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REVIEW ARTICLE

Fibrin Sealant: A Review of Its Applications in Periodontal Surgery

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ABSTRACT

Aim: Fibrin sealant is a biological tissue adhesive mimicking the final stage of coagulation. It has a wide variety of application in the field of periodontics. The aim of this article was to review current applications and identify potential use of fibrin sealant in periodontal surgical procedures on an evidence-based conclusion.

Materials and methods: An online search was performed in PubMed, Google Scholar and Cochrane Library databases using keywords fibrin sealant, fibrin glue, fibrin, regeneration, wound healing, tissue adhesive, gingival recession/therapy, surgical therapy, periodontal, and periodontitis in a mutually inclusive manner. The studies were evaluated by two independent reviewers for inclusion in this literature review.

Results: Out of 196 research papers identified, 59 articles were selected by the authors for this literature review, giving preference to clinical trials related to periodontal application.

Conclusion: Use of fibrin sealant is a simple, safe, cost-effective, and rapid way to fix flaps and grafts avoiding any postoperative bleeding. Fibrin sealant has the property for regeneration when used in conjunction with a barrier membrane for formation of new connective tissue attachment. It is effective in microsurgical procedures and closing flaps around implant site. They initiate early wound healing through collagen synthesis and fibroblast proliferation. Fibrin sealant may be an alternate biomaterial for periodontal surgery which may stimulate periodontal wound healing and regeneration.

Keywords: Fibrin glue, Periodontal flap surgery, Regeneration, Tissue adhesive, Wound healing.

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INTRODUCTION

Periodontium is specialized tissues that both surround and support the teeth. Periodontitis is an infectious disease affecting the supporting structures of the teeth.[1] Periodontal disease is primarily caused by specific groups of organisms which colonize the tooth surfaces in the form of a biofilm called plaque which leads to inflammation, loss of attachment and bone loss.[2,3] The ultimate goal of periodontal therapy is to stop and reverse the loss of periodontal attachment resulting from disease and regenerate periodontal tissue and promote early wound healing.[4,5] Any agent toward this objective would be valuable for getting better result of periodontal surgical treatment. Several products have been used to aid in periodontal surgical procedures which could promote early wound healing and augment tissue regeneration.[6-8]

Human fibrinogen, when activated by thrombin, initiates the final leg of coagulation.[9] This forms the basis for the biologic tissue adhesive, fibrin sealant. The soluble fibrinogen polymerises into fibrin leading to the formation of a stable clot.[9,10] Fibrin sealant, also known as fibrin glue has found applications in surgery as a sealant as well as for hemostasis.[11,12] It has been used to secure gingival grafts and mucoperiosteal flaps.[13,14] Fibrin sealant can be used for wound closure replacing the need for sutures, even in locations and circumstances where suturing would be detrimental to optimal wound healing and integrity. The adhesive property effectively seals tissue and eliminate potential spaces.[15] In addition to binding tissues, fibrin sealant acts as a natural wound bed. This bed functions as a scaffold facilitating the proliferation and differentiation of mesenchymal and endothelial cells.[16] Fibronectin as one of its main constituents has the potential for regeneration of periodontal supporting structures. A temporary shield is created for the safe population of potential periodontal ligament cells capable of regeneration of functional periodontium.[17] This barrier prevents the entry of cells of epithelium and gingival connective tissue from reaching the potential regenerative space. Recently, fibrin sealant has been investigated as a targeted local cell and drug delivery system.[18,19]

This literature review will attempt to describe the various aspects of fibrin sealant including development, property, and its current and potential application in

surgical procedures of periodontal therapy. In this review, many of those applications are discussed in the realm of early wound healing, regeneration and cell delivery.

