Fibrin Glue- Path to Sutureless Periodontal Surgery

Abstract

Surgical periodontal therapy has evolved by leaps and bounds over the years, however, sutures have been of prime importance in all of the surgical periodontal therapy. Many clinicians, considering its advantages and disadvantages, have considered sutures a double-sided sword.

Sutures are considered the gold standard for wound closure in periodontal surgery, however, its has its own limitations like being time consuming, possible risk of infection, chances of formation of snail track ulcer, scarring of the tissue, requires technical skill. These drawbacks led to the development of various alternatives such as staples, adhesive tapes, and tissue adhesives likecyanoacrylates and fibrin glue have been become popular because of their perceived ease of placement.

Tissue adhesives like human fibrin glue offer a unique and novel means of wound closure since they may result in equivalent tensile strength, improved esthetics of the scar, and lower infection rates when compared with sutures, adhesive tapes and staples. Another advantage of tissue adhesives is that the patient does not need to visit doctor again for removal at a later date, thereby avoiding wound disruption and potential reactivity.

This review article aims to shed more light on the potential and dynamics of the next generation tissue adhesive i.e. fibrin glue.

Key Words : Fibrin glue; Tissue adhesive; Tisseel kit; Fibrin sealent

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Introduction

The goal of periodontal therapy is to restore and maintain the health and function of the periodontium for a lifetime. This therapy has evolved over many years to include an initial nonsurgical phase of therapy and subsequent surgical treatment followed by periodic maintenance therapy. Both non-surgical and surgical therapies are applicable in treatment of periodontal disease.

Elimination of local etiologic factors is of penultimate importance in determining the success of periodontal therapy. Non-surgical therapy i.e. scaling and root planing help attain this goal. However, in certain cases all the local factors cannot be eliminated via non-surgical therapy due to poor or impaired access, visualization, etc. This is one of the major drawbacks of non-surgical therapy or closed approach. In such cases, open approach or surgical phase therapy is the method of choice as it provides adequate visibility and access to the underlying bone and root surface. This would also summarize the main objective of periodontal flap. Open flap debridement is characterized by raising a full or partial thickness periodontal flap, debridement followed by scaling and root planning and then sutures are taken to attain obtain adequate primary wound closure and stabilization of the tissues.

The correct approximation of the edges of a wound during flap periodontal surgery is essential for the success of the surgical technique, because it favors hemostasis, nutrition and repair. This close approximation of the tissues is achieved by suturing, which is a very important surgical step in hastening the healing of surgical wound (Castro et al. 1974; Chambrone et al. 1982; Carvalho et al. 1986). Establishing a non-tension primary wound closure of various soft-tissue flaps is essential for optimal postsurgical wound healing.[1]The primary objective of dental suturing is to position and secure surgical flaps in order to promote optimal healing. Suturing is a common procedure undertaken after surgical periodontal therapy, but it is time consuming, requires technical skill & expertise, and an additional patient visit for its removal.[3]

In search of a solution of these problems, concept of tissue adhesive came forward. Fibrin sealant is a synthetic substance used to create fibrin clot.[3] It is composed of fibrinogen and thrombin where thrombin acts as an enzyme and converts the fibrinogen to fibrin which can act as a tissue adhesive.[1] Fibrin sealant in addition to adhesive property also has an anti-enzymatic effect which promotes fibroblast aggregation, their growth and adhesion.[16]

Fibrin glue is "Fibrin Fibronectin Sealing System" (FFSS). It is available as two-component system: first component contains highly concentrated fibrinogen, factor XIII, fibronectin, and traces of other plasma proteins. The second component contains thrombin, calcium chloride, and anti-fibrinolytic agents such as aprotinin. Mixing of two components promotes clotting with the formation and cross-linking of fibrin. Fibrin glue is commercially available as Tisseel VH (Baxter, U.S.A.) and Tissucol (Termotrattato, Wien).[18]

Fibrin glue is a widely used material in the field of medicine like in cardiopulmonary bypass, colostomies, treatment of splenic injuries, etc. However, the role of fibrin glue for wound closure in periodontal surgery has been evaluated on a limited basis. On the contrary, sutures have always been considered as a gold standard for wound closure in periodontal surgery as well as other surgical procedures. However, suturing has its limitations like it is time consuming, possible risk of infection, chances of formation of snail track ulcer, scarring of the tissue, requires technical skill while suturing as well as at the time of suture removal by operator and also an additional visit by the patient is required for its removal.[14]Fibrin glue is an attempt to eliminate some or all of the disadvantages of sutures.

