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Review Article

LOCAL HEMOSTATIC AGENTS IN THE MANAGEMENT OF BLEEDING IN ORAL SURGERY

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ABSTRACT

Bleeding intraoperatively and postoperatively in oral surgery poses a great threat to the patient and can lead to serious untoward consequences if uncontrolled. The dentist should be familiar with the range of hemostatic agents available and their application during different types of bleeding episodes. Bleeding complications can occur in healthy as well as systemically compromised patients. Having a broad knowledge of the management approaches will allow the clinician to know when to apply a particular approach. Unfortunately, some of the most useful preventive measures and management techniques are not utilized because of a lack of understanding of the coagulation process and/or the approaches and materials that are available. The purpose of this article is to review the literature regarding the applications of various local hemostatic agents in the management of bleeding in oral surgery, their mechanism of action, and contraindications. Furthermore, the novel hemostatic agents such as HemCon dental dressing and Quikclot are also discussed. Local hemostatic agents are very useful in controlling bleeding during oral surgical procedures in patients with congenital and acquired bleeding disorders and also in patients who are on antithrombotic medications for their systemic conditions.

Keywords: Hemostasis, Local hemostatic agents, Oral surgery, Bleeding.

INTRODUCTION

Bleeding during and after surgery can be troublesome for both patient and the surgeon and if uncontrolled can lead to serious consequences. It may also compromise visibility and possibly the procedure itself. Bleeding normally occurs when a vessel is cut or interrupted during surgery or due to trauma which can be managed successfully in most cases by applying pressure. The source of bleeding can be either from hard tissue (bone) or soft tissue (gums), and they can be classified as arterial, venous, or capillary bleeding based on the source of the vessel involved. Identification of the source of the bleeding requires good illumination, adequate retraction, and thorough suctioning.

In major oral and maxillofacial surgical procedures, electrocautery and suture ligatures are most commonly used to control bleeding from small and major vessels. However, when generalized oozing is present, and the use of pressure is not effective, the use of electrosurgical instruments could endanger teeth or nerves, topical hemostatic agents may be needed [1]. In bony surfaces, parenchymal tissues, inflamed or friable vessels, or tissues with multiple and diffuse capillaries, it is extremely difficult to achieve hemostasis with mechanical and thermal methods. In such situations, one of the more common methods of intraoperative hemorrhage control involves the use of a topical hemostatic agent. Local hemostatic agents provide control of external bleeding by enhancing or accelerating the natural clotting process through various physical reactions between the agent and blood or by mechanical means. A general knowledge of the coagulation process will allow the clinician to better understand how the hemostatic agents work and when they should be applied. The rationale of this article is to review the literature about the local hemostatic agents in the management of bleeding in oral surgery, their mechanism of action, uses, and contraindications.

HEMOSTASIS

It involves three major steps: (1) Vasoconstriction, (2) formation of a platelet plug, and (3) coagulation (secondary hemostasis). The first step is an immediate constriction of damaged blood vessels caused by vasoconstrictive paracrine released by the endothelium which results in a temporary decrease in blood flow within the injured vessel. The second step is a mechanical blockage of the defect by a plug that forms as platelets stick to the exposed collagen (platelet adhesion) and become activated, releasing cytokines (serotonin, thromboxane A2, and endothelin 1) into the area around the injury. Released platelet factors (adenosine diphosphate, fibronectin, thrombospondin, fibrinogen, and platelet-derived growth factor) reinforce the vasoconstriction and activate more platelets that stick to one another (platelet aggregation) to form the platelet plug. At the same time, exposed collagen and tissue factor initiate the third step, a series of reactions known as the coagulation cascade that ends in the formation of fibrin polymer. The fibrin protein fiber mesh reinforces and stabilizes the platelet plug to become a clot. The clotting cascade (secondary hemostasis) is traditionally broken up into two basic pathways: the intrinsic pathway and the extrinsic pathway. The intrinsic pathway is primarily activated by collagen, which is exposed and binds Factor 12 to initiate this cascade. The extrinsic pathway is stimulated by tissue factor, which is exposed by the tissue injury and through Factor 7 activation initiates this pathway. These two pathways then converge in a common pathway where thrombin converts fibrinogen to fibrin and then the final clot [1].

