REVIEW

Haemostasis in periradicular surgery

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Summary

The successful performance of endodontic surgical procedures is predicated on many factors. However, the ability of achieve sustained tissue haemostasis in the surgical site is crucial to the performance of these procedures. This achievement improves vision in the surgical site, minimizes surgical time, enhances the surgical procedures (root-end resection, preparation and filling), and reduces surgical blood loss, postsurgical haemorrhage and postsurgical swelling. A multitude of materials have used in dentistry and medicine to achieve both generalized and localized haemostasis, many without full assessment of their biological implications. The purpose of this paper is to provide a thorough and critical review of these materials from the perspective of surgical endodontics, highlighting their development, application and potential role in achieving proper haemostasis.

Keywords: haemostasis, periradicular surgery, biocompatibility.

Introduction

Local tissue haemostasis during periradicular surgery is essential to ensure the successful management of the resected root end (Gutmann & Harrison 1994). Haemorrhage control not only enhances visibility and assessment of root structure, but it also ensures the proper environment for the placement of contemporary root-end filling materials, such as IRM (LD Caulk Co., Milford, DE, USA), super-EBA (Harry J. Bosworth Co., Skokie, IL, USA), Diaket (ESPE, Seefeld/Oberbay, Germany), composite resins and glass ionomers (Gutmann & Harrison 1994, Cohen & Burns 1994)

It has been 100 years since Horsley (1892)

Correspondence: James L. Gutmann DDS, Professor and Director, Graduate Endodontics, Baylor College of Dentistry, 3302 Gaston Avenue, Dallas, Texas 75246, USA. introduced wax as a haemostatic agent for bone surgery. Since that time, bone wax has been both praised and condemned. Recently, innovative biocompatible and biodegradable materials have been developed for all surgical procedures, including periradicular surgical application. The purpose of this review is to detail and highlight the development and assessment of methods and materials which have had an impact on haemorrhage control during periradicular surgery.

A search of the literature relative to haemorrhage control during periradicular surgery reveals scant detail. Much of the present information has been gleaned from studies in areas other than periradicular surgery, including oral maxillofacial surgery, podiatry and thoracic surgery. Pertinent studies involved the control of haemorrhage in bone surgery or investigated bone repair when haemostatic agents were used.

The scope of the paper will not permit a review of the problem of haemostatic control in those patients with forms of bleeding disorders or on anticoagulation therapy, and the reader is referred to contemporary authoritative sources for pertinent in-depth information (Johnson & Leary 1988, Sindet-Pedersen 1991, Weibert 1992). However, a through medical history is essential to determine if a patient has such conditions prior to treatment planning endodontic surgical intervention. Likewise, a working knowledge of the coagulation pathway is essential for any practitioner who performs endodontic surgery (Fig. 1).

Presurgical considerations

A thorough medical history increases the likelihood of uncovering an undiagnosed condition that has the potential to effect the outcome of periradicular surgery and the ability to obtain haemostasis. The medical history should minimally consist of a review of systems, a through medical and dental history, known allergies, and all medications the patient is taking. In the latter situation, it is important to investigate the nature of the



Coagulation pathways

Fig. 1 Synopsis of coagulation pathways.

medication, including both prescribed and overthe-counter drugs. Many of the latter medications, which are aspirin based, will effect the clotting mechanism through changes in the balance between platelet synthesized thromboxane A_2 (TXA₂) and vessel wall generated prostacyclin (PGI₂) (Fig. 2). Aspirin produces irreversible inhibition of cyclo-oxygenase by acetylation of a serine residue at the enzymes active sight. However, both TXA₂ and PGI₂ are affected as cells in the vessel walls can produce cyclo-oxygenase in a matter of hours, whereas platelets are unable to produce this enzyme. TXA₂ promotes vasoconstriction and platelet aggregation, while PGI₂ inhibits platelet aggregation and is a vasodilator (Ganong 1993).

The patient's vital signs such as blood pressure, heart rate and respiratory rate, should also be assessed, as hypertension and tachycardia may be indicative of an undiagnosed heart pathology or other systemic conditions (Paramesvaran & Kingon 1994). Vital signs can also be used to monitor the anxious patient. Increases in blood pressure and heart rate above a patient's known normal values are indications of elevated stress levels. Controlling the level of patient anxiety prior to surgery will decrease the possible haemostatic potentiating effect of elevated cardiac output during surgery. Mental stress and anxiety, such as that caused by bleeding and surgery, may also provoke increased fibrinolysis (Petruson 1974). Patient anxiety and stress management is achieved through pre-planning, which may involve sedation prior to the surgical procedure, and the assurance of profound anaesthesia (Gutmann & Harrison 1994).





Fig. 2 (Top) Diagrammatic representation of the haemostatic cascade following vessel injury. (Bottom) SEM of a blood clot taken from the apical area during periradicular surgery. Note the fibrin clotting and attached erythrocytes (original magnification, $\times 3000$).

