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Research Article

THE ENIGMA OF STICKY BONE – A REVIEW

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A B S T R A C T

Alveolar bone loss being one of the main challenges faced today in the field of periodontics, all the treatment modalities aim towards regaining and repairing the lost alveolar bone, which is a part of the periodontium. In areas of these bone defects, various treatment options are available today, which include augmentation using graft materials available from both autologous and external sources. The work done by the bone graft can be enhanced by using different additives among which autologous fibrin glue with its biocompatible properties has emerged to be supreme. Thus, using these factors derived from the patient's blood along with bone graft is a novel method of augmenting tissue repair and hastening healing. This led to the new concept of sticky bone. Thus, this article aims to describe the evolving role of the sticky bone, which is a combination of autologous fibrin glue and bone graft, in Periodontics.

INTRODUCTION

The modern era is all about getting things done in the most convenient, easiest and the fastest way. Falling in line with the trend, modern surgical techniques also aim to get the maximum amount of healing with the minimum invasive procedures. Thereafter the concept of regenerative therapy has been introduced widely in the field of medical sciences.[1]

Regeneration is the restoration of the lost hard and soft tissues to rejuvenate its structure and function.This newly evolved abstraction combines various aspects of medicine, molecular biology, tissue engineering and biomaterials which are all aimed to repair, regenerate, or replace lost tissues.[2]

Platelets being a rich source of growth factors play a very important role in both hemostasis and wound healing. As these growth factors are mainly seen in blood plasma and platelets, platelet aggregates have been immensely used in dental and medical fields to hasten tissue repair and regeneration. Platelets along with growth factors are seen to secrete fibrin, fibronectin, and vitronectin. These act as adhesion molecules for cell migration and as a matrix for the connective tissue. This led to the thought that, these agents could be used for the process of regeneration.[3]Platelet Rich Plasma (PRP), Plasma Rich in Growth Factors (PRGF), Platelet Rich Fibrin(PRF),Concentrated Growth Factors (CGF)are the different platelet derivatives which have been tried and tested in the last 50 years. Periodontal therapy, as per its definition in itself aims to eliminate the inflammatory process, prevent the progression of periodontal disease and also to regenerate the lost periodontal tissues.[4] Thus the regeneration of the lost periodontal tissues is a part and parcel of periodontal therapy. Bone regeneration is of prime importance as alveolar bone along with periodontal ligament and cementum supports the tooth and keeps it in its place. Alveolar Bone and teeth are mutually dependent on each other. If the teeth are lost, the alveolar bone starts resorbing with time. The good news is that the lost hard and soft tissues can be regained or regenerated by augmentation. Regeneration of the periodontal tissues is a complex process orchestrating cell adhesion, differentiation, proliferation and migration in a sequential manner. Periodontal regeneration, as mentioned involves soft tissue and hard tissue augmentation, use of barrier membranes, root biomodification and various other regenerative methods. However, all the recent researches though aim to develop therapeutic options that are non-toxic, harmless, bio-compactible and cheap, they have their limitations. Hence no material has emerged that can be considered as a gold standard todate. [5,6,7]

Areas with intense bone loss and severe atrophy which were considered to be unsuitable for bone augmentation have been made possible with new methods of hard and soft tissue augmentation procedures using blood derivatives.[8] Periodontal therapy in itself is nonsurgical and surgical. The different augmentation methods employed, are categorized under surgical methods. Bone grafting is a surgical placement of graft material, which is biocompatible into spaces around a bone defect or areas of bone loss.[9] The areas of defect can be augmented using graft materials from the patient's own body or other external sources. The grafts do not augment the deficiencies alone but also helps to regrow the lost bone.[10]The

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work done by the bone graft can be enhanced by different additives available in the market, as well as derived by autogenous means. Among these fibrin glue has emerged as a promising adjunct which meets its many properties of being used as a sealant, a hemostatic agent, and most importantly as a scaffold for new bone formation, by notably minimizing the bulk of the spaces between bony particles and hastening the revascularization, thus improving the bone graft integration and remodeling.[11]This led to the new concept of sticky bone which is growth factors rich bone graft, introduced by Sohn in 2010.[12] Hence this review article aims at introducing and elaborating the new concept of sticky bone which is an excellent choice for regenerative procedures.