Intrinsic pathway (contact activation pathway)

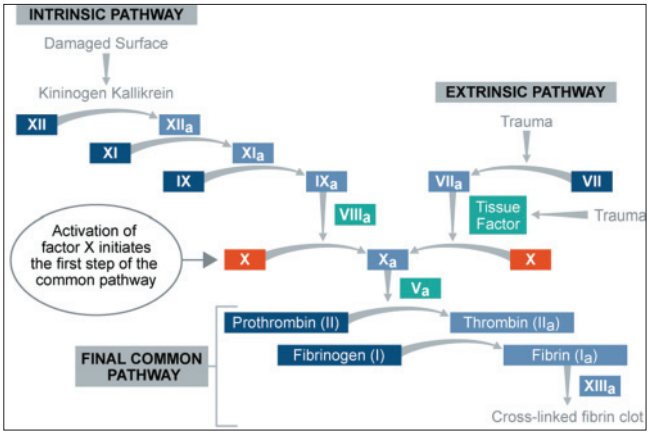
It is initiated when contact is made between blood and exposed negatively charged surfaces. On contact activation, prekallikrein is converted to kallikrein, which activates Factor 12 to 12a, which in turn activates Factor 11 to 11a. With Ca+ present, Factor 11a activates Factor 9 to 9a, which cleaves Factor 10 to 10a, the beginning of the common pathway.

Extrinsic pathway (tissue factor pathway)

Factor 3 (tissue factor) is released from the tissue immediately after injury and initiates the extrinsic pathway. Factor 3 forms a complex with Factor 7a, which catalyzes the activation of Factor 10, which cleaves to become Factor 10a.

Common pathway

The intrinsic and extrinsic coagulation cascades converge at activated Factor 10a, resulting in the conversion of prothrombin (Factor 2) to thrombin (2a). Thrombin activation occurs on activated platelets. Thrombin then converts fibrinogen to fibrin monomers, activates Factor 13 to 13a (transglutaminase), which then cross-link the monomers — with the aid of calcium — to form fibrin polymer and thus the clot.



Coagulation cascade

LOCAL HEMOSTATIC AGENT

A hemostatic agent (antihemorrhagic) is a substance that promotes hemostasis (i.e., stops bleeding). The ideal hemostatic agent should be effective, and the agent itself, along with its metabolic breakdown products, should be safe to use within the body and affordable.

Local hemostatic agents can be classified into: (1) Passive agents and (2) active agents [2].

Passive hemostatic agents provide a framework where platelets can aggregate so that a stable clot can form. The central mechanism of passive hemostatic agents is to form a physical, lattice-like matrix that adheres to the bleeding site; this matrix activates the extrinsic clotting pathway and provides a platform around which platelets can aggregate to form a clot. Because passive hemostats rely on fibrin production to achieve hemostasis, they are only appropriate for use in patients who have an intact coagulation cascade. Passive hemostats are generally used as first-line agents because they are immediately available, require no special storage or preparation, and are relatively inexpensive. Passive topical hemostatic agents do not adhere strongly to wet tissue and thus have little effect on actively bleeding wounds; however, they can be effective in the presence of heavier bleeding because of their larger absorption capacity and the greater mass provided by their more fibrous/dense structures [3]. Since they have the potential to expand many times than their mass when they come in contact with fluids, it is recommended to use the minimum amount of the agent required to achieve hemostasis and remove as much of the agent as possible once hemostasis has been achieved [3,4]. If not they can compress the surrounding structures (nerves, vessels, etc.). Passive topical hemostatic products include collagens, cellulose, gelatins, and polysaccharide spheres.