Surgical considerations

The most significant determinant of surgical haemostasis is the surgeon. Attention to detail throughout the procedure will limit the potential for possible haemorrhage problems. Periradicular surgery involves the management of delicate fibril tissues and varying amounts of cortical and cancellous bone. Therefore, the ability to control all facets of the surgical process is essential. The use of biologically sound techniques in anaesthesia, tissue flap design, elevation, reflection and osseous removal, can greatly effect the ability to obtain and maintain haemostasis throughout the surgical procedure (Gutmann & Harrison 1994).

Local anaesthesia

The need for profound anaesthesia with resultant haemostasis cannot be overstated in endodontic surgical procedures. The ability to attain deep penetrating anaesthesia and work within its duration of action will directly relate to the patient's comfort level (Gutmann 1993a) and the ability to maintain haemostasis in the surgical field (Curtis et al. 1966). The majority of local anaesthetics contain a vasoconstriction agent to enhance the action of the anaesthetic. Most of the vasoconstrictors used are classified as adrenergic, having an effect on the α - and β -receptors of the sympathetic nervous system (Gutmann 1993b). The increased vasoconstriction of the blood vessels in the region will decrease the blood flow to the surgical site, decreasing the rate at which the local anaesthetic solution is removed. Currently, the anaesthetic vasoconstrictor combination of choice, where no contraindication exists, is 2% lignocaine with 1:100 000 adrenaline, supplemented with infiltration of 2 % lignocaine with 1:50 000 adrenaline (Gutmann et al. 1996). When anaesthetic solutions containing 1:50 000 adrenaline are unavailable, a concentration of 1:80 000 is recommended.

The clinical use of 1:50 000 adrenaline has been proven to be clinically superior in controlling haemostasis than lower catecholamine concentrations (Buckley *et al.* 1984, Gutmann 1993b). Injections of 2% lignocaine with 1:50 000 adrenaline into the submucosa, throughout the field of operation, acts on the blood vessels of the periosteum, submucosa, attached gingiva and periodontium to produce vasoconstriction. The adrenaline functions via a sympathomimetic action on the α_1 -receptors within these tissues. Buckley *et al.* (1984) showed that the use

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of 1:50 000 adrenaline resulted in a clear visualization of the surgical wound, reduced surgery time, decreased post-operative bleeding and decreased blood loss. However, injection into the surrounding muscle tissue produces an effect opposite to the desired, with the anaesthetic acting on a different type of receptor. Here the catecholamine adrenaline will act on the β_1 -receptors in the region, inducing vasodilatation rather than vasoconstriction (Milam & Giovannitti 1984, Gage 1988). The rate of injection will also effect the degree of haemostasis achieved. Rates exceeding the recommended 1-2 ml min⁻¹ will result in localized pooling of the solution in the immediate supraperiosteal tissue, with little diffusion into the surrounding soft tissues (Roberts & Sowray 1987). Thus, a minimal haemostatic effect will be observed on the microvasculature within these tissues and the underlying bone.

Flap design, tissue elevation and tissue reflection

Sound knowledge of the gingival apparatus and submucosa is essential in planning the appropriate access to the affected wound site. The supraperiosteal blood vessels of the attached gingiva lie in the reticular layer superficial to the periosteum and extend from the alveolar mucosa running parallel to the long axis of the teeth (Gutmann & Harrison 1994). A vertical relaxing incision as opposed to an angled incision will limit the number of vessels served, consequently decreasing the potential for haemorrhage (Macphee & Cowley 1981). Reflection and elevation of a full thickness mucoperiosteal flap, retaining the microvasculature within the body of the tissue flap, futher decreases the potential for loss of haemostatic control during surgery. This approach has also been shown to enhance healing (Sciubba *et al.* 1978).

Once the tissues are reflected, the fibrinolytic activity of saliva may also contribute to bleeding during the surgical procedure. Saliva contains activators of fibrinolysis, but does not contain physiological inhibitors of fibrinolysis (Gersel-Pedersen 1979, Moody 1982a,b, Sindet-Pedersen *et al.* 1987).

Local haemostatic agents

Non-collagen-based agents

Many non-collagen-based agents have been advocated to control haemostasis during surgery (Table 1). The action of these materials, their ability to control bleeding and their effect on healing vary considerably. Historically, bone wax has been advocated for both haemostasis and debris control within the apical bony crypt during periradicular surgery (Selden 1970). Bone wax is a nonabsorbable product of 88% beeswax and 12% isopropyl plamitate. Histologically, healing is best described as poor in the presence of this material. The bony crypt typically contain fibrous connective tissue and is devoid of any bony or hematopoietic tissue (Finn *et al.* 1992) (Fig. 3). Bone healing is retarded and the wax causes a predisposition to infection (Culliford *et al.* 1976, Nelson *et al.* 1990) by producing chronic inflammation with a foreign-body reaction (Aurelio *et al.* 1984) displaying numerous multinuclear giant cells (Finn *et al.* 1992, Solheim *et al.* 1992) and impairing bacterial clearance (Johnson & From 1981) (Fig. 4).



Fig. 3 Bone wax implanted in bone. Fibrous connective tissue surrounds a bony cyrpt containing residual wax. (H&E, \times 40).