Historical Background

Fibrin was first used as a hemostatic agent by Grey (1915),[2] and it was first used as a tissue sealant by Young et al (1940). [3] Later, fibrinogen and thrombin were successfully employed to fix cutaneous grafts using fewer or no sutures Cronkite et al (1944).[4]

With the discovery of Factor XIII and the use of aprotinin as an anti-fibrinolytic substance, the fibrin-sealing technique was substantially improved. In 1975, Matras et al. [5] a fibrin sealant derived from autologous material plus aprotinin (Tissucol) was used in peripheral neurosurgery.

Since that time, fibrin glue has been used in many fields of surgery; it was first used to retain heterologous bone grafts in periodontal defects by Bosch et al. (1980)[6] and to fix periodontal flaps and grafts by Prato and Bartolucci et al. (1982).[7,8] Later, Pini Prato et al. (1985) [9] & De Paoli et al. (1979)[10] proved it to be effective in improving periodontal wound healing in both animal experiments and clinical trials.

Fibrin Adhesive System

Fibrin adhesive system (FAS) is a topical biological adhesive consisting of a solution of concentrated human fibrinogen, which is activated by the addition of bovine thrombin and calcium chloride. The resultant clot supports hemostasis and tissue sealing, and is completely absorbed during wound healing without foreign body reaction or extensive fibrosis. Fibronectin, a family of related proteins found in blood plasma and on fibroblast surfaces is a chemo-attractant for fibroblasts and enhances the interaction and adherence of fibroblast to surfaces. Fibronectin may serve to anchor a blood clot to surrounding collagen owing to its property of being covalently linked to fibrin and collagen by factor XIII a.[13]

Conventional sutures provide only a marginal fixation, while the fibrin sealing system makes the tissues adhere on its whole surface. It saves time and makes it easier to fix tissues.[1] In the field of medicine, fibrin sealant is indicated as an adjunct to hemostasis in surgeries involving cardio-pulmonary bypass, treatment of splenic injuries and also closure of colostomies. It is a satisfactory hemostatic agent in fully heparinized patients undergoing cardio-pulmonary bypass. In dentistry, fibrin-sealing system is effective as a means of fixing tissues after periodontal surgery. Sutures cause inflammation around themselves, while fibrin glue enhances early wound healing. In periodontal plastic surgeries of esthetically important areas, it gives better results than sutures. It has osteoconductive potential and significantly produces more new bone and new connective tissue when used with bone graft material like β-tricalcium phosphate.[13]

Fibrin Glue - Physiology of Hemostasis

A basic understanding of normal hemostatic mechanisms is necessary in order to understand the action of fibrin adhesives. For hemostasis to occur *in vivo* interactions between platelets, blood flow, coagulation factors, and the vasculature must occur. Fibrin adhesives represent the end products of the common coagulation cascade, which explains their adhesive properties. [11]

Fibrinogen is the primary protein precursor to the formation of blood clots. Thrombin, a serine protease, activates plasma fibrinogen to the fibrin monomer. [18] Fibrin monomers are arranged into progressively larger fibrils, and then fibers, in a three dimensional network. In the presence of calcium ions (Ca^{2+}), thrombin converts Factor XIII into its activated from Factor XIIIa by proteolytic cleavage. Factor XIIIa then converts the non-covalent bonds between fibrin monomers into covalent bonds by transamination, forming fibrin polymers. Polymerization decreases the susceptibility of the clot to proteolytic digestion and increases its strength and stiffness. In the final phase, the fibrin polymers are cross-linked into a

dense mesh called the fibrin clot. The covalent cross-linking of fibrin is also enhanced by the plasma proteins fibronectin and plasminogen, which also enhance adhesion of the clot to collagen substrates.[11,12]

The fibrin clot is enzymatically degraded by plasmin. The plasma protein plasminogen is enzymatically cleaved to form plasmin. Plasminogen may be activated by a number of endogenous enzymes such as urokinase, tissue plasminogen activator (tPA) and Factor XII, and exogenous enzymes such as streptokinase.[11] Plasmin itself can also act as an activator of plasminogen. Anti-fibrinolytics block the conversion of plasminogen to plasmin or form complexes with the active site of plasmin to inhibit fibrinolysis. Endogenous anti-fibrinolytics include α_2-macroglobulin, α_2-antiplasmin, and antithrombin III. Exogenous anti-fibrinolytics include aprotinin and *e*-aminocaproic acid.[11]

