowable. They can spread infectious pathogens, thus people who are allergic to products derived from cows shouldn't use them.

Topical Thrombin (Thrombin- Recothrom® and Evithrom®)

Recothrom® and Evithrom® The conversion of fibrinogen to fibrin is facilitated by thrombin. Topical thrombin hemostats can be made from human or bovine plasma or recombinant DNA technology. Thrombin-JMI (Pfizer), which is made from bovine plasma, might cause either fatal severe thrombosis because of the development of antibodies against bovine thrombin or fatal bleeding because of the development of antibodies against bovine factor V that are cross-reactive to human factor X. Due to these reasons, thrombin produced from human plasma (Evithrom®) and recombinant human thrombin (Recothrom®) were approved by the Food and Drug

Administration in 2008. as alternatives to bovine thrombin. Applying thrombin can be done as a spray, paste, dry powder, or in conjunction with collagen or gelatin, as Gelfoam®. According to a study by Browman et al. comparing recombinant human thrombin and bovine thrombin, rhThrombin has a far lower risk of immunogenicity and viral transmission than bovine thrombin and is just as effective at attaining hemostasis within 10 minutes of treatment [64].

Antifibrinolytics (Tranex®, Ugurol®, Lysteda®, Cyklokapron®, Amicar®,

(Caprolisin®) Synthetic analogues of the amino acid lysine, such as Epsilon-Amino-caproic Acid (EACA) and Tranexamic Acid (TXA), are antifibrinolytics that stop plasminogen from being converted into plasmin by binding to the lysine-binding sites on plasmin. EACA is not as effective as TXA. Although it is more commonly applied topically. In their analysis of randomized clinical studies comparing mouthwash (TXA) and other hemostatic medications in anticoagulating patients, McCormack PL et al. showed that TXA had a greater protective impact on bleeding following minor oral surgery than both aminocaproic acid and a placebo. In the same way, when compared to a placebo [68], Ockerman et al. showed that TXA mouthwash was effective in lowering the rate of oral bleeding during or immediately following dental extractions in patients on non-vitamin K oral anticoagulants (NOACs) [65].

1.8 Some pictures of topical hemostatic agents:

Figure1-5 (Picture1-5 show surgifoam type of passive agents)

<https://www.osseodent.com/wp-content/uploads/2022/11/SurgiFoam-12.jpg>

Figure 1-6 (Picture 1-6 Show fibrin sealants type of active agents)
<https://images.app.goo.gl/2kQcjU6qwzSgcGwn7> , 2019

Figure1-7 (Picture 1-7 show surgiflo from (Zhang, 2011) <https://tse3.mm.bing.net/th/id/OIP.0MWmbRfj-YXZMxoORFew-wHaE8?pid=Api&P=0&h=180>

1.9 Efficiency of various biosurgical hemostatic dental agents

Traditional techniques like manual pressure and ligation can aid in hemostasis, but they are ineffective for controlling bleeding in difficult-to-reach areas and complex injuries. Additionally, controlling bleeding is particularly difficult for people who have congenital or acquired coagulation abnormalities.

The term "topical biosurgical hemostatic agents" refers to a broad category of treatments designed to reduce the risk of bleeding. The effectiveness, benefits, and drawbacks of biosurgicals have been examined in a number of clinical trials conducted in recent years. Comparisons between the various biosurgical kinds and other non-biologic agents have also been conducted. Despite the fact that these local hemostatic drugs can help control bleeding during dental operations, there is currently little and conflicting information on how effective and efficient they are. There are notable methodological differences between research, including the absence of a common therapy and similar treatment plans, as well as the smaller number of randomized controlled trials [66]. As of right now, there isn't a clear, evidence-based method to help dentists choose local hemostatic agents. To choose the best solution for each unique clinical scenario, they need to be knowledgeable about the properties of each hemostatic drug. Furthermore, according to the data currently available, no topical

treatment can be considered better or more effective than the others. To identify the most economical bio surgical hemostatic drugs in dentistry, more experimental investigation and carefully monitored clinical trials are necessary[67].