MATERIALS AND METHODS

Data Search

Electronic and manual search was performed in June 2013, for publications that investigated or could explain the use of fibrin sealant for periodontal surgery. Medline/PubMed (National Library of Medicine, Bethesda, Maryland), Google Scholar and Cochrane Library databases were searched for appropriate articles using the following keywords in various combinations: 'fibrin sealant,' 'fibrin glue,' 'fibrin,' 'tissue adhesive,' 'wound healing,' 'periodontal,' 'gingival recession/therapy,' 'regeneration,' 'surgical therapy' and 'periodontitis.' Databases were explored from conjuring to 2013. Titles and abstracts of articles that satisfied the eligibility criteria were screened and checked for agreement by two reviewers (SJP and SN). The full text of the articles judged by title and abstract to be relevant were read and independently assessed against the selection protocol. This was followed by hand-searching of the reference lists of original and review studies that were found to be relevant in the previous step and once again, any disagreement between the authors was resolved through discussion. All articles were selected that were relevant to fibrin sealant application either done in humans and animal. The authors selected the most appropriate articles, giving preference to patient-based outcome data and clinical trials relevant to periodontal application. Letters to the editor, historic reviews, articles published in language other than English and unpublished articles were excluded. Out of 196 research papers identified,[59] articles were selected by the authors for this literature review.

History of Fibrin Sealant

Bergel[20] (1909) used fibrin emulsion to promote wound healing. Grey[11] (1915) used fibrin tampons and thin fibrin plaques was used later in 1940.[21] Young and Medawar[12] (1940) repaired severed nerves in animal using fibrinogen. In 1944, fibrin sealant was first used for the anchoring of skin grafts in burned soldiers by allowing a solution of isolated fibrinogen to be activated by thrombin.[21] Since, that time fibrin sealant has been used in many fields of surgery. Bösch P et al[22] (1980) applied it to retain heterogeneous bone graft in periodontal defect while Bartolucci et al[13] (1982) fixed periodontal flap and grafts. Prato GP et al[9,10,14] found that fibrin sealant's excellent hemostatic and tissue adhesive properties will be useful in periodontal surgical wounds and there was less inflammation when compared to silk sutures.

Since, 1970s fibrin sealant has been widely marketed in Europe, but limited its use in the United States due to viral transmission. Tisseel® (Baxter Healthcare, Deerfield, Illinois, USA) became the first approved fibrin sealant in the United States in 1998.[23]

Sources of Fibrin Sealant

Fibrin sealant can be prepared from the patient's own blood (autologous) or derived from donated blood.[24-26] Autologous fibrin sealant ensures no chance of any pathogen transmission.[23] Thrombin component is isolated from the supernatant of centrifuged plasma while fibrinogen is recovered from the precipitate. Bovine thrombin can also be used as a replacement to combine with concentrated fibrinogen. Aprotinin, tranexamic acid or epsilon aminocaproic acid are anti-fibrinolytics which prolong the life of a clot formed through fibrin sealant. A higher concentration of fibrinogen is obtained from the cryoprecipitate of fresh frozen plasma than fresh blood. Precipitating plasma using ammonium sulphate, ethanol, and polyethylene glycol are other means of obtaining concentrated fibrinogen.[25] Autologous samples contain low concentration of fibrinogen than commercially prepared sealants.[23]

Tisseel® (Baxter Healthcare, Deerfield, Illinois, USA) and Crosseal® (Omrix Biopharmaceuticals, Ltd, Israel) are the two commercial fibrin sealants currently marketed in the United States. In Europe Evicel® (Johnson and Johnson), Beriplast® (ZLB Behring), Quixil® (Johnson and Johnson) and TachoSil® (Nycomed) are available.[24] In India ReliSeal® (Reliance Industries, India) is available with similar components.[23] The Tisseel® sealing system is available as a kit consisting of five units: Tissel (fibrinogen, clottable protein, plasma fibronectin, Factor XII and plasminogen), thrombin, 4 NIH (National Institute of Health) or thrombin 500 NIH, aprotinin solution, calcium chloride solution. Crosseal and Quixil includes tranexamic acid as its antifibrinolytic agent in place of bovine aprotinin.[24] The use of human thrombin rather than bovine thrombin makes the commercial fibrin sealant safer than blood-bank fibrin sealant.[25]