Fig. 4 Enlargement of specimen in Fig. 3 revealing chronic inflammatory and foreign-body reaction displaying multinucleated giant cells (H&E, $\times 100$).

Table 1 Haemostatic products

Product	Company	Physical and chemical characteristics
Non-collagen		
Bone wax	Ethicon Inc,. Somerville, NJ, USA	88% Beeswax & 12% isoproplypalmitat—tamponding effect
Astrigedent	Ultradent Products Inc., Salt Lake City, UT, USA	Ferric sulfate 15.5%–20%—produces coagulation of proteinaceous material
ViscoStat	Ultradent Product Inc., Salt Lake City, UT, USA	Ferric sulfate 20.0%—produces coagulation of proteinaceous material
Cut-trol	Ichthys Enterprises, Mobile, AL, USA	or the autor manage process or should according to a
Monsel's solution	City Chemical Corp., New York, NY, USA	
Surgicel	Johnson & Johnson Medical, New Brunswick, NJ, USA	Regenerated aplha-cellulose enchances clotting cascade
Oxycel	Deseret Medical, Salt Lake City, UT, USA	through adhesion and aggregation of platelets
Interceed	Johnson & Johnson Medical, New Brunswick, NI, USA	
Gelfoam	Upiohn Co., Kalamazoo, MI, USA	Gelatin-based sponges stimulate intrinsic clotting pathway by
Spongostan	Ferrosan Copenhangen Denmark	promoting platelet disintegration
Astronlast	Wallace Cameron & Co. Glasgow Scotland	Non-woven sodium calcium alginate stimulates platelet
Kaltostat	Britcair Aldershot IIK	activation and mechanically occludes the wound site
Berinlast	Bebringwerle Cermany	Fibrin sealant provides aframework for platelet adhesion and
Tiseel	Immuno AC Vianna Austria	aggregation and activation of the clotting nathways
Tisqueol	Immuno AC, Vienna, Austria	aggregation, and activation of the clothing pathways
Thromhogon	Infinitutio AG, Vietnia, Austria	Tonical thrombin acts to initiate the artringic and intrinsic
Thombogen	Johnson & Johnson Medical, New Brunswick, NJ, USA	clotting pathways
Thrombostat	Parke-Davis, Morris Plains, NJ, USA	
Thrombinar	Jones Medical	
Collagen		
Avitene	Medchem Products Inc., Woburn, MA, USA	Collagen-based products that platelet adhesion aggregation
Hematex	Bioplex Corp., Montvale, NJ, USA	and release reaction, activate factor XII, mechanical
CollaPlug	Colla-tec, Inc., Plainsboro, NJ, USA	tamponade effect and the release of serotonin
CollaTape	Colla-tec, Inc., Plainsboro, NJ, USA	our leann an de service en maander staat en het de service
CollaCote	Colla-tec, Inc., Plainsboro, NJ, USA	
Hemofibrine	Specialites Septodont, Paris, France	
Novacol	Bioplex Corp., Montvale, NJ, USA	
Hemocollagen	Specialities Septodont, Paris, France	
Collastypt	Braun, Melsungen, West Germany	
Instat	Johnson & Johnson Medical, New Brunswick, NI, USA	
Collastat	American Medical Products Corp., Freehole, NI, USA	
Superstat	Edward Weck Inc., Research Triangle Park, NC, USA	annen officere devised freedometric rectories that the statistical
Hemostogen	Vygon Laboratory, Ecouen, France	Fibrin collagen dextran sponge tamponding effect
Absele	Ethicon Ltd. Edinburgh, Scotland	Fibrin collagen dextran glycerose paste tamponding effect
ACP	Unknow	and or the second s
Experimental		
Histoakryl	Braun Melsungen West Cermany	Cyanoacrylate mechanically occludes the wound site
Bucrylate	Johnson & Johnson Medical New Brunewick ML USA	Cyanoaci yiate incontanteatiy occidues the woulld site
Adaptic	Johnson & Johnson Medical, New Brunswick, NJ, USA	Rayon and cellulose acetate immersed in hydrophilic
ruaphe	Johnson & Johnson Medical, New Drunswick, NJ, USA	nayon and centrose acciate infinersed in frydropfinic
Alzamor	Alza Corporation Pale Alte CA USA	Pene way like biogradible polyorth costar
r madiller	Aiza corporation, rato Aito, CA, USA	bone-wax-nke bioerouible polyorthoester

With the availability of more biocompatible and biodegradable products, in conjunction with bone wax's impairment of osteogenesis, its use can no longer be recommended for periradicular surgery (Gutmann & Harrison 1994).