Based upon the normal physiologic coagulation cascade reactions, fibrin adhesive systems are classically comprised of two components. The primary ingredient in the first component is concentrated fibrinogen along with FXIII, fibronectin, and other plasma proteins. The second component is thrombin. Various exogenous anti-fibrinolytic agents, such as aprotinin or *e* - aminocaproic acid, and ionized calcium (usually $CaCl_2$ i.e. calcium chloride) have been added to thrombin to impede clot dissolution and enhance polymerization respectively.[11,12] When these two components are mixed, a stable fibrin clot should form. It has been demonstrated that the application of autologous fibrinogen alone may be sufficient and possibly superior when fibrin glue is used to enhance tissue adhesion. In fact, in one study superior shear bonding strength was achieved using fibrinogen activated by endogenous thrombin alone, when applied to skin flaps.[12]

Applications of Fibrin Glue in Dentistry[14]

Fibrin-sealing system is effective as a means of fixing tissues after periodontal surgery, as fibrin glue is easier and quicker to use than sutures. Sutures cause inflammation around themselves, while fibrin glue enhances early wound healing. In periodontal plastic surgeries of esthetically important areas it gives better results than sutures.The split mouth clinical trials done to see effect of treating deep wide buccal gingival recession with guided tissues regeneration procedure after root conditioning with tetracycline HCI and FFSS give good results.

Recent animal studies showed that FFSS has osteoconductive potential & significantly produced more new bone and new connective tissue when used with bone graft material like β - tricalcium phosphate.

Applications of Fibrin Glue in Oral & Dental Surgery[16]

- Local hemostatic measures in patients with bleeding disorders and patients on anticoagulants.
- Sealing of oro-antral fistula.
- Correction of periodontal bony defect.
- Tissue adhesive with bone chips to treat bone defect.

Application in Periodontics

Initial wound stability has been shown to be important to the healing periodontal wound.[21] Procedures designed to prevent gingival flap recession either by improved anchoring techniques,[20] coronal reposi-tioning,[20] or wound stabilizing implants[21] have also proven beneficial in prevention of apical migration of junctional epithelium and enhanced new attachment formation. Further studies have established the importance of early clot adhesion on periodontal wound healing.[22] Clot adhesion to the root surface by a fibrin linkage in the early stages of periodontal wound healing may be of primary importance in successful regeneration.[23] This adhesion may serve as a barrier to the apical migration of junctional epithelium.[23] The extent of epithelial migration has been shown experimentally to be largely determined in the first ten days of healing. Various agents have been employed in the biomodification of root surfaces to enhance clot adhesion, such as fibronectin,[24,25] stannous fluoride,[25] citric acid, tetracycline,[24] and heparin.[25] These agents have yielded varying degrees of success.

Commercially available tissue adhesives containing concentrated fibrinogen, fibronectin, and factor XIII [23] have been used as a means of promoting an early and stable bond between the gingival flap and the exposed root surface and for benefits provided to wound healing. Fibrin and factor XIII are known to promote fibroblast adhesion and multiplication.[20] The adhesive strength of fibrin glue has been shown to be proportional to its fibrin concentration.[18] Increased fibroblast growth and collagen production has been demonstrated with tissue adhesives providing enhanced early wound strength. Also, by an as yet undefined mechanism, fibrin glues may have antibacterial properties as evidenced by studies on skin grafts in infected sites.[22]

Application of Fibrin Glue in Field of Medicine[16]

- Local hemostatic measures for both surgical and medical cases.
- Surgery in the patient with bleeding disorders i.e. hemophilia, severe thrombocytopenia and non-bleeding cases with suspected blood oozing.
- Surgery in non-suturable organs (e.g. brain, liver, pancreas, thymus) or to repair unhealthy tissue (e.g. irradiated bowel or tissue of elderly patients).
- Microvascular surgery and vascular grafts (e.g. aneurysm repair).
- Nerve grafts.
- Skin grafts, particularly plastic surgery.
- Surgery of small or difficult to reach organs (e.g. Tympanoplasty, eye).
- Sealing of body cavities, fistulae, pneumothorax, etc.
- Anastomosis of gastrointestinal tract and other ductal organs.
- Sealing of fertilized ovum to the wall of the uterus in animal experiments.

