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EDITORIAL

ANTI-HEMORRHAGIC AGENTS IN ORAL AND DENTAL PRACTICE: AN UPDATE

A. SCARANO[1], G. MURMURA[1], A. DI CERBO[2], B. PALMIERI[2], V. PINCHI[3], L. MAVRIQI[1] and G. VARVARA[1]

[1]Department of Medical, Oral and Biotechnological Sciences, University of Chieti–Pescara, Chieti, Italy; [2]Department of General Surgery and Surgical Specialties, University of Modena and Reggio Emilia Medical School, Modena, Italy; [3]Departmental Section of Legal Medicine, University of Florence, Florence, Italy

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Many oral surgeons in their daily practice have the problem of controlling postoperative bleeding. In surgical, oral and maxillofacial practice, standard anti-hemorrhagic protocols, especially in high risk patients, are obviously required and need to be continuously updated. The purpose of this review is to give a rational insight into the management of bleeding in oral and dental practice through modern drugs and medical devices such as lysine analogues and serine protease inhibitors, desmopressin, fibrin sealants, cyanoacrylates, gelatins, collagen and foams, protein concentrates, recombinant factors, complementary and alternative medicine and other compounds.

Through the use of replacement factors, oral surgical procedures in patients with bleeding disorders rarely require hospitalization and transfusions where they could risk viral infection or various factor inhibitors, even if the advent of new non-plasma-derived products has reduced such risks (1). Postoperative bleeding management of patients on oral anticoagulant therapy (warfarin or heparin) or with bleeding disorders (von Willebrand disease, Hemophilia, factor V, VII, X and XIII deficiency) usually requires local treatments to maintain the blood levels of anticoagulation and achieve hemorrhage control at the same time. These procedures include synthetic vasopressin packaging and infusions, absorbable gelatin sponges and fibrin sealants or clotting factor concentrates (2), etc.

Our paper reviews old and new products for an updated use in common practice.

Lysine analogues and serine protease inhibitors

Tranexamic acid (TXA), trans-4aminomethyl cyclohexanecarboxylic acid, and epsilon-aminocaproic acid (EACA), 6-aminohexanoic acid, are known to be lysine synthetic by-products with a high antifibrinolytic activity exerted by competitively inhibiting the binding of plasminogen and plasmin to fibrin. In particular, EACA acts by binding to the lysine-binding sites of plasminogen and plasmin and, once bound, displaces plasminogen from fibrin, inhibiting the tendency of plasminogen to split fibrinogen (3). However, a protecting role of EACA towards fibrin degradation has been proposed. The healing properties of EACA in dental surgery have been recently underlined by Ipema et al. (4). From

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Mailing address: Dr Giuseppe Varvara,
Department of Medical,
Oral and Biotechnological Sciences,
University of Chieti-Pescara,
Via dei Vestini 31 66100 Chieti, Italy
Tel.: +39 0871 3554125 Fax: +39 0871 3554148
e-mail: gvarvara@unich.it

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histological analysis, a good healing repair within 7 days, was achieved when sockets were previously treated with EACA and then with the fibrin adhesive. TXA exerts its antifibrinolytic activity identically to EACA but is almost 10 times more potent per unit dose than EACA (7-11). It is widely used during coumadin treatment and in literature has shown high haemostatic efficiency in patients with congenital α2-plasmin inhibitor (α2-PI) deficiency (5). In a double-blind cross-over randomised control trial TXA was compared with factor replacement therapy in 13 haemophiliacs and, after dental scaling, no statistically significant difference was found in gingival bleeding for either treatment (6). TXA and EACA inhibit the transformation of plasminogen to plasmin through clot-bound tissue plasminogen activator (tPA) *vs* circulating tPA; therefore they may not be effective when elevated levels of tPA elicit a systemic increase in circulating plasmin (6). Thus increasing bleeding times associated with elevated fibrinogen degradation products might take place. In this case, serine protease inhibitors, Bt-KTI (from Bombus terrestris) (7) or aprotipin, might be more suitable. Bt-KTI consists of a 58-amino acid mature peptide with an inhibiting action towards plasmin; whereas aprotinin is associated with preventing fibrin degradation by inhibiting plasmin and kallikrein formation (7).