Ferric sulphate (Cut-Trol, Astringedent), a necrotizing agent of extremely low pH (0.8-1.6) (Woody *et al.* 1993, Land *et al.* 1994), is one of the few products that has been specifically investigated for use in periradicular

surgery. The action of this solution is similar to cautery, in that it produces coagulation of proteinaceous material (Costich & Hayward 1958). Lemon *et al.* (1993) and Jeansonne *et al.* (1993) studied the effect of ferric sulphate on the periradicular tissue in the rabbit model. They reported haemostatic control for 5 min and near normal healing with only a mild foreign-body reaction, provided the surgical wound was adequately curettaged and irrigated with saline prior to closure. Failure to

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remove ferric sulphate from the surgical wound site resulted in severely impaired healing, a foreign-body type reaction, and in some cases, abscess formation. There is a great potential for acute inflammation and necrosis of the surrounding soft tissue if this solution is not used carefully (Larson 1988). Additionallly, ferric sulphate 15.5-20.0% is an active demineralizing agent that has been shown to remove smear layer in teeth prepared for metal ceramic restorations to the extent that peritubular dentin was effected after exposure for $5 \min$ (Land *et al.* 1994). However, the extent of removal of smear layer, demineralization and collagen denaturation by this product at the root end has not been investigated.

A similar product, Mosel's solution (20% ferric subsulfate), has been used for haemostasis in dermatological procedures. Recently, the popularity of Monsel's solution has decreased, as its application to the wound site has resulted in tissue necrosis for up to 2 weeks (Davis *et al.* 1984), along with differences in the degree of epidermal maturation and tattoo formation (Traub & Tennen 1936).

Surgicel is a chemically sterilized substance, prepared by the oxidation of regenerated alpha-cellulose (oxycellulose). The basic element of Surgicel is polyanhydroglucuronic acid, formed from molecules of α -glucose and β -glucose joined by a C1-C4 glucosidic link (Miller *et al.* 1961), with carboxyl content of at least 16% (Rosenquist & Finne 1974), This is spun into threads, then woven into a gauze, and finally, sterilized with formaldehyde. The pH of Surgicel is 3.0-4.0 (Rosenquist & Finne 1974, Petersen et al. 1984) and its mode of action is principally physical, in that it does not enhance the clotting cascade through adhesion or aggregation of platelets, such as the collagen products. Initially, Surgicel acts as a barrier to blood, and then as a sticky mass acting as an artificial coagulum or plug. Whilst it is insoluble in acid and water solution, it is soluble in alkaline solution (Lucas 1966). Similar oxidized regenerated cellulose products include Oxycel and Interceed.

The nature of healing when Surgicel is retained in the surgical wound has been investigated by Nappi & Lehman (1980). Six- and 12-month radiographic evaluations failed to demonstrate bone formation. Histologically, healing was retarded and there was little evidence of resorption of the material at 120 days. Rosenquist & Finne (1974) elucidated impeded bone formation with Surgicel retained in the wound site at 2 and 4 weeks (Fig. 5); however, the contrast in healing to that of the control was described as small. A similar histological picture of slightly delayed healing has been



Fig. 5 Bony response to Surgicel is delayed, showing large intraosseous spaces (H&E, $\times 16$).

described at 8 weeks post-surgery (Mattsson et al. 1990). The nature of the material and the acidic pH in the surgical site (Bjorgenson et al. 1986) was shown to evoke a foreign-body response and impaired the function of alkaline phosphatase in new bone formation (Geary & Frantz 1950). Difficulty is removing Surgicel from bony wounds has been also highlighted, with even minimally retained fragments causing inflammation and a foreignbody reaction (Ibarrola et al. 1985) Therefore, complete removal of Surgicel from the surgical wound is indicated, and indeed, this is the manufacturer's recommendation (Johnson & Johnson 1989). However, Olson et al. (1982) demonstrated no long-term difference in histological healing between Surgical placed in extraction sockets of dogs and a control. Clinically, the use of Surgicel in extraction sockets has resulted in a greater pain experience in patients when compared to a control in a split-mouth designed study (Petersen et al. 1984). Oxidized regenerated cellulose retained in the pelvic peritoneal tissues has also been associated with a histiocytic inflammatory reaction (Kershisnik et al. 1994).

Gelfoam and Spongostan are gelatin-based sponges that are water insoluble and resorbable. Gelfoam has been recommended for use in periradicular surgery (Guralnick & Berg 1948) and in the non-surgical repair of endodontic procedural errors (Walia *et al.* 1988). Initially, the reaction to Gelfoam in the surgical site is one which decreases the healing rate (Hjortdal 1970). Boyes-Varley *et al.* (1988) examined early healing in the extraction sockets of monkeys. Histologically, the socket containing Gelfoam displayed a greater inflammatory cell infiltrate, marked reduction in bone in-growth and a foreign-body reaction at 8 days. Chronic inflammation to Gelfoam has been demonstrated superficial to the crestal bone at 60 days post-surgery. However, at 90 days, the gelfoam site was indistinguishable from the control (Olson *et al.* 1982) (Fig. 6). The pH of Spongostan is neutral (Petersen *et al.* 1984), and it stimulates the intrinsic clotting pathway by promoting platelet disintegration, and the subsequent release of thromboplastin and thrombin (Evans 1977, Petersen *et al.* 1984). In a human study comparing Spongostan to Surgicel and a control, Spongostan displayed a greater degree of protracted healing and post operative pain (Petersen *et al.* 1984).