Advantages of Fibrin Glue[16]

- Minimize or no blood component required for surgery.
- Reduce risk of transfusion complications. Example: Infection such as HIV, hepatitis, transfusion reactions.
- Reduce pre- and post-operative bleeding and blood oozing.
- Reduce clotting factors used intra-operation and post-operation in hemophilia and allied diseases.
- Multiple surgical procedures can be done in one session, e.g. 2-6 joint operations at one session in hemophilia, which reduces cost of surgery.
- Reduce workload for physicians and nurses.
- Reduce duration of hospitalization.
- Reduce cost of treatment.
- Sustain release of antibiotics or growth factor in the surgical wound, increase wound healing, adhesion and reduces infection.
- Reduce discomfort and number of sutures in many surgeries.

Occasional Complications May be Encountered with use of Fibrin Glue[16]

- Infection of the surgical wound.
- Separation of anastomoses.
- Adhesion in the GI tract.
- Bleeding of the surgical wound.
- Risk of transfusion transmitted disease if using unsafe blood product for preparation.

Tisseel Kit

Tisseel Kit™ consists of a two-component fibrin sealant system which offers highly concentrated human fibrinogen to seal tissue and stop diffuse bleeding. Fibrin glue is commercially available as Tisseel VH (Baxter, U.S.A.) and Tissucol (Termotrattato, Wien).[14]

Composition of Tisseel Kit

The fibrin-sealing system is now available as a kit, consisting of 5 units: (1) lyophilized Tissucol (fibrinogen, Factor XIII, fibronectin, platelet-derived growth factor (PDGF), plasminogen, antiplasmins); (2) aprotinin; (3) thrombin; (4) calcium chloride; and (5) distilled water. TISSEEL™ KIT is used to achieve hemostasis, to seal or glue tissue, and to support wound healing. In certain applications biocompatible material, such as collagen fleece, is used as a carrier substance or for reinforcement.

Indications[17]

Hemostasis: Hemostasis in diffuse bleedings, after joint and bone surgery, adenoidectomy and tonsillectomy as well as after maxillodental surgery in patients with bleeding disorders, sealing of the prostatic bed after prostatectomy.

Sealing: Coating and sealing of vascular prostheses, tympanoplasty, management of C.S.F. fistulae and dura lesions, treatment of premature rupture of the membranes in pregnancy by sealing of the lower amniotic region, air-tight sealing of sutures in lung parenchyma and pleura, of sutures in trachea, bronchus and esophagus, management of malignant pleural effusion, sealing of the lens after injuries with perforations, sealing of suture lines to prevent leakage of intestinal anastomoses, additional sealing of sutured microvascular anastomoses,etc.

Tissue gluing: Gluing of parenchyma in surgery on the kidney, liver, spleen and pancreas, spongiosa grafting when packing bone cavities and defects, pleurodesis in spontaneous pneumothorax, fixation of skin grafts and flaps, fixation of osteochondral fragments and implants, gluing of peripheral nerves, plastic surgery after opening of the maxillary sinus etc.

Support of Wound Healing: Skin grafting on devascularised and infected recipient sites, management of skin necrosis and mucosal ulcers, incorporation of homologous bone grafts.

Safety and Efficacy[17]

- It is manufactured using processed, screened pooled human plasma, a vapor heating process, and a solvent detergent process.
- It is satisfactory and safe for use in fully heparinized patients undergoing cardiopulmonary bypass.
- Tisseel Kit can even be applied in fully heparinized patients.

Precautions and Limitations[14]

Fibrin sealant cannot be used in individuals who are known to be hypersensitive to bovine protein.Fibrin sealant cannot be indicated for the treatment of massive and brisk arterial or venous bleeding. To avoid risk of allergic anaphy-lactic reaction and/or thromboembolic events, which may be life threatening, fibrin sealant should not be applied intravascularly or into the tissues.

Conclusion

In conclusion, fibrin glue, as a tissue adhesive, has in store a tremendous amount of potential for use in periodontal as well as oral surgery. Further clinical trials and clinical work, would only reinforce its efficacy and potential as a possible alternative to the conventional sutures, which till date have been considered the gold standard for wound closure in surgical procedures.

References

References are available on request at editor@healtalkht.com