Desmopressin

The action mechanism of desmopressin, 1-deamine-8-D-arginine vasopressin, in preventing bleeding is to induce a release of von Willebrand factor (8) as well as P-selectin (9) from endothelial Weibel Palade bodies (8). Upon activation, P-selectin is stored and rapidly expressed on the endothelial surface. Moreover, it is a key mediator in the cascade of leukocyte-endothelial rolling, adhesion and extravasation and plays a crucial role in platelet-endothelial and platelet-leukocyte interactions leading to reduced organ perfusion and function (9). In patients with bleeding disorders, such as hemophilia A, persistent bleeding following extraction of the upper right first molar was treated with desmopressin infusion. After suture removal no bleeding was observed. Desmopressin has also been successfully combined with recombinant activated factor VII in the bleeding management of a patient with Glanzmann's thrombasthenia (12). TXA, fibrin glue and desmopressin prevented bleeding complications in 53 of 63 (84%) patients, thus reducing the need for concentrates and consequently their high costs (11).

Fibrin sealants

Fibrin sealants, improperly nicknamed fibrin glues, claim to be some sort of tissue adhesive from human or animal source, but with very weak adhesive and intrinsic properties. Their main components, thrombin and fibrinogen, induce a stable clot of fibrin. In addition to the haemostatic role of fibrin sealants, they are commonly used for wound healing, suture support, and tissue sealing. Fibrin sealants made of thrombin, calcium chloride, fibrinogen, factor XIII and aprotinin, were used by Chuansumrit et al. to counteract the hemorrhaging during dental extraction in patients with bleeding disorders (12). However, single thrombin powder was also successfully used, after tooth extraction in patients on anticoagulant therapy, despite powder solubility within the moist oral environment. A thrombin-like effect is the main action mechanism of various snake venom extracts. Specifically, a hemorrhagic metalloproteinase present in *Bothrops caribbaeus* venom (type P-III), has shown a platelet aggregation/agglutination induction *in vitro*. Moreover, *Bothrops caribbaeus* venom is able to hydrolyze fibrinogen *in vitro*, and to induce a partial drop of fibrinogen levels with an increase in fibrin/fibrinogen degradation products levels *in vivo*. Strong thrombin-like activity followed by a kallikrein-like one was observed in *Bothrops isabelae* crude venom. The fibrinogenolytic activity of this venom at a ratio of 100:1 (fibrinogen/venom) induced a degradation of A alpha and B beta chains at 15 min and 2 h respectively. At a ratio of 100:10 a total degradation of the two chains at 5 min as well as of gamma chains at 24 hours occurred, mimicking the physiologic role of plasmin (14). BJ-48, a highly glycosylated serine protease isolated from *Bothrops jararacussu*, revealed a cleaving ability towards α and β chain of fibrinogen, with a preference for the β. Trypsin and thrombin, BJ-48 showed greater stability to low pH and heating, making it a good candidate for dental bleeding management. Also Reptilase®-R, (Pentapharm, Basel, Switzerland), a purified thrombin-like snake-venom enzyme from *Bothrops*

atrox, resulted more stable than thrombin and was not inhibited by heparin and hirudin (15). It acts by splitting the 16 Arg-17 Gly bond in the A(alpha)-chain of fibrinogen, releasing fibrinopeptide A and leading to clot formation through aggregation of formed fibrin I monomer or Des-AA-monomer. Due to its heparin insensitivity it is used to detect fibrinogen polymerization disorders even in the presence of heparin. The use of fibrin sealants has been fully described by several literature reports. Martinowitz et al. (16) achieved a good clot formation, with the fibrin sealant Beriplast P (Hoechst-Marion-Roussel, Tokyo, Japan), at the surgical wound site in patients undergoing anticoagulant therapy. He also compared the haemostatic effect of fibrin sealant, gelatin sponge and sutures with gelatin sponge and sutures or gelatin sponge, sutures, and TXA mouthwash (17). The postoperative bleeding rate was comparable in all treatments. A considerable perioperative blood loss reduction was observed in patients with bleeding disorders treated with fibrin sealants (18). Due to the presence of coagulation factors from bovine sources in fibrin sealants and topical thrombin preparations, some risk of immunogenicity and potential viral transmission has to be taken into account (19). A fibrin glue from autologous fresh frozen plasma has been proposed for wound bleeding treatment after oral surgical operations. The autologous fibrin glue showed a concentration of fibrinogen, Factor-VIII, Factor-XIII, von Willbrand factor and fibronectin and an α2-Plasminogen inhibitor 10 times and 1.5 times greater than the autologous fresh frozen plasma, respectively (20).