Active hemostatic agents have biologic activity and directly participate in the coagulation cascade to induce a clot. Active agents include thrombin and those products, in which thrombin is combined with a passive agent to provide an active product [5,6]. Thrombin is a useful choice for patients who are receiving antiplatelet and/or anticoagulation medications. Although it is costly, it is very useful in achieving hemostasis and is normally used with gelatin foam. In most of the cases, an active agent may be combined with a passive agent to improve the overall hemostasis. In general, most of the hemostatic agents are contraindicated in contaminated wounds.

Two other categories are flowable agents and sealants, which include fibrin sealants, polyethylene glycol (PEG) polymers, albumin and glutaraldehyde, and cyanoacrylate [5,6].

PASSIVE HEMOSTATIC AGENTS

Collagen-based products

Hemostatic collagen products are derived from either bovine tendon or bovine dermal collagen and are non-toxic and non-pyrogenic and may be further divided into microfibrillar and absorbable collagen products.

Microfibillar collagen (Avitene)

It is derived from purified bovine dermal collagen; it is a fibrous, water-insoluble partial hydrochloric salt. They are available in a loose fibrous form and also as sheets or sponges. These products are stored at room temperature, are immediately available for use, and should not be resterilized. It attracts platelets and stimulates aggregation of platelets into thrombi in the interstices of the fibrous mass resulting in the formation of a physiologic platelet plug, degranulation, and release of clotting factors, thus initiating the clotting cascade. Thrombin is ineffective with this agent due to pH factors. It is useful in the management of moderate to severe bleeding, i.e., capillary, venous, or small arterial bleeding. It must be applied dry directly to the site of bleeding without the addition of saline or thrombin and excess material to be removed. Adverse effects of this product include: Allergic reaction, adhesion formation, inflammation, foreign body reaction, and potentiation of wound infections and abscess formation [4,6,7]. It is Contraindicated in patients with known allergies or sensitivities to materials of bovine origin and must be avoided in any area where it may exert pressure on adjacent structures because of fluid absorption and expansion [4,6,7]. This form is generally less useful for oral surgical procedures.

Other collagen-based agents are Colla-Cote, Colla-Tape, Colla-Plug, Helistat, which provide a matrix for coagulation cascade. It gets absorbed in 10-14 d.

Absorbable collagen hemostat sponge (Helistat)

It is collagen derived from purified and lyophilized (i.e., freeze-dried) bovine flexor tendon and is available as soft, white, pliable, non-friable, coherent, sponge-like structures. The products are highly absorbent and able to hold many times their own weight of fluid. Their indications are for wound protection and for control of oozing or bleeding from clean oral wounds. As for application, these products should be held in place for approximately 2-5 minutes to achieve hemostasis and then may be removed, replaced, or left *in situ*. Because absorbable collagen hemostatic sponges do not disperse-like microfibrillar collagen does, these products are easier to handle and place. It must be handled dry, only the amount necessary to be used and excess must be removed. All of these collagen materials are completely resorbed within 14-56 days [8]. In addition to serving as a mechanical obstruction to bleeding, these materials affect the coagulation process. In contact with blood, collagen causes aggregation of platelets, which bind in large numbers to the collagen fibrils. The aggregated platelets degranulate, releasing factors such as thromboxane A2 [9] that assist in the formation of a clot. The sponge also provides a three-dimensional (3D) matrix for strengthening the blood clot.It is contraindicated in infected or contaminated wounds, in patients with known allergies or sensitivities to materials of bovine origin [8]. The agents may serve as a nidus for abscess formation and may potentiate bacterial growth. Possible adverse reactions are the formation of adhesions, allergic reactions, foreign body reactions, and subgaleal seroma formation (subgaleal seroma is an accumulation of blood serum beneath the scalp) [10].

Cellulose-based products

Oxidized regenerated cellulose (Surgicel) is derived from plant-based alpha-cellulose and is available in an absorbable white, knitted, fabric (single or multiple sheets) that is either high- or low-density. It is prepared as a sterile fabric meshwork and is expensive. It provides an absorbable physical matrix for clotting initiation, expands on contact with blood 7-10 times its own weight; however, the rate at which the body absorbs it depends on the amount used, the extent of blood saturation, and the tissue bed [4,6,7]. It achieves hemostasis by mechanical pressure. It has acidic properties due to a low pH, and this may cause inflammation and necrosis. Thrombin is ineffective with this agent due to pH factors. This is thought to be relatively bacteriostatic when compared with other hemostatic agents, due to a low pH. They are used

to control capillary, venous, and small arterial bleeding. It must be used dry without addition of saline or thrombin. Loescher and Robinson [11] reported that Surgicel can cause temporary sensory disturbances. Absorption of Surgicel will occur in approximately 4-8 weeks. It should not be used (1) in closed spaces because of swelling, (2) on bony defects (fractures) as it may interfere with bone regeneration, and (3) for control of hemorrhage from large arteries. Adverse reactions include: (1) Encapsulation of fluid and foreign body reaction, if the product is left in the wound, (2) stenosis of vascular structures if cellulose is used to wrap a vessel tightly, (3) burning sensation when placed in unanesthetized nasal passages. Excessive amounts of the material should be removed if possible to prevent delayed healing, (4) surgical granulomas, and (5) neurological complications.

ActCel and Gelitacel

It is a new topical hemostatic agent made from treated and sterilized cellulose, available as meshwork-like Surgicel. On contact with blood, it expands 3-4 times its original size and gets converted into gel. It dissolves completely in 1-2 weeks into biodegradable end products glucose and water and does not affect wound healing. ActCel's mechanisms of action are multiple, enhancing the coagulation process biochemically by enhancing platelet aggregation and physically by 3D clot stabilization. It is used in third molar sites and supposed to prevent dry sockets. Furthermore, it is used in periodontal and orthognathic surgeries. One study has demonstrated that ActCel adheres to calcium ions [12], making calcium more available for the clotting cascade, and ActCel has a role in the modifying intrinsic pathway. It is indicated for the control of bleeding from open wounds and body cavities (e.g. mouth, ears, nose, throat, and vagina) and does not contain chemical additives, thrombin, or collagen and is hypoallergenic. Another special characteristic of this material is its bacteriostatic properties, [13] which are especially important in contaminated wounds or in body cavities, in which it is difficult or impossible to maintain a sterile field. Gelitacel is a fast-working, oxidized resorbable cellulose hemostatic gauze of natural origin made from highest alpha-grade selected cotton. It resorbs as quick as 96 hrs, therefore giving it decreased risk for encapsulation. Gelitacel is cheaper than Surgicel.

Gelatin-based products

Gelfoam is one of the more commonly employed agents for the control of minor bleeding. Gelfoam is a porous, pliable, absorbable gelatin sponge that is prepared from purified pork skin gelatin. It is manufactured as films, gelatin sponges (Gelfoam), or powder that is mixed to form a paste. This product has properties that allow it to absorb about 40 times its weight in blood, and it can expand to 200% of its initial volume. It provides a clotting framework and effectively arrests small vessel bleeds, but large arterial bleeds may dislodge gelfoam. Gelfoam has very little tissue reaction and liquefies in the oral cavity within a week, fully absorbing within 4-6 weeks. It is very useful in managing post-operative bleeding after dental extractions and addition of thrombin improves its efficacy. Gelfoam can be placed dry or after moistening it with saline or thrombin. Gelatin conforms easily to wounds making it suitable for use in irregular wounds. Absorbable gelatin sponges do not need to be removed before wound closure; however, surgeons often remove them when possible to prevent compression of adjacent structures from the gelatin's swelling [14]. Its use is not associated with excessive scar formation. Gelatine-based devices have been reported to induce a better quality clot than collagen-based hemostats [15]. Absorbable gelatin hemostatic products should not be used: for patients with known allergies or sensitivities to porcine products; for skin incision closure; in intravascular compartments because of embolization risk; in the presence of infection or areas of gross contamination because bacteria can become enmeshed in the sponge, leading to the formation of an abscess; or around nerves because of the risk of swelling and nerve compression [4,6,7]. Adverse reactions include: Abscess formation, foreign body reactions, encapsulation of fluid, hematoma and localized infection [4,6,7], giant cell granuloma, excessive fibrosis, toxic shock syndrome, fever, and failure of absorption.

Polysaccharide hemospheres

This is a relatively new type of topical hemostatic agent derived from vegetable starch and contains no human or animal components. It is available in powder form with a bellows applicator. Polysaccharide hemospheres are used to control capillary, venous, and small arterial bleeding by producing a hydrophilic effect, dehydrating the blood, and concentrating its solid components thereby increasing barrier formation. It should be used carefully in diabetics patients as it consists of sugars.

Most often a hemostatic matrix such as oxidized regenerated cellulose, absorbable gelatin, or collagen with suture is applied to the extraction socket to manage post-operative bleeding. The hemostatic properties of these agents are based on their ability to activate the coagulation cascade locally. They have no intrinsic coagulation factors or activity but are designed to stimulate clot formation by providing a 3D scaffold used for clot organization [16-18]. Initially, placing these agents in a heme-rich environment raised concerns regarding the potential for infection. However, it has been shown *in vitro* that the agents might confer protective bacterial resistance against a variety of bacterial pathogens, perhaps owing to the decrease in pH in the local environment in which the agent is placed [17]. However, it is important to remember that these agents are not effective in coagulopathic patients without a functional coagulation cascade [16-18]. The efficacy of passive hemostats varies among products. The research found that microfibrillar collagen was the most effective of the passive topical hemostatic agents, followed by collagen sponge, gelatin sponge, and then oxidized regenerated cellulose [19,20]. In a study on an animal model which compared various hemostatic agents, early bone healing was significantly impaired by the presence of microfibrillar collagen and impeded by the presence of oxidized regenerated cellulose. Alkylene oxide copolymer (ostene) did not inhibit bone healing when compared to untreated (control) defects and thus may be a good clinical agent in cases where bony fusion is critical and where immediate hemostasis is required [21].

ACTIVE HEMOSTATIC AGENTS

Thrombin

Topical thrombin products are derived from either bovine or human plasma, or they are manufactured using recombinant DNA techniques (i.e., recombinant thrombin). Thrombin may be used topically as a dry powder, as a solution for use with gelatin sponges, mixed with a gelatin matrix, or as a spray. It has a rapid onset of action (e.g., within 10 minutes). It converts fibrinogen to fibrin. It is commonly used with gelfoam to treat moderate to severe bleeding. Thrombin should never be injected into the bloodstream or allowed to enter the bloodstream through large, open blood vessels because it can cause extensive intravascular clotting which can be fatal.

FloSeal (flowable hemostatic agent)

FloSeal matrix hemostatic sealant is a proprietary combination of two independent agents and consists of bovine-derived gelatin granules coated in human-derived thrombin that works in combination to form a stable clot at the bleeding site. When applied to a bleeding site, the gelatin granules swell by about 10-20% as it contacts blood, causing a seal at the bleeding site. The thrombin portion of the product activates the common pathway of the coagulation cascade and converts fibrinogen to a fibrin polymer, forming a clot around the stable matrix. It is resorbed by the body within 6-8 weeks, consistent with the time frame of normal wound healing. Because of the products flowability, it can adapt to irregular wounds. It has been used as first-line hemostatic agent in major oral surgical cases and can be used in all surgical procedures (other than ophthalmic) as an adjunct to hemostasis when conventional procedures are ineffective. It is effective on both hard and soft tissues. It has a risk of transmitting infectious agents (viruses) and is contraindicated in patients who are allergic to materials of bovine origin. Adverse reactions to flowable hemostatic agents include anemia, arrhythmia, arterial thrombosis, atelectasis, atrial fibrillation,

confusion, edema, fever, hemorrhage, hypotension, infection, pleural effusion, respiratory distress, and right heart failure [6,14,22].

Sealants

Sealants work by forming a barrier that is impervious to the flow of most liquids [22]. Four types of sealants to manage surgical hemostasis are: Fibrin sealants, PEG polymers, albumin with glutaraldehyde, and the new cyanoacrylate sealant [22,23].

Fibrin sealant (tisseel)

Fibrin sealant is a natural or synthetic combination hemostatic agent and also tissue adhesive which has an impact on angiogenesis and wound healing. Fibrin sealants are usually comprised fibrinogen (Factor 1a), fibrin-stabilizing factor, thrombin (Factor 2a), and aprotinin 2 and when applied to the surgical site forms a fibrin clot. These products can be applied using a syringe-like applicator or sprayed over a larger area using a gas-driven device [23,24]. It can be used in bone grafting procedures particularly sinus lift surgery. Fibrin sealants can be used in patients with coagulopathies who have insufficient fibrinogen to form a clot and can also be used on patients who are receiving heparin. Fibrin sealants control local as well as diffuse bleeding; however, they do not control vigorous bleeding. Davis and Sándor [25] conducted a study that included 71 patients who underwent various oral and maxillofacial procedures (dentoalveolar, cosmetic, and reconstructive) in which Fibrin gel was used. 70 patients had successful outcomes 6 months postoperatively with 1 recurrent oroantral fistula. It is contraindicated in patients who are sensitive to bovine proteins. An excessively thick sealant layer may prevent revascularization at the surgical site, causing tissue necrosis.

Albumin-derived hemostats (bioglue)

Tissue adhesives have been used widely for decades, for both their hemostatic and sealant properties. The main disadvantage of bioglue is that it can leak through suture tracks.

NEWER HEMOSTATIC AGENTS

Chitosan-based products

Polymers containing N-acetyl glucosamine include hyaluronic acid, chitin, and chitosan. Chitosan has been recognized as the most effective of these for local hemostasis. Chitosan is a naturally occurring, biocompatible, electropositively charged polysaccharide that is derived from shrimp shell chitin. This charge attracts the negatively charged red blood cells forming an extremely viscous clot, which seals the wound and causes hemostasis. Chitosan enhances hemostasis by interacting with cellular components forming a cellular lattice that entraps cells to form an artificial clot. The formation of a clot occurs independently of the intrinsic or extrinsic clotting pathways and is effective for patients on anticoagulant medications. It is a new generation hemostatic agent which achieves early hemostasis as well as improves post-operative healing. They do not cause any adverse reactions in shell-fish sensitive patients [1].

HemCon dental dressing is an N-acetyl glucosamine polysaccharide, a chitosan-based product which comes in a sponge form is both hemostatic and bacteriostatic and adapts well into oral surgical wounds. A recent study showed that hemostasis was achieved in <1 minute in patients where HemCon dental dressing (HemCon Medical Technologies, Incorporated) was used, which was significantly faster than the control average hemostasis time, 9.5 minutes. Approximately 32% of HemCon dental dressing-treated sites had significantly better healing compared with the control sites [26]. Another study found unique bacteriostatic properties in the chitosan-based agent against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Proteus mirabilis* [27]. Dailey *et al*. [28] compared the hemostatic efficacy of a chitosan-based bandage with that of collagen-based bandage after dacryocystorhinostomy. They reported that the chitosan bandage outperformed the collagen, with 12 of 14 post-operative bleeding episodes associated with the latter product [28,29].

Polysaccharide-based hemostats

Poly-N-acetyl glucosamine-based materials

It is a more fully acetylated chitosan derived from microalgae that have shown great efficacy as a local hemostatic agent. It concentrates red blood cells, clotting factors, and platelets at the site of bleeding and stimulates release of vasoconstrictors such as thromboxane an endothelin [30-32]. It has shown to be hemostatic agents in genetically acquired, medically induced, and environmentally induced coagulopathy conditions. They have outperformed other local hemostatic agents in various animal studies [33-37]. They are not yet approved for dental use but seems to be very promising in the future.

QuikClot (inorganic hemostat)

Zeolites are porous aluminosilicate minerals commonly used as adsorbents are the main ingredients in QuikClot. The structural porosity of zeolites allows them to accommodate a large quantity of cations, such as calcium, a cofactor in the coagulation cascade. The mechanism of hemostasis involves adsorbing water from blood, concentrating clotting factors, activating platelets, and subsequently, promoting steps in the coagulation cascade [38,39]. This exothermic reaction produces significant heat that may create secondary injury. Its granular form makes it difficult to apply and hold in place. Rhee *et al*. [38] produced a survey including first-hand interviews of 103 individual uses of QuikClot. Of these incidents, 69 were related to US military personnel in Iraq, 20 to civilian trauma surgeons, and 14 to civilian first responders. In total, the survey documented 83 applications to external wounds and 20 intracorporeal uses. The investigators reported the overall efficacy of hemostasis as 92% but with 3 burns that occurred with the intracorporeal use of the product [38]. QuikClot effectively controls external hemorrhage by pouring it into a wound followed by a pressure dressing to achieve hemostasis. At present, there is no known use in oral surgery.

Hemostatic solutions

Styptics

Styptics, e.g., aluminum solutions when applied locally cause hemostasis by contracting tissue to seal injured blood vessels.

Tannic acid

Tannic acid is a commercial compound that is similar to the plant polyphenol tannin, which stops bleeding from mucous membrane via vasoconstriction.

Lysine analogs

Tranexamic acid, epsilon-aminocaproic acid

Tranexamic acid

Tranexamic acid 4.8% oral rinse is an antifibrinolytic agent that stabilizes clots and facilitates clot formation by competitively inhibiting plasminogen, the enzyme responsible for activating plasmin. The main role of plasmin in the body is clot degradation or fibrinolysis; hence, tranexamic acid non-competitively inhibits plasmin and stabilizes clot formation. Oral tranexamic acid has been shown to be beneficial in the management of patients with both inherited and acquired bleeding diatheses undergoing minor oral surgeries [40-42]. It can also be useful as a prophylactic mouthwash in patients who are on anticoagulant medications which require oral surgery. It can be used preoperatively, intraoperatively, or postoperatively to manage bleeding. It is very popular as a post-operative hemostatic mouthwash. Ramström *et al*. [43] demonstrated a significant reduction in post-operative bleeding in the anticoagulated patient when a 4.8% solution of tranexamic acid mouthwash was used postoperatively, 10 ml 4 times daily, for 7 days. Studies have not shown any significant decrease in hemorrhage control when tranexamic acid is used intraoperatively (irrigation, soaked gauze). An intraoperative tranexamic acid injection can also be used as a hemostatic measure. Choi *et al.* [44] showed that total blood loss during

maxillary surgery was significantly reduced when a bolus of tranexamic acid was given preoperatively. It is more potent than aminocaproic acid, with fewer side effects and less dose is sufficient to achieve hemostasis. Sindet-Pedersen *et al*. [45] studied the hemostatic effect of tranexamic acid mouthwash after minor oral surgery in 39 patients who continued their anticoagulant agents perioperatively. Before suturing the wounds, 19 patients received 10 ml of a 4.8% solution of tranexamic acid and the remaining 20 received a placebo solution. Mouth rinses were continued 4 times daily for 7 days postoperatively. The investigators reported that 8 patients in the placebo group experienced 10 post-operative bleeding episodes, but only 1 patient in the tranexamic acid group experienced a bleeding episode [45]. Carter and Goss [40] compared a 4.8% solution of tranexamic acid mouthwash used for 2 days versus 5 days in anticoagulated patients and found that 82 of the 85 patients experienced no post-operative bleeding.

Epsilon aminocaproic acid

It is an antifibrinolytic agent less potent than tranexamic acid but can be used as an alternate to it.

Hemocoagulase (botroclot)

Hemocoagulase is based on the coagulative and antihemorrhagic properties of those fractions isolated from the venom of "*Bothrops jararaca*" or "*Bothrops atrox* 2, 3." Hemocoagulase reduces the bleeding time and promotes wound healing by promoting the growth of capillaries in wound space. Hemocoagulase has two different enzymatic activities, which promote blood coagulation. One of these accelerates the conversion of prothrombin to thrombin (thromboplastin-like enzyme) while the other one causes a direct transformation of fibrinogen to fibrin monomer, which can be converted by thrombin into fibrin clot (thrombin-like enzyme). Contraindications: Venous and arterial thrombosis, disease with tendency to intravascular coagulation. In a study conducted by Majumder *et al*. [46], it was found that hemocoagulase topical solution when used after minor oral surgery not only provides faster hemostasis but also enhances healing.

Bone hemostats

Bone wax

Bone wax is a sterile mixture of water-insoluble beeswax, paraffin, and isopropyl palmitate (a softening agent) that is packaged in individual foil envelopes and is useful when bleeding is from a visualized local vascular channel within bone, commonly referred to as a "bone bleeder," at the surgical site. This occurs commonly during the extraction of mandibular third molars, and if not adequately addressed during surgery can be a reason for post-operative bleeding. The wax is pliable enough to be placed within a vascular channel and burnished, immediately tamponading the vascular source and achieves bone hemostasis. It is insoluble and therefore non-resorbable, and it interferes with bone healing at the site of application and causes infection by decreasing bacterial clearance in cancellous bone. Caution should be used where regeneration of bone is expected (e.g., a future implant site). In a study evaluating the infection rates following spinal surgery, surgical site infections occurred in 6 of 42 cases (14%) when bone wax was used and 1 of 72 cases (1.4%) when it was not used [47]. Bone wax has also been shown to increase inflammation [48], causing a foreign body giant cell reaction at the site of application due to its water insolubility and longevity.

Ostene

It is a bone wax-like preparation of water-soluble alkylene oxide copolymers. It is a synthetic bone hemostatic material first used in cranial and spinal surgeries. It is inert and eliminated from the body unchanged within 48 hrs [49]. It avoids the negative effects of bone wax, as it does not cause infection, inflammatory reactions, or interference in the osseous union. Wellisz *et al*. [50] showed that ostene-treated rabbit tibial cortical defects had a significantly lower rate of osteomyelitis and positive bone cultures compared with the bone wax-treated defects. It is applied in a similar fashion-like bone wax and to a thickness of 1-2 mm. It is expensive than bone wax.

Literature recommending local hemostatic agents for achieving hemostasis

Many studies including Bornert *et al*. [51] and Peisker *et al*. [52] have documented that local hemostatic agents are very useful in the management of post-operative bleeding in oral surgery patients with congenital hematologic disorders.

Many other studies have recommended that dental extractions can be carried out safely without discontinuation of antiplatelet and anticoagulant therapy, and the post-operative bleeding can be safely managed by local hemostatic agents alone [53-65].

SUMMARY

Hemostasis is an integral and very important aspect of surgical practice. The first step in bleeding control is direct pressure, and hemostatic agents should always be considered secondarily. A thorough knowledge about these agents is necessary to make a right choice of them when required. Factors affecting the selection of an appropriate topical hemostat include the type of procedure, cost, severity of bleeding, site of bleeding, systemic condition of the patient and the personal experience and preference of the surgeon.

CONCLUSION

Local hemostatic agents are very useful in controlling bleeding during oral surgical procedures in patients with congenital and acquired bleeding disorders [26,66] and also in patients who are on antithrombotic medications for their systemic conditions [67].

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