Kaltostat, a haemostatic wound dressing originally developed for superficial wounds (Attwood 1989), has been used in periradicular surgery to manage haemostasis (Odell *et al.* 1994). The principal component of Kaltostat is a polymer of the 1,4 β isomer of mannuronic acid and the 1,4 α isomer of glucuronic acid. This polymer is similar to cellulose, with the alcohol groups being replaced by carboxyl groups. The carboxyl groups react with ammonium or metallic salts





Fig. 6 (Top) Low power view of Gelfoam (arrows) being replaced by bone; no inflammation noted (H&E, $\times 100$). (Bottom) Higher power view of bone replacing residual Gelfoam (arrows); no inflammation noted (H&E, $\times 100$).

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to generate a corresponding non-woven sodium calcium alginate salt (Gilchrist & Martin 1983). The action of Kaltostat is to stimulate platelet activation and wholeblood coagulation via the release of calcium ions. Theoretically, a gel forms, which then breaks down into simple glucose-like monomer which can be readily absorbed by the tissues (Gilchrist & Martin 1983). Histological investigation into the healing pattern of Kaltostat revealed a delayed osseous regeneration and a mild foreign-body reaction, with remnants of the material persisting up to 12 weeks post-surgery (Mathews et al. 1993). Odell et al. (1994) reported a case in which Kaltostat had been used in periradicular surgery where the foreign-body reaction was described as servere, with healing delayed as long as 26 weeks post-surgery. The ultimate histological repair seen with Kaltostat is similar to that seen with Surgicel.

Tissue adhesives as haemostatic agents is an appealing concept. Such products could be applied to the surgical wound in a spray or solution to occlude bleeding vessels within bone and soft tissue. Therefore, the use of fibrin glue, a tissue adhesive, as haemostatic agent is not a novel idea. The initial work on fibrin to control bleeding began in 1909 with Bergel (Matras 1985) reporting on the haemostatic impact of fibrin powder. Grey (1915) and Harvey (1916) described the application of fibrin tampons and thin fibrin plaques to control surgical haemorrhage. In the 1970s, Matras et al. 1973) described a technique using such a glue to unite neural endings. Adhesives have been recommended by several authors for wound closure, haemostasis and promotion of wound healing in oral and maxillofacial surgery (Matras 1982, 1985, Petersen 1985). Stajcic et al. (1985) described a technique for the successful closure of oroantral communications with the aid of a fibrin sealant.

Investigation into the use of fibrin sealants as a method of primary closure in periodontal surgery, both in human and animal studies, have been favourable (Bartolucci & Prato 1982, Prato *et al.* 1983, Pini Prato *et al.* 1985, Warrier & Karring 1992). The use of fibrin glue for haemostasis in cardiovascular surgery has increased in the past decade (Borst *et al.* 1982, Garcia-Rinaldi *et al.* 1989). Tisseel and Beriplast, both fibrin glue products have been used successfully to attain haemostasis in patients on anticoagulation therapy (Zusman *et al.* 1992), and in patients with bleeding disorders undergoing tooth extraction (Rakoez *et al.* 1993). In a study to examine the efficacy of Tisseel in healing extraction sockets, Møller & Petersen (1988) demonstrated no difference in pain, swelling, post-

operative infection or overall rate of healing. The action of this product is similar to that of collagen-based products, providing an initial framework for platelet aggregation and adhesion, and subsequently, activating the clotting pathways. The adhesive contains thrombin. fibrinogen, factor XIII and aprotinin. Thrombin converts fibrinogen to an unstable fibrin clot, factor XIII stabilizes the clot and aprotinin prevents clot degradation (Martinowitz et al. 1990). It has been investigated as a means of achieving primary closure of reflected mucoperiosteal tissues in endodontic surgery. Healing using this method proved to be better than that of conventional sutures (Creel 1990). Presently, this material does not have Food & Drug Administration (FDA) (Anon 1978) approval, and therefore, is not available in the USA. There is also some concern with regard to the potential for transmission of viral diseases, principally HIV and hepatitis, from the homologous pooled plasma source (Tawes et al. 1994). Cases of anaphylactic reaction to the topical application of fibrin glue (Beriplast) have also been reported (Mitsuhata et al. 1994).