Working Mechanism of Fibrin Sealant

The two components in a fibrin sealant, thrombin and fibrinogen, when mixed together imitate the final stage of natural clotting pathway to form a fibrin clot. Aprotinin or a suitable fibrinolysis inhibitor prevents early fibrinolysis by the host plasmin, allowing the fibrin formed to stay longer for tissue adhesion.[23,27]

The following are the function of each component of fibrin sealant:[14]

- *Fibrinogen*: It is a high molecular weight protein which polymerises into a stable fibrin, the element of clot, activated by thrombin and factor XIII. The fibrin clot acts as a scaffold and attracts fibroblasts leading to granulation tissue formation.
- *Fibronectin*: It is a high molecular weight glycoprotein, which when catalyzed by factor XIII covalently links to polymerized fibrin. It facilitates the adhesion and migration of various cells including fibroblasts and acts as a substrate for interaction between cells leading to reparation/regeneration of tissues.
- *Factor XIII*: This transglutaminase enzyme stabilizes the link between fibronectin and fibrin in the clot as well as the link between the clot with collagen and glycosaminoglycans. It gives dimensional stability by linking antiplasmins to the clot.
- *Plasminogen*: Is a glycoprotein (MW = 90,000)? Active thrombin coverts it into plasmin for the proteolysis of the fibrin-fibronectin clots.
- *Thrombin*: It is a serum protease with many functions including the conversion of fibrinogen into fibrin, activation of factor XIII and stabilization of the fibrin network. The speed of coagulum formation is directly related to thrombin concentration.
- *Aprotinin*: It is a polypeptide that blocks plasmin and other serum proteases. It is one of the best inhibitor of fibrinolysis which in turn can enhance healing by extending the life of the fibrin mesh.
- *Calcium chloride*: Ca^{++} ions are important and are needed in many coagulation steps including conversion of prothrombin to thrombin and activation of factor XIII. Presence of Ca^{++} accelerates the polymerization processes.

The highly stable clot seen following coagulation processes is the result of the above-described molecules in a systematic way. The cleavage of fibrinogen into fibrin is facilitated by thrombin. Factor XIII polymerises these soluble molecules into insoluble fibrin stranded clot. Calcium ions influence and accelerate both activated factor XIII and thrombin.

Properties of Fibrin Sealant

Surgical glues approximate and retain wound edges, provide hemostasis and reinforce tissues through adherence. Hence, they are required to possess properties like tissue adhesiveness, enhancing coagulation and mechanical strength and stability.[28] Other factors, like availability, ease of use, cost, biocompatibility and transmission of diseases, can affect the selection of surgical glue.[28] The two basic tissue adhesives are: synthetic (commonest is n-butyl-2-cyanoacrylate) and biological (fibrin sealant). Table 1 compares between suture, fibrin and cyanoacrylate when used for wound approximation. Cyanoacrylate was a popular synthetic tissue adhesive. It forms a solid, insoluble mass within tissues leading to foreign body inflammatory reaction in certain individuals but exothermic reaction and harm to soft tissues limited its use in periodontal surgery.[29] Fibrin sealant is a naturally derived tissue adhesive and hence is tolerated by most persons with nil or minimal inflammatory reactions. Its adhesive property can help to seal a periodontal pocket preventing bacterial contamination.

Evaluation of the tensile strength, elasticity and adhesive strength gives an accurate indication on the clinical ability of fibrin sealant in retaining tissues. The internal bond strength in a fibrin sealant together with the adhesive strength to tissues underlies the overall strength of the sealant.[30] This is directly proportional to the fibrinogen concentration and reaction time.[15,25,30] A prolonged clotting time in a low fibrinogen concentration leads to formation of weak strands of elastic fibrin which breaks easily on stress. Fibrin polymerized from a shorter clotting time of a high concentration of fibrinogen results in high elasticity with adequate strength and is preferred in majority of tissues.[30] Thrombin concentration directly influences the clotting time and is used to affect the working time of fibrin sealant.[25]