Cyanoacrylates

In patients undergoing oral anticoagulant therapy (OAT) cessation or decrease of OAT before oral surgery may expose them to the risk of thromboembolism. However, it has been shown that OAT can be continued even before oral surgery due to new local measures, such as Histoacryl (Braun Medical, Seesatz, Switzerland) able to enhance or stabilise clot formation at the surgical site (21). For patients with hereditary bleeding disorder management, Glubran 2 (Gem S.R.L,, Viareggio, Italy), acrylic glue (co-monomer of N-Butyl-2-Cyanoacrylate), and Glubran tissue skin adhesive (Gem s.r.l.) were used after dental extractions and for circumcisions, respectively. The latter showed good results in all treated patients whereas Glubran 2 (Gem s.r.l.) on the contrary, was effective only for 50% of patients. However, after a 6-month follow-up no complications were observed in any of the patients (22).

Gelatins, collagen and foams

Gelatin sponges are haemostatic devices suitable for absorbing blood, soaking up many times their weight. Blinder et al. evaluated the difference of 3 different haemostatic treatments (gelatin sponge and sutures; gelatin sponge, sutures, and mouthwash with TXA; fibrin glue, gelatin sponge and sutures) in 150 postoperative bleeding patients on OAT (23). Gelatin sponge and sutures resulted sufficient for the local haemostasis management (23). Absorbable gelatin sponge (Gelfoam, Upjohn, Kalamazoo, Michigan, USA) and fibrin sealants (Tisseel, Immuno AG, Wien, Austria) were used on 69 patients on OAT in order to prevent prolonged or excessive hemorrhages after teeth extraction. Only 3 of 69 patients had minor bleeding which was stopped within the following day (23). In patients on OAT, plasma gel induced an adequate haemeostasis after dental extraction in 22/40, 16/40 had a mild bleeding which resolved within 3 days and only 2/40 had hemorrhagic complications (24). Collagen biomaterials, on the contrary, have been widely used in reconstructive surgery and in wound healing without causing any adverse post-operative reaction. A modified bovine type I collagen membrane used with dogs for instance, showed an improved rate of wound healing and a topical haemostatic effect without causing any post-operative adverse reaction. Unfortunately, collagen and gelatin, which are animal-derived products, have the potential risk of blood-borne pathogens and immunization. However a synthetic, biodegradable material such as polyurethane, would prevent these risks (25). This material, with uniform hard segments composed of butanediol and 1,4-butanediisocyanate and soft segments of DL-lactide, ε-caprolactone and polyethylene glycol, has shown good haemostatic properties in respect to collagen- and gelatin-based hemostats. In particular, an improved haemostatic effect was observed when polyethylene glycol concentration was increased within the foam (25). Studies conducted on a bovine

bone sponge revealed a shortening of bleeding time as well as a lower rate of alveolar bone reabsorption compared to commercial haemostatic agents (26).

Protein concentrates

A common symptom in patients with bleeding disorders is the excessive bleeding after dental procedures. In this case replacement therapy with clotting factor concentrates is generally recommended. Ver Elst et al. evaluated the efficacy of a double virus inactivated FVIII/VWF concentrate (Immunate®, Baxter, Vienna, Austria) in 10 patients with type 2 and 3 von Willebrand disease before surgery or dental extractions (2). However, Immunate® (Baxter) dosing, based on FVIII:C levels, showed inadequate hemostatic effect in 2 out of 10 patients (3). Usually when an acute bleeding or emergency surgery occurs in vitamin K-based anticoagulant therapy patients, a rapid reversal is required. Prothrombin complex concentrates (Octaplex®, Octapharma AG, Lachen, Switzerland) are able to induce a more rapid effect with a better clinical outcome. Moreover, a volume overload is not observed in respect to fresh-frozen plasma (27). Moreover, prothrombin complex concentrate induced a sufficient local haemostasis in patients on high-level anticoagulant therapy and with heparin-induced thrombocytopenia requiring tooth extraction. Castaman et al. in a multicentre, prospective and observational study assessed the efficacy, the safety and the ease of use of a new, volume-reduced (VR) formulation of VWF/FVIII concentrate (Haemate® P, CGL, Behring, Wien, Austria) in bleeding management or prophylaxis for invasive procedures (28). One hundred and twenty-one patients were enrolled and the response to treatment was rated as good to excellent in > 93–99% of the interventions; moreover, it was easy to use, infusion duration decreased two-fold and it was as effective and well-tolerated as the previous formulation.