Antifibrinolytic agents have been advocated for use in cardiovascular surgery to prevent the breakdown of existing clots, thus preventing further bleeding. Tranexamic acid and epsilon-aminocaproic acid are both powerful synthetic local antifibrinolytic agents, acting in vitro and in vivo by preventing plasminogen activation (Nilsson 1980). Plasminogen and plasmin bind to fibrin via their lysine-binding sites. In the presence of lysine analogues, tranexamic acid and epsilonaminocaproic acid binding is reduced and fibrinolysis in delayed (Hunt 1991) (Fig. 7). Tranexamic acid is six to 10 times more potent than epsilon-aminocaproic (Nilsson 1980). After a pre-injection of tranexamic acid at the incision site, enhanced tensile strength of the healing incision has been demonstrated, whereas epsilonaminocaproic caused a decrease in the wound strength (Björlin & Nilsson 1988). Epithelization in normal rabbit extraction sockets is also enhanced by the application of tranexamic acid (Vinckier & Vermylen 1984). Both substances have been investigated for their ability to achieve and maintain haemostasis at the local level, both operatively and post-operatively in patients on anticoagulation therapy. Rinsing with a solution of tranexamic acid pre-operatively has been shown to control haemorrhage effectively without altering the patient's anticoagulation therapy (Lucas & Albert 1981, Sindet-Pedersen & Stenbjerg 1986, Sindet-Pedersen et al. 1989. Borea et al. 1993, Ramström et al. 1993). The use of this product in routine periradicular surgery in the uncompromized patient has not been investigated.



The fibrinolytic system

Fig. 7 The fibrinolytic system.

Topical thrombin, Thrombogen, has been developed for haemostasis wherever wounds are oozing blood from small capillaries and small venules (Johnson & Johnson 1990). The thrombin acts to initiate the extrinsic and intrinsic clotting pathways. It is designed for a topical application and must not be injected. Injection of Thrombogen can result in entry into a large blood vessel where the effect would be intravascular clotting and possible death. Topical thrombin has been investigated as a haemostatic agent to abate bleeding in cancellous bone. While there was less bleeding than the control. topical thrombin was not as effective as a collagen-based haemostatic agent in reducing bleeding. Three months post-operatively, no impedance in bone healing was evident (Codben et al. 1976). Thrombogen has been used successfully in neurosurgery, cardiovascular surgery and burn surgery to achieve localized haemostasis; however, it use in periradicular surgery has not been investigated.

Collagen-based agents

The collagen-based haemostatic agents consist principally of collagen in differing microstructures and densities (Table 1). Chyapil et al. (1973) indicated that collagen has the potential to act as a mild allergen. However, the problem of allergenicity and unwanted tissue reaction does not occur when animal collagen of a highly purified nature is used (Bell et al. 1981). The mechanism by which collagen products enhance haemostasis has been elucidated and it is believed that four principle mechanisms are involved: (1) stimulation of platelet adhesion, platelet aggregation and release reaction (Caen et al. 1970), Kay et al. 1977); (2) activation of factor XIII (Hageman factor) and possibly other factors in the clotting cascade (Mason & Read 1974, 1975) (Figs 1 & 2); (3) mechanical tamponade by the structure that forms at the collagen blood wound interface (Mattsson et al. 1990); and (4) the release of serotonin (5-hydroxytryptamine, 5HT) (Shaw 1991).

Collagen products have been used successfully to aid in the surgical closure of oroantral communications (Mitchell & Lamb 1983). One of these products, Avitene, a microfibrillar collagen haemostat (MCCH), has been used for haemostasis in soft tissue (Alexander & Robinwitz 1978), bone surgery (Asher & Craig 1975) and for controlling haemorrhage in extraction sockets of haemophiliacs (Evans *et al* 1979). It potential use in periradicular has been demonstrated by Haasch *et al.* (1989).

Avitene is a purified bovine dermal collagen shredded into fibrils and converted into an insoluble partial hydrochloric acid salt. It functions through topical heamostasis, providing a collagen framework for platelet adhesion. This initiates the process of platelet aggregation, adhesion and the formation of a platelet plug (Mason 1975). The MCCH has been shown to be a more effective haemostatic agent than either thrombin soaked gelatine foam or thrombin powder (Codben et al. 1976). Avitene has been recommended as a viable means of controlling haemorrhage in periodontal surgery (Wirthlin et al. 1980, Kramer & Pollack 1982, Baumhammers 1983). Haasch et al. (1989) showed that use of Avitene resulted in minimal interference in the wound healing process, exhibiting a limited foreignbody reaction. Likewise, there was no increase in the incidence of infection (Georgiade et al. 1975), with only a slight delay in early bone repair (Hunt & Benoit 1976). In similar study designed to examine osseous regeneration in the presence of Avitene, Finn et al. (1992) found



Fig. 8 (Top) Low-power view of Avitene being replaced by new bone (arrows); no inflammation noted (H&E, \times 40). (Bottom) higher power view of Avitene being replaced by new bone (arrows); no inflammation noted (H&E, \times 100).

that bone formation proceeded uneventfully without a foreign-body reaction (Fig. 8). The application of Avitene may prove difficult and tedious because of its adherence to wet surfaces, particularly instruments and gloves (Sammonds 1986). To overcome these problems, it has been recommended that Avitene be applied to the surgical site by using a spray technique, as this allows removal of pre-accumulated blood and the direct adherence of Avitene to bleeding points (Decker 1991, Takeuchi *et al.* 1993). Avitene has been recommended for use in oral surgery, both as a haemostatic agent and as a protective dressing over denuded bone (Evans 1978).