Patients with disorders or on medication affecting their coagulative process are benefitted by fibrin sealant.[31] It also can control bleeding during surgical procedures. As it is a naturally derived product, the host can absorb fibrin sealant thereby limiting risks of infection, inflammation and postoperative pain when compared to sutures.[32-34]

Application of Fibrin Sealant in Periodontal Surgery

Fibrin sealant is an adhesive and hemostatic agent but has the potential for regeneration of periodontal tissue. The value of fibrin sealant in surgery has been underscored

Table 1: Characteristics/properties of sutures, fibrin sealant and cyanoacrylate

Characteristics/ properties	*Sutures*	*Fibrin sealant*	*Cyanoacrylate*
Adequate tensile strength	Present	Present	Present
Tissue response/ inflammation	Present	Present	Present
Significant postoperative pain	Present	Absent	Absent
Risk of transmission of disease	Absent	Present	Absent
External use only	Absent	Absent	Present

by many researchers over the last three decades. The properties of fibrin sealant make it easy to handle for numerous applications for periodontal surgery. In light of special characteristics, many authors have evaluated this material in various aspects of periodontal surgery. The following are the significant uses:

Fibrin Sealant as Surgical Glue in Periodontal Flap Surgery

Fibrin sealant proves to be a better alternative for fixation of tissues compared to sutures. There is close approximation with better hemostasis. This leads to early wound healing as oral hygiene can better maintained in a patient. The clinical signs of inflammation were less. The grafts and flaps were more fixed and stable which results in a better healing at 1 or 2 weeks after surgery.[14,29,35] The better fixation is due to fibrin sealant being able to seal the whole under surface than just the marginal fixation possible with sutures. The application of fibrin sealant requires less skill while providing firm adhesion leading to reduction of pocket depth.[35] There is a smooth adaptation of flaps to the tooth surface resulting in lesser accumulation of plaque.[13]

Fibrin sealants stimulate early wound healing and connective tissue growth by accelerating revascularization and facilitating the migration of fibroblasts.[36,37] The sealant is biocompatible eliciting very minimal inflammatory reaction. It is able to induce angiogenesis, highly stable epithelium-connective tissue interface and connective tissue more resistant to proteolytic enzymes. There is more mature epithelium, connective tissue, increased density of fibroblasts, mature collagen after 1 week of healing period of fibrin sealant application whereas sutured site showed increased inflammatory cells.[38]

Fibrin Sealants for Periodontal Regeneration

The clot stabilization achieved by the use of fibrin sealant has been advocated for isolating and protecting the regenerative space for periodontal tissue regeneration.[39] A biologic barrier which promotes repopulation of regenerative cells of periodontium has been noticed when using fibrin sealant.[39] There is new bone formation by osteoinduction[18,40-42] and formation of new capillaries and connective tissue. Use of the sealant with bone graft filling materials leads to better handling properties with good adhesion to the defect wall.[39] Fibrin sealant with bovine bone mineral has shown promising results in bone fills.[43,44] The fibronectin present in fibrin sealant promotes migration and adherence of fibroblasts and periodontal ligament progenitor cells to the root surface thus forming new attachment.[45,46] An antienzymatic effect was seen in fibrin sealant promotes fibroblast aggregation and growth of type I collagen.[10,38,45-47] Periodontal regeneration has been reported when the barrier membrane in guided tissue regeneration (GTR) was stabilized with fibrin sealant.[42,48] There were no detrimental effects on the GTR process when fibrin sealant was used.

Fibrin Sealant for Mucogingival Surgery

Immobilization of free gingival grafts and coronally displaced flaps by fibrin sealant showed more advanced healing compared to sutures.[9,10,14,49] Fibrin sealant improved the clinical outcome when used for gingival recession coverage.[50-53] The presence of a stable thin fibrin sealant facilitated clot could be the reason for the improved outcomes.