Recombinant factors

Factor XI as well as factor VIIa deficiency for instance, are two of the bleeding disorders which in the past were commonly treated with their respective concentrates. However, due to their side-effects, such as activation of the coagulation cascade, thromboembolism and immunogenicity, they have been substituted by recombinant products capable of fully replacing the role of the single factor. Chuansumrit et al. mixed recombinant activated factor VII (rFVIIa) with fibrin glue and a celluloid splint in patients with bleeding disorder (12). In 3 out of 4 surgical teeth removals a single dose of rFVIIa (180–200 μg/kg) had a successful outcome. Only in one case four doses of rFVIIa plus an oral rinsing solution of TXA (25 mg/kg) were required. Sakurai et al. reported a successful hemostatic management of a type 3 von Willebrand disease patient, who underwent multiple tooth extractions, using a recombinant factor VIII (29).

Complementary and alternative medicine

As to the use of herbs, seeing that the worldwide market has greatly expanded in the last 10 years we are obliged to add it this short chapter. Tachjian et al. reported that18% of patients who took prescription medications were contemporarily using herbal products or high-dose multivitamins with the risk of drug interaction (30). This figure increased up to 20% on a monthly basis among US citizens in 2010 with a cohort of patients that refused chemical drugs and treated themselves only with natural products (31). Herbal products are not regulated by the FDA as conventional prescription or over-the-counter medications or as food additives but by the Dietary Supplement Health and Education Act (DSHEA) (31). Ladas et al. recently described the use of *Purpose Yunnan Baiyao,* (YNB) (a blend of seven herbs that includes *Panax notoginseng, Ajuga forrestii Diels, Dioscoreae Parviflora Ting, Herba Inulae Cappae, Herba Geranii* and *Herba Erodii, Rhizoma Dioscoreae,* and *Rhizoma Dioscoreae Nipponicae*) for bleeding management and circulation improvement in traumatic injuries (32). Adolescents with advanced cancer receiving YNB and conventional haemostatic interventions showed a bleeding control improvement, especially for haemorrhage recurrence prevention. In Taiwan, a pilot study on 32 patients with acute subarachnoid haemorrhage aimed to evaluate the effect of complementary therapies of Chinese medicine (*Astragalus menbranaceus (Fisch) Bunge, G. elata Blume, Acorus gramineus Soland* and *Pheretima aspergillum*) and the standard treatment *vs* standard treatment only (clipping of the aneurysm) (33).

Three months after admission, the first group showed an increase of Glasgow Outcome Scale scores; moreover, a reduction was observed in the total of days of recovery.

A Turkish herbal extract (Ankaferd Blood Stopper), for the management of external hemorrhage and dental surgery bleeding, was recently approved (34). The product comprises a mixture of plants such as: *Thymus vulgaris, Glycyrrhiza glabra, Vitis vinifera, Alpinia officinarum* and *Urtica dioica.* In rats pretreated with acetylsalicylic acid or enoxaparin, Ankaferd Blood Stopper reduced both the duration and the amount of bleeding volume. Clotting and anesthesiologic properties of *Dichrocephala intergrifolia* have been described by Agbor et al. (34). In Cameroon, this plant is commonly used to control bleeding and pain after tooth extraction. In particular, it is firstly placed on the fractured, painful or carious tooth, left for 2-3 minutes and removed. After extraction, it is put into the extraction site for about 1 h to enhance clotting and arrest bleeding. One hundred and forty-two (95.3%) out of 150 interviewed patients reported no problems after an extraction (34).