Table 1 The evolution of sticky bone and growth factors

Author	Year	Material	Further Details
Kingsley[13]	1954	PRP	Designated the term PRP for thrombocyte concentrates in various blood coagulation experiments.
Matras[14]	1970	fibrin glue	As the concentration of fibrinogen in donor plasma was low, it led to the stability and quality of it being suboptimal.
Various Research Work[15]	1975-1978	platelet-fibrinogen-thrombin mixtures	Various research works during this period uplifted the usage of blood extracts and hence assigned them this term.
Knighton *et al*[16]	1986	platelet-derived wound healing factors (PDWHF)	Skin ulcers were successfully treated with these.
Kingsley *et al*[13] and Knighton *et al*[17]	1988, 1990	platelet-derived wound healing formula	A somewhat different term was used to describe the platelet concentrates
Whitman *et al*[18]	1997	platelet gel	Though initially it was named as PRP during the preparation phase, the final product showed consistency similar to a fibrin gel.
Choukroun *et al*[19]	2000	PRF	Because of the strong fibrin gel polymerization present in this preparation of platelet concentrates, it was named as PRF.
Bielecki *et al*[20]&Cieslik-Bielecka *et al*.[21]	2006	Platelet Rich Gel	Defined: PRP as an inactive substance PRG as an activated fibrin matrix rich in leukocytes and platelets.
Sacco[22]	2006	Concentrated Growth Factors	2400-2700 rpm was used to separate cells from the venous blood. Fibrin blocks obtained were larger, richer and denser.
Everts *et al*[23]	2008	inactivated product: "platelet-leukocyte rich plasma (P-LRP) activated: gel named as the platelet-leukocyte-gel" (PLG)	focused was on: Leukocyte component
Dohan Ehrenfest *et al*[24]	2009	(P-PRP) - or leukocyte-poor plateletrich plasma (LP-PRP); (2) Leukocyte-and platelet-rich plasma (L-PRP); (3) Pure PRF (P-PRF) - or leukocyte-poor PRF; and (4) Leukocyte- and platelet-rich fibrin (L-PRF).	A classification based on separation of the products using the fibrin architecture and the cellular content.
Sohn[12]	2010	sticky bone	This concept of autologous fibrin glue mixed with bone graft (sticky bone) was first introduced
Mishra et[25]	2012	Type 1: L-PRP solution; Type 2: L-PRP gel; Type 3: P-PRP solution; Type 4: P-PRP gel.	Proposed a classification, restricted to PRP and could be applied to sports medicine alone.
Choukroun[26]	2014	APRF	introduced an advanced PRF which stated to possess more monocytes called APRF
Tunalı et Al[27]	2014	T-PRF (Titanium prepared PRF).	Introduced T-PRF (Titanium prepared PRF).
Mourão *et al*[28]	2015	i-PRF	He gave a detailed technical description on i-PRF preparation

Precursors

Fibrin Sealant Tissue Adhesives

Fibrin sealant tissue adhesives have been used as a part of the surgical assemblage for the last 30 years. Other than its application as a hemostat or a sealing agent, it is being used for delivering drugs and other bioactive agents such as growth factors to different sites of the human body. These are being used along with cancellous bone and marrow as an adjunct in mandibular reconstruction procedures. Here they accelerate the revascularization process, and the migration of fibroblasts, thus stimulating the healing process.

Fibrin sealant's adherence property has been reported in the many works by different authors which include de Moraes AM *et al*., Saltz R, Dimick A *et al*., Chakravorty RC *et al*. [29,30,31,32] Its use as a delivery medium for antibiotics and growth factors which promotes healing is gaining wide popularity and has been documented widely. [29,33,34]

Thus, the role of fibrin as an adhesive and as a vehicle for the healing process is worth mentioning and has given a kick start to the newly evolving idea of sticky bone in the field of regeneration and repair.