Conclusion

The use of (Ha) in the oral cavity is an essential strategy for managing bleeding during surgical procedures, trauma recovery, and treatment of various oral diseases. Hemostatic agents, such as topical agents, gel-based products, and active clots, provide a critical adjunct to traditional methods of controlling bleeding, particularly in patients with hemostatic challenges or those undergoing surgical interventions.

Incorporating (Ha) not only enhances surgical outcomes by promoting faster hemostasis but also minimizes the risk of complications associated with excessive bleeding, thereby improving patient comfort and recovery times. The choice of agent should be guided by the specific clinical scenario, considering factors such as the type and extent of the procedure, the patient's underlying health status, and the desired speed and efficacy of hemostasis.

Recommendations 1. The selection of Ha should be based on the type of surgical procedure and the patient's needs. 3. Ensure thorough hemostatic control during procedures to minimize complications. 4. Educate patients on post-operative care to enhance recovery and minimize bleeding. 5. Monitor for any allergic reactions or adverse effects post-application of hemostatic agents. 6. Stay updated on the latest advancements and protocols regarding (Ha) in dentistry.

7. Consider combining (Ha) with other local hemostatic techniques for improved efficacy.

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List of Abbreviations

No.	Name	
1	Hemostatic agents	Ha
2	bleeding time	BT
3	complete blood count	CBC
4	desmopressin	DDAVP
5	epsilon aminocarpronic acid	EACA
6	international normalized ratio	INR
7	nitric oxide	NO.
8	peripheral blood smear	PBS
9	platelets count	PLT
10	point of care	POC
11	partial prothrombin time	PPT
12	prothrombin time	PT
13	tranexamic acid	TXA
14	von willbrand disease	VWD
15	worldhealth organization	WHO
16	calcium chloride	CaCl2

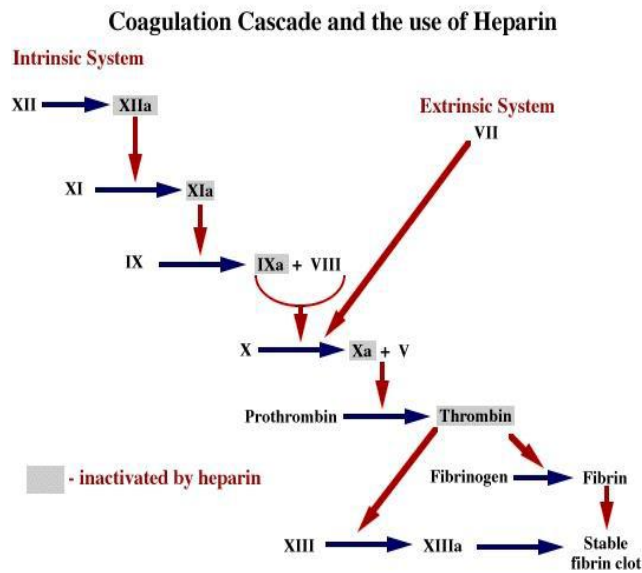


Figure1-1Coagulationcascade
<https://www.ch.ic.ac.uk/local/projects/McIntosh/Howitworks.html>

Von Willebrand Disease Classification			
Type	Defect	Inheritance	Clinical Manifestations
Type 1 (Accounts for ~¾ of cases)	Quantitative defect (i.e. not enough vWF)	Autosomal dominant	Bleeding: None – severe
Type 2 (Type 2A, 2B, 2M, 2N)	Qualitative defect (i.e. dysfunctional vWF)	Autosomal dominant (common) Autosomal recessive (uncommon)	Bleeding: Moderate – severe
Type 3 (Accounts for <5% of cases)	Profound quantitative defect (i.e. a total or near total absence of vWF)	Autosomal recessive	Bleeding: Severe (Clinically similar to hemophilia A)

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Table 1-2 Classification of VWD: major types and subtypes

Severity	Plasma level of factor VIII (%)	Dental management
Mild	6%-50%	- Preventive dentistry in the primary care setting should be emphasized. - All dental treatment can be delivered in the primary care setting. However, shared care with prior consultation with a hematologist is recommended.
Moderate	2%-5%	- Dental care providers should consider managing patients with a moderate level of hemophilia A as if they were patients with a severe level who require management in a secondary care setting. - Patients at these levels may require preoperative prophylactic factor replacement therapy. Therefore, consultation with the treating hemophilia center or hematologist is necessary. - Following consultation with the patient's hematologist, preventive dentistry measures, including oral hygiene instructions, diet analysis, pit and fissure sealing, and fluoride applications, are important.
Severe	<1%	