Fibrin Sealant and Implant

Fibrin sealant has been shown as a better alternative to suturing of flaps during implant placement, especially in the esthetic zones.[54] There is also stronger and greater peri-implant bone contact interface.[55] When used with bone alloplastic materials, fibrin fibronectin system showed regeneration of peri-implant defects.[56] It has also been used to preserve the alveolar ridge following tooth extractions.[56]

Fibrin Sealant as a Vehicle for Delivery Growth Factors and Stem Cells

Slow lysis, customisable matrix which can act as a scaffold for cells and interacting molecules makes fibrin sealant an attractive product to investigate as a drug and cell delivery system. Fibrin sealant can bind active molecules and act as a reservoir for growth factors like vascular endothelial growth factor (VEGF), transforming growth factor-β1 (TGF-β1), insulin growth factor (IGF) and basic fibroblastic growth factor (bFGF).[57,58] There was interaction seen between TGF-β1 and fibrin sealant with the release of the growth factor influenced by the concentration of fibrinogen. There was improved tissue regeneration when fibrin sealant was used as a scaffold for the growth factors' release.[59,60] Basic fibroblastic growth factor released from the scaffold formed by fibrin sealant also showed enhanced healing.[61] The growth factors appear to be temporarily stored in the fibrin scaffold, thus prolonging their effects.[53,54]

Fibrin sealant can be a suitable delivery system of stem cells for tissue engineering.[18] The angiogenesis and presence of factor XIII in fibrin sealant enhances the recruitment and proliferation of stem cells. Mesenchymal stem cells (MSCs) from bone marrow when delivered through fibrin sealant have shown good results in regeneration of

alveolar bone defects.[62] There is better healing with good quality of bone formation seen.[18] There is enhancement in the survival of the stem cells due to the presence of a suitable local microenvironment.[63] Fibrin sealant has been shown as a better scaffold for stem cell proliferation.[64]

Future Use of Fibrin Sealant

Fibrin sealant material impregnated with antibiotics can be considered as a better alternative to the local drug delivery agents in use for periodontal infections. Mader et al[65] (2002) showed that osteomyelitis could be resolved by antibiotic impregnated fibrin sealant implant. The antibiotic is released by dissolution of the fibrin sealant.[34,65] The controlled release of antibiotic at the appropriate concentration along with wound healing property of fibrin sealant would be well suited for early resolution of periodontal infections by inhibiting the microbial etiology and assisting the host. Fibrin sealant has been currently used for odontogenesis, which can regenerate tooth tissue by tissue engineering.

LIMITATIONS

One of the drawbacks of fibrins sealants is that fibrin sealants prepared from donors carry the risk of transmitting diseases.[23] To minimize the risk of viral diseases transmission, donor screening and pathogen reduction steps like vapor heating and solvent detergent cleansing is done. Antigen and antibody evaluation of plasma using serologic and nucleic acid techniques can be done to ensure safety of the plasma and the use of recombinant thrombin is also recommended.[15] Besides that, intense inflammation would occur at the site of surgery in the first few weeks after fibrin sealants were applied due to the presence of factor XIII which increases neutrophil chemotaxis.[24] Even though the occurrence of allergic reactions toward fibrin sealant is low, anaphylactic reactions due to the use of fibrin sealant have been recorded. It is mostly due to aprotinin present in fibrin sealant which is of bovine origin in certain sealants.[24] Choosing a fibrin sealant without aprotinin (Quixil® and Crosseal®) decreases the hypersensitivity risk.

CONCLUSION

Due to the many complications from sutures, fibrin sealants are now gaining more importance in the surgical field. It is versatile surgical glue which can function as a hemostat, sealant or adhesive and they can enhance the overall clinical outcome of surgical treatments. Several authors have confirmed the effectiveness of the product and have also demonstrated the excellent local tolerability and the complete absence of undesirable effects and contraindications. In addition, it also promotes periodontal wound healing. The literature, however, contains conflicting reports, and additional studies are needed to establish the most effective use of these biologics. Dentistry is varying with induction of modern science to practice dentistry.

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