Collagen has also been utilized to achieve haemostasis in a non-woven pad, as opposed to the fine powdered form of Avitene. Hematex is one such collagen product that is derived from bovine Achilles tendon and is available in double-sheathed sterile packs free from noncollagenous proteins, toxic heavy metals and glycosaminoglycans (Shaw 1991). Additionally, an increasing number of commercial collagen-based products are now available, including Collaplug, Hemofibrine, Hemocollagen, Instat, Collacote and Collastat (Fig. 9). Essentially, these materials act in a similar way to those described, and the surgical area undergoes a similar tissue response and healing pattern (Stein *et al.* 1985, Manni *et al.* 1986, Show 1991).

While a number of collagen and fibrin-based combination products have recently become available, results of biocompatibility and efficacy studies into these products have been variable. Astroplast is a non-woven gauze material with alginate as its main constituent. Hemastogen is a sponge-like material produced from combined bovine stabilized fibrin, collagen and dextran. In a study comparing Astroplast, Hemastogen and bone wax, Mattsson et al. (1990) found that all three products resulted in a strong, adverse tissue reaction. Hemastogen produced an early foreign-body reaction in combination with bone resorption. Two weeks post-surgery, the wound site was dominated by a lymphocytic, multinucleated giant cell and mast cell infiltrate. By week 4, the Hemastogen had dispersed, but granulation tissue remained with the central body of the wound surrounded by a cell-rich connective tissue capsule containing numerous macrophages. Bone formation was evident at the osseous surface. Eight weeks postoperatively, a mild chronic inflammation still persisted with isolated particulate remnants of the material. Newly forming trabeculae of bone had invaded the cavity from the periphery. The authors speculated that lack of purity may have lead to allergenic components in these products.

Absele has been promoted as a possible bone haemostatic agent (Köndell et al. 1988). It is a malleable pastelike substance with a similar haemostatic effect to bone wax, with the possible added benefit of fibrin and collagen. Absele is a combination of stabilized ox fibrin (17.5% w/w), solubilized ox collagen (17.5% w/w), dextran 70 (8.0% w/w), glycerose BP (30.0% w/w) and water (ad. 100% w/w) (Köndell et al. 1988). Köndell et al. (1988) clinically investigated the response in humans, and histologically, the healing patterns of Absele in rabbits. Clinically, Absele provided good haemostasis and uneventful healing for human subjects undergoing periradicular surgery. Histologically, however, there was an early vascular granulation around the material in rabbits. Multinucleated giant cells were observed in a peripheral cell rich zone subjacent to the granulation tissue. Four weeks post-operatively, some new bone trabeculae could be observed at the periphery of the experimental wound. Compared with the control site, osteoblastic activity was described as minimal. Haemostatic material persisted at 8 weeks post-operatively, and a multinucleated giant cell reaction with nonspecific residual chronic inflammation could been seen adjacent to these particles. A similar histological pattern has been reported by Solheim et al. (1992) in rats. In contrast, ACP a similar absorbable collagen-based paste made from stabilized fibrin, soluble collagen, glycerol and dextran (individual concentrations not given) showed complete histological healing over an 8-week period when placed in the rat mandible (Mattsson et al. 1990). Initially, there was an area of granulation tissue localized to ACP in which multinucleated giant cells





Fig. 9 SEMs of Hemofibrine (\times 940) (left) and Hemocollagené (\times 1300) (right) taken from the apical surgical area during periradicular surgery. Note the adherence of erythrocytes and fibrin strands.

were observed; however, this had dissipated 2 weeks post-surgery.

Experimental agents

In 1959, Coover et al. (1959) discovered the adhesive properties of cyanoacrylate (CH2=C[CN]-COOR). Its tremendous bond strength and ability to bond to wet surfaces are highly desirable properties for potential applications in medicine and dentistry. The majority of the early research with regard to the clinical application of cyanoacrylate focused on the methyl-2 member of the group. Cyanoacrylate has been investigated mainly as an adhesive material to establish primary closure of surgical wounds. The healing pattern in the presence of cyanoacrylate has been studied (Bhaskar et al. 1967, Howard et al. 1973, Eklund & Kent 1974, Vezin & Florence 1980) and appears to be dependent on which from of the product is involved. Research has revealed that the period of biodegradation varies inversely with the length of alkyl chain (Vezin & Florence 1980). Degradation of cyanoacrylate results in the formation of formaldehyde and alkyl cyanoacetate (Cameron et al. 1965, Leonard et al. 1966). The shorter chain ethyl and methyl cyanoacrylates biodegrade rapidly to produce a higher concentration of these substances and have subsequently been shown to be more toxic than the longer chain cyanoacrylates (Leonard 1970). Javelet et al. (1985) compared the healing of isobutyl cyanoacrylate and sutures in a clinical and histological study when both were used to close mucosal incisions in monkeys. The typical histological response to cyanoacrylate was one of delayed healing with foreign-body reaction.