Gelatin Platelet- Gel Foam

Gel foam is another hemostatic device that has been in use for the last 40 years. The structural support for the forming clot and its formation is quickened due to its spongy nature. [35,36] But the drawback of all these is that these were used mainly for their gluey effect and the effect of growth factors was not considered much.[3]

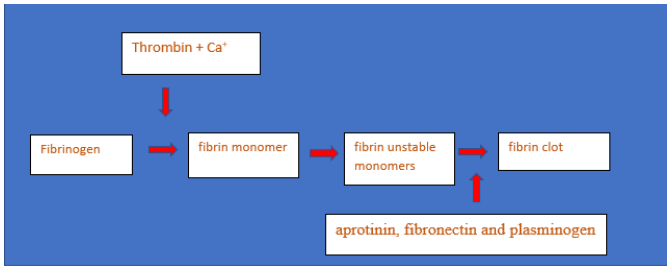
Sticky Bone

Methodology [12,37](flow chart 1)

The making of sticky bone

Fibrin glue

Fibrin glue is an adhesive with two-components which are fibrinogen and thrombin, imitating the coagulation process of the body. Fibrinogen (from heterologous/autologous cryoprecipitate or plasma), a glycoprotein that functions mainly to occlude blood vessels during an injury, is converted to fibrin by thrombin during a vascular injury to form a blood clot. Prothrombin is cleaved to form thrombin (human, bovine, or recombinant) a serine protease which in turn converts fibrinogen into fibrin. (flow chart 2)



Fibrin Glue is available in both commercial (with homologous and xenogenic components) and autologous (from patient's venous blood samples) forms. Being autologous the risk of contamination and other immunological responses are minimized. The only disadvantage of this preparation is low reproducibility as it varies from person to person. These are used for various purposes including as a sealant, a hemostat, or adhesive, thus adhering to the surrounding tissues.[38] Numerous works from various authors have used these as tissue adhesives for surgical procedures where it is seen being used as adhesive agents for bone regeneration, to attach a periosteal graft to an osteochondral defect, as an adjunct in cartilage and bone repair. Important properties like tissue adhesiveness, tensile strength, and elastic properties cause it to be an important additive in various microsurgical procedures.[39,40] The adhesive property of this relates to the polymerization process of thrombin and fibrinogen mixtures and depends much on the activity of thrombin and the concentration of fibrinogen. Various research works have shown that the adhesive strength of these adhesive sealants (commercial fibrin sealant) when tested with human tissue to be 811.1 mN/cm2 and 531.2 mN/cm2 in autologous cases.[41,42]

Blood processing for obtaining fibrin glue is performed with a standard centrifuge which is equipped for extracting autologous blood derivatives (flow chart 1)

Fibrin has multiple advantages over other biomaterials, due to which it can be used as an ideal material for various tissue engineering procedures. Following tissue injury, it forms a scaffold to initiate hemostasis and forms a temporary structure that paves the path for cellular activities and deposition of extracellular matrices.[43,44]

Bone graft

Bone has a peculiar regenerative capacity if not under any structural or functional impairment. However, if the osseous defect is more than the regenerative capacity of the osseous tissues it will not regenerate spontaneously.[45] Bone grafts have been in use since the time of Hegedus (1923) for the treatment of intrabony defects.[46] From then the use and application of these have been under constant turnover for the better. Each bone graft has its advantages and disadvantages. The various bone grafts used are Autogenous bone, Allograft, Xenograft, Non-bone graft materials and alloplastic (Carranza's (1999) classification of bone graft materials). Bone grafts act like a scaffold upon which the body generates its own, new *bone*.

Sticky bone (Autologous Fibrin Glue and Bone Graft)

Autogenous or autologous materials have always won the race in being the gold standard in the regenerative race.[47,48] Autologous fibrin glue similarly has also proven to be better when compared to commercial ones.[41,49] This fibrin glue, when combined with bone graft, completes the story of sticky bone. Autologous bone is the most supreme of all the bone grafts to date which possess osteogenic, osteoconductive and osteoinductive properties.[50,51] However, a second surgical site has a lot of disadvantages which include a limited amount of graft available, displacement of graft particles when being placed,[52]deformity and morbidity of the donor site,[53,54] increased risk of infection, time and cost of the treatment.[55,56] Additionally, there could be deficient vascularization leading to poor viability.[57]