Table 1-3 Severity levels of bleeding A and general recommendations for dental management
<https://dimensionsofdentalhygiene.com/article/treatin-g-patients-bleeding-disorders/>

Causes of Bleeding in Adult Inpatients		
	Common	Rare
Acquired	- Anatomic/traumatic causes (ulcers, surgery, trauma, etc) - Medication effect (anticoagulants, antiplatelets, NSAIDs, etc) - Thrombocytopenia (acquired) - Liver disease (coagulopathy, variceal bleeding, etc.) - Renal failure/uremia - Consumptive coagulopathy - Vitamin K deficiency (with dietary restriction/antibiotics)	- Acquired bleeding disorders (FVIII inhibitors, acquired VWD, etc.) - Vitamin C deficiency
Inherited		- Inherited bleeding disorders (hemophilia, VWD, qualitative and quantitative platelet disorders, etc) - Connective tissue disorders

Table1-1 Common bleeding disorders
<https://www.sciencedirect.com/science/article/pii/S0006497123001441>

Possible diagnosis	PT	APTT	Platelet count
Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged ^a	Normal
VWD	Normal	Normal or prolonged ³	Normal or reduced
Platelet defect	Normal	Normal	Normal or reduced

Table 1-4 Interpretation of screening tests.

Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.*		
Drug Category	Drugs Implicated in Five or More Reports	Other Drugs
Heparins	Unfractionated heparin, low-molecular-weight heparin	
Cinchona alkaloids	Quinine, quinidine	
Platelet inhibitors	Abciximab, eptifibatide, tirofiban	
Antirheumatic agents	Gold salts	D-penicillamine
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin	
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid	Diazepam
Histamine-receptor antagonists	Cimetidine	Ranitidine
Analgesic agents	Acetaminophen, diclofenac, naproxen	Ibuprofen
Diuretic agents	Chlorothiazide	Hydrochlorothiazide
Chemotherapeutic and immuno-suppressant agents	Fludarabine, oxaliplatin	Cyclosporine, rituximab

* For a more extensive list, see Aster,² Warkentin,¹² and George et al.¹³ and the University of Oklahoma Web site (<http://moon.ouhsc.edu/george/DITP.html>).



Figure 1-2 gingival hyperplastic lesion from palatal view

Table 1-5 Drugs commonly implicated as triggers of drug-induced thrombocytopenia <https://www.grepmed.com/images/3201/thrombocytopenia-differential-medications-druginduced-hematology>

Topical hemostatic		Commercial name
Passive or Mechanical Agents	Gelatins	Surgifoam®, Gelfoam®, Gelfilm®, Gelita-spon®, 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	Surgiflo®, Floseal®
	Bovine collagen + thrombin	

Table 1-6 Types and trade name of some biosurgical agents–adapted from (

*Local biosurgical (Ha) can be classified into (A) passive or mechanical, (B) active, and (C) flowables [50].



Figure1-3 Oxidized Regenerated Cellulose
<https://tagumedica.com/en/producto/oxidized-celulo-cyanoacrylates> (Tissu-Glu®, Histoacryl®, Dermabond®, Surgiseal®, Tisuacryl®)



Figure 1-4 Cyanoacrylates

<https://catalogs.bbraun.com/en-01/p/PRID00000458/histoacryl-tissue-adhesive>



Figure1-5 (Picture1-5 show surgifoam type of passive agents)

<https://www.osseodent.com/wp-content/uploads/2022/11/SurgiFoam-12.jpg>



Figure 1-6 (Picture 1-6 Show fibrin sealants type of active agents)
<https://images.app.goo.gl/2kQcjU6q wzSgcGwn7>, 2019



Figure1-7 (Picture 1-7 show surgiflo from (Zhang, 2011) <https://tse3.mm.bing.net/th/id/OIP.0MWmbRfj-YXZMxoORF ew-wHaE8?pid=Api&P=0&h=180>)