The potential of cyanoacrylate as haemostatic agent has been assessed, with the application of isobutyl-2cyanoacrylate to extraction sockets in rats (Greer 1975). Within 2-15 s of application, the haemorrhage ceased. However, isobutyl-2-cyanoacrylate has been demonstrated to display a prolonged giant cell response up to 9 months after the initial application (Greer 1975). Dogan & Heeley (1978) examined the haemostatic and healing properties of fluoroalkyl cyanoacrylate using a primate model. Histologically, macrophages were observed to be actively removing the polymerized fluoroalkyl cyanoacrylate. There appeared to be little difference between the experimental and control in the initial organization of the blood clot, or in the quantity and rate of bone deposition. Islands of polymerized fluoroalkyl cyanoacrylate were seen within the sockets during the early phases of healing. By 6 months, however, this had

decreased substantially, and by 307 days post-operatively, there was no evidence of the material within the socket. Application of topical cyanoacrylate (Histoakryl), in spray from, has been used to help control post-operative haemorrhage in patients with prolonged oral bleeding. Patients appeared to tolerate this treatment well (Bossermann 1977).

Adaptic, a rayon and cellulose acetate which has been immersed in a hydrophilic petroleum has also been assessed for its haemostatic properties. Its mode of action is through physical pressure on the broken blood vessels. Hassch *et al.* (1989) compared its healing response in bone to that of Avitene. The Adaptic material caused a foreign-body reaction with residual fibrous encapsulation evident at 120 days post surgery.

Alzamer, a bone wax-like bioerodible polyorthoester, has also been advocated as a haemostatic agents (Solheim et al. 1992). Prior to being readily resorbed in bone and muscle, it has been shown to exhibit a transient foreign-body reaction. Little impairment of ultimate bone healing was evident (Sudmann et al. 1993). The polyorthoester adheres to bone surfaces and provides local haemostasis by plugging spongy bone, while secondarily, it promotes the concentration of platelets and coagulation factors (Solheim et al. 1992). However, the principle use of the material is as a drug delivery system (Pinholt et al. 1991). The wax-like, biodegradable nature of Alzamer and its apparent lack of impairment in healing, should warrant further investigation of its use in periradicular surgery. However, this product is no longer available commercially.

Chitosan is a complex carbohydrate biopolymer of Nacetyl glucosamine units linked by β -1, 4 O-glycosidic bonds into a polymer of 2000-3000 units that is derived from shellfish exoskeleton (Subar & Klokkevold 1992). It has been shown or be non-toxic, biodegradable and has a molecular mass of 800 to 1500 kD. Chitosan is currently being used in preparation of sustained release formulations of drugs (Nigalaye et al. 1990) and experimentally in transdermal drug delivery systems (Thacharodi & Rao 1995). Chitosan's mechanism of action in haemostasis remains unknown, as it is speculated that it has the ability to form a coagulum on contact with erythrocytes. It rapidly forms a coagulum in heparinized blood, defibrinated blood and washed red blood cells. The suggestion is that Chitosan enhances haemostasis by interaction with cellular components to cross-link cells to one another, or by forming a lattice which entraps cells to form an artificial clot (Malette 1983, Arand & Sawaya 1986). Klokkevold et al. (1991)

have demonstrated a 32% decrease in bleeding time in rabbit tongue incision with chitosan when compared to a placebo, and a 56% decrease in similar incisions in rabbits with induced platelet dysfunction (Klokkevold *et al.* 1992). Histological analysis of the incision site from 1 to 14 days post-operatively showed no significant difference between the chitosan-treated and control wound. None of the wounds displayed a foreign-body reaction or excessive inflammation. A combination of chitosan and imidazole has been used experimentally for its potential to enhance repair in bone wounds (Muzzarelli *et al.* 1994).

Miscellaneous agents

Historically, thermal control of haemostasis was advocated by many ancient civilizations. This approach frequently assumes the form of cold compresses, hot oils and cautery (Atterbury 1978). More recently, the use of both cold packs (Lapervrolerie 1973) and cautery via electrical heat have been used to provide haemostasis (Evans 1977). A technique using an electrosurgical knife in combination with topical thrombin to control haemorrhage in split-thickness skin graft vestibuloplasty has been described in the literature (Formann et al. 1984) However, the effects of hot and cold on haemorrhage are at best very transient and superficial. Cautery stops the flow of blood by coagulation of blood and tissue protein, leaving an eschar which the body will attempt to slough. Therefore, healing is impaired. Irrigation with cold saline reduces blood flow through limited vasoconstriction. As already mentioned, the effect is extremely transient (Costich & Hayward 1958).

A technique utilizing a rubber dam and a cement spatula with a aperture made through the blade of the spatula to isolate the root end has been described in the literature. The author suggests the use of this approach in anterior teeth with large periradicular lesions (Guerra 1992).

Clearly, cognitive dissonance (Seltzer & Bender 1965) has played a role in the promotion and selection of haemostatic agents in the past and will undoubtedly do so in the future. However, it is worth remembering that a surgical process based on sound scientific knowledge and an accompanying skill level, with the use of biologically compatible and biodegradable haemostatic agents as an adjunct, will adequately manage haemostasis. However, the need to investigate haemostatic agents used in other fields of surgery that could possibly have a role in periradicular surgery is obvious.

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