Bone tissue engineering without the use of autologous grafts has emerged recently.[58,59] Here three-dimensional scaffolds are combined with the cells to enable a tissue-like form that can replace the parts of organs and tissues which are lost.[60] The scaffold selected should allow appropriate cell adhesion reactions, and should be biodegradable and biocompatible.[61,62] These scaffolds should also increase ingrowth of bone, should be flexible, should not cause any adverse reactions on the surrounding tissues, must be adaptable to the defect sites and convenient to use.[63] Many synthetic materials like polylactic acid, polylactic-co- glycolic acid polyglycolic acids are being used commonly. But these materials lead to inflammatory responses due to acid products being released.[64] Thus Fibrin has emerged as an excellent natural scaffold because of its biodegradable and biocompatible properties and the initial stability it provides to the graft materials.[61,65] It yields cell migration into the site of repair and releases growth factors for a long period, thus acts as a scaffold for bone and cartilage tissue.[66,67,68]

A notion for the creation of bone graft enriched with growth factors using autologous fibrin glue has been revealed since 2010. This being termed as Sticky bone. [3,12] The properties of sticky bone broadly begin with stabilizing the bone graft in the defect present, hence quickening tissue healing thus minimizing bone loss during the healing phase.

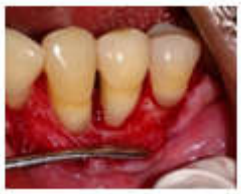


Figure 2 Reflection of full thickness flap showing vertical defect in 33 regions

Figure 2 Autologous Fibrin Glue

Figure 3 Sticky Bone (Autologous fibrin glue + Bone Graft)

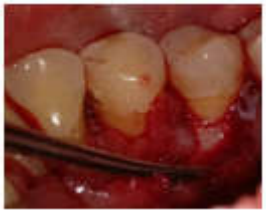


Figure 4 Sticky Bone placed in the intra bony defect

Figure 5 Centrifuge used for preparation of PRF and Fibrin Glue

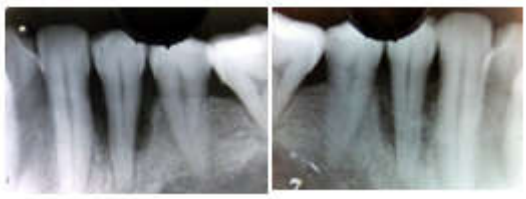


Figure 6 Figure 7 Pre-op and Post-op IOPA showing the defect

Implications of sticky bone with various growth factors

PRP along with PRGF are first-generation platelet concentrates. PRF and CRG belong to the second generation. These are autogenous sources of clotting factors and platelets, hence it contains tissue modulation and growth factors. Bovine thrombin and Calcium chloride added to PRP initiate the clotting process and the activation of the alpha granules. The growth factors hence released, bind to selective cells in the site of interest. Osteoblasts and osteoblast precursors, fibroblasts, progenitor marrow cells, and endothelial cells are the target cells in bone grafts.PRF contains a matrix of autologous fibrin.[69,70] Concentrated growth factors and PRF which are second-generation growth factors use the patient's blood solely for platelet activation and fibrin cross-linking.[71] In surgical sites, PRF serves different purposes depending on the type of placement. The main requirement for these is chemical additives like thrombin and anticoagulants for fibrin cross-linking before they can be added to any surgical site. In surgical sites it can be used as a resorbable GBR membrane, thus promoting the mineralization of the underlying clot. PRF membrane protects the surgical site, promotes repair of the soft tissues and helps in wound healing when mixed with bone graft. It acts as a biological connector, thus attracts stem cells and paves the way for the osteoprogenitor cells to migrate to the center of the graft. Thus, making provision for neo-angiogenesis.[70] PRF also makes its role of prime importance by its action as a biologic adhesive to hold the bone particles together thus enabling the manipulation of bone grafts.

CONCLUSION

This concept of making bone graft enriched with growth factors using autologous fibrin glue, first introduced by Sohn has been in existence since 2010. This provides stabilization of bone graft, acceleration of tissue healing and minimizing bone loss during the healing phase. The combination of sticky bone along with various growth factors hasten the healing process and is very efficacious in the regeneration of the lost tissues. This including intrabony defects, ridge augmentation, edentulous alveolar ridge defects. Sticky bone not only enhances the rate of new bone formation but also increases the quality (density) of the newly-formed bone.[37] Very limited studies have been done regarding this newly evolving concept to date and the studies did are only in cases where the placement of implant was of primary importance.[37] Hence further studies and a lot of researchhave to be done to elevate and establish its effectiveness as a regenerative material.

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