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GTR membranes : The barriers for periodontal regeneration

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Abstract

The concept of GTR and incorporation of GTR membranes in clinical practice has changed significantly the outlook for periodontal regeneration. Different types of membranes to cover periodontal defects are used for regeneration. A membrane should be biocompatible, enable cell exclusion, maintain space, ensure tissue integration and ease to use with biological activity for future generation membrane. Membrane**s** can be non-absorbable and absorbable. Non-absorbable membranes require another surgery for their removal hence today, they are used less frequently. Non- absorbable membranes are made from polytetrafluoroethylene, composite, rubber dam and resin/glass – ionomer. Absorbable membranes do not require their removal which reduce patient discomfort and eliminate surgery related complications. Absorbable membranes can be made from natural materials as collagen, pericardium, dura mater, laminar bone, connective tissue or periosteum, and from synthetic materials as polyglycolic acid, polylactic acid, polyglactin 910, polyester, polyurethane or polydioxanon. They are mostly used today. The future of GTR promises to be exciting, as new materials or modified ones, especially in combination with biological activity will become available.

Key words - Regeneration; membrane; barrier ; absorbable; non-absorbable.

Introduction

The term “Guided Tissue Regeneration (GTR)” was given by Gottlow in 1986. The 1996 World Workshop in Periodontics defined GTR as “procedures attempting to regenerate lost periodontal structures through differential tissue responses. Barriers are employed in the hope of excluding epithelium and gingival corium from the root surface in the belief that they interfere with regeneration”. The rationale behind using GTR membranes is to exclude epithelium and gingival connective tissue, maintain space

between the defect and tooth, and stabilize the clot. According to Melcher hypothesis [1] certain cell populations residing in the periodontium have the potential to create new cementum, alveolar bone and periodontal ligament, when they have provided the opportunity to populate the periodontal wound. Melcher hypothesis was experimentally established and histologically verified by Karring et al. [2]. They have shown that such conditions arise when gingival epithelial cells or fibroblasts are excluded from the wound space and periodontal ligament cells are allowed to migrate and populate the wound space. The necessity for exclusion of epithelium and connective tissue cells of the gingiva from wound led to development of periodontal devices know as barriers or membranes for guided tissue regeneration. The first GTR membrane used in the periodontal surgery was cellulose acetate laboratory filter paper by Nyman et al. [3] in 1982. This barrier lacked several characteristics necessary for guided tissue regeneration.

Characteristics of GTR membranes

Characteristics or design criteria for GTR membranes have been proposed by Scantlebury [4] in 1993 are biocompatibility, cell exclusion, space maintenance, tissue integration and ease of use. An additional characteristic, biological activity should be considered for future regeneration devices. Black [5] defined biomaterial as a nonviable material used in medical device, intended to interact with biological systems. Any device introduce***d*** into the body to address a particular need has to fulfill two major requirements, safety and efficacy. Safety is addressed through a wide selection of in vitro and in vivo assays, designed to address specific aspects of biocompatibility. Biocompatibility is defined by Williams [6] as the ability of a material to perform with an appropriate host response in a specific situation, which means that neither the material adversely and significantly affects the body nor the physiological tissue environment adversely and significantly affects the material. Ten assays used to evaluate biocompatibility are cell culture cytotoxicity, skin irritation***,*** subcutaneous implantation, blood compatibility, hemolysis, carcinogenesis, mutagenicity, pyrogenicity, sensitization, and short-and long – term histological tissue reaction. Cell exclusion requires the membrane to separate gingival flap from the maturing fibrin clot in the wound space. No experiments specifically addressing this aspect of GTR membrane. Space maintenance for regeneration requires mechanical properties and/or structural features allow membrane to withstand the force of flap (tissue tension) or occlusion and prevent collapse of soft tissue and elimination or reduction of wound space. Tissue integration dictates the incorporation of structural elements in the membrane to promote tissue ingrowth which concurrently

achieve cell exclusion. Easy to use means membrane should be clinically manageable i.e. competent clinician can use membrane without undue difficulty.

Membrane can be non-absorbable or absorbable:

Non absorbable barriers:

Non-absorbable membranes maintain their structural integrity for as long as they are left in the tissues. The function of membrane is temporary and once function is completed, there is no longer any need for it to remain in place. Although tissue integrity of membrane can be achieved, membrane is susceptible to risk of latent or post-surgery bacterial contamination which indicates removal of membrane to be in the best interest of the patient. POLYTETRAFLUOROETHYLENE (PTFE) is a non-absorbable membrane having formula ($-CF_2-CF_2-$)n hence, it is a fluorocarbon polymer. Solid/dense PTFE (dPTFE : TefGen-FD) [7] is non-porous, does not allow tissue ingrowth and does not elicit foreign –body reaction. Expanded PTFE (ePTFE : Gore-Tex) is porous microstructure of solid nodes and fibrils, allows