Other compounds

The efficacy of resorbable oxycellulose and fibrin adhesive was compared for postextraction hemorrhage management on patients on anticoagulants therapy (35). Both agents had the same effect with only postoperative pain events within the resorbable oxycellulose dressing group. Scarano et al. reported the use of calcium sulfate, a biocompatible material, as a possible haemostatic agent in the surgical and orthodontic treatment of impacted teeth (36). Sixty-six patients received several layers of calcium sulfate cement, in order to fill the gap between teeth and bone, plus a dry gauze compression. After hardening the calcium sulfate with a potassium sulfate solution, a bracket was applied to the surface of the tooth. As a result, the separation of the bracket on the surface of the tooth was not observed. Leukocyte- and platelet-rich fibrin (L-PRF), a biomaterial commonly used to improve healing and tissue regeneration, was successfully used in 38 out of 50 (76%) heart surgery patients on oral anticoagulant therapy who needed dental extractions. Ten patients (20%) showed a mild bleeding which spontaneously resolved less than 2 hours after surgery and only 2 (4%) patients needed further compression and haemostatic topical agents (37). Nurden et al. successfully reported the use of autologous platelet-rich clots, after tooth extraction and dental surgery in patients with inherited bleeding disorders (38). The procedure resulted simple, safe and inexpensive while providing extra security for those patients with a higher bleeding risk. In a study involving 80 patients (divided into 2 groups), who received oral antiplatelet therapy, the effectiveness of a chitosan (a linear polysaccharide composed of randomly distributed β-(1-4)-D-glucosamine and N-acetyl-D-glucosamin) -coated gauze (HDD, HemCon Medical Technologies, Beaverton, Oregon, USA), in controlling both post-extraction bleeding and wound healing, was evaluated (39). Compared to the conventional method of a pressure pack with sterile gauze under biting pressure possibly followed by suturing, HDD-treated patients achieved haemostasis sooner (mean=53 seconds *vs* mean=918 seconds). A lower postoperative pain and a significantly better postoperative healing were also observed. It is worth noting that even if anti-platelet drugs are effective in the prevention and treatment of cardio-cerebrovascular diseases, glycoprotein IIb/IIIa antagonists (such as abciximab, eptifibatide and tirofiban) have shown adverse events related to thrombosis or bleeding. Platelet adenosine diphosphate P2Y(12) receptor antagonists (clopidogrel, prasugrel, cangrelor, and ticagrelor) and protease-activated receptor (PAR) antagonists (Vorapaxar and Atopaxar) have recently provided a new insight into antiplatelet therapy. These drugs demonstrated their protective effects by decreasing the risk of ischemic events without significantly increasing the rate of bleeding. Clinical and electron microscopic observations have recently shown that Blue-violet light emitting diode (LED) used after tooth extraction accelerated coagulation up to 20 s compared with an average of 180 s of spontaneous induction (40).

CONCLUSIONS

In surgical, oral and maxillofacial practice, standard anti-hemorrhagic protocols are obviously required and need to be continuously updated, especially in high risk patients. The number of

patients with cardiovascular problems undergoing long standing anticoagulant treatment is increasing and minor surgical procedures do not always rule out the use of antithrombotic agents or drugs. This review is focused on old and new strategies to prevent undue blood loss and minor or major life-threatening complications.

TXA, as well as absorbable hemostats and absorbable sutures, could be relevant in both low-income and high-income countries, avoiding the unnecessary or unavailable replacement therapy with specific coagulation factors. The rational use of the described compounds and medical devices like fibrin glue and gelatin sponge in high-risk bleeding patients undergoing oral surgical procedures can reduce the drop-out time of anticoagulant drugs from 2 up to 6 days before dental extraction. Fibrin sealants have an excellent outcome when delivered in the bleeding sites. These agents, are made of 2 components: 1) fibrinogen and plasma proteins, and 2) thrombin and calcium chloride. When these components are combined, thrombin converts fibrinogen into fibrin so that clotting is initiated and the mixture is solidified. The haemostatic role of the herbal extract Ankaferd Blood Stopper, along with various other properties, is that of being anti-infective, wound healing, and antineoplastic. It triggers the physiological haemostatic process effectively, inducing a protein mesh which provides focal spots of erythrocyte aggregation. Calcium sulfate also works in controlling hard tissue and periosteal prolonged bleeding, by turning on a net negative electric charge and activating the intrinsic coagulation pathway, therefore reabsorbing blood proteins. Lasers and optoelectronic devices (LED) recently support the haemostatic effect by direct photochemical activation of the coagulation cascade. The light tissue absorption is transformed in thermal energy that promotes coagulation by partial denaturation of proteins.

Finally, we add further technical recommendations of surgical skill to prevent or reduce the postoperative bleeding risk. In the operated area, fibrin sealants or other topical compounds can be inserted and pressed firmly for 3-5 minutes. Primary suturing requires non-absorbable stitches, and possibly a suture material with some elasticity (polypropylene, nylon), to comply to the surgical margin deflation in the 24-48 postoperative hours when the oedema has been partially drained. Bulky coagulating biomaterial (cellulose, chitosans or collagen) can be enclosed in the suture line to enhance the coagulation process across the surgical wound edges.

Wound dressing under compression through strong dental occlusion is recommended for at least half an hour intermittently, as well as avoiding mouth rinsing that might dilute the intrinsic autochthonous coagulating factors and adequate antibiotic administration to avoid bacterial induced fibrinolysis after 8-24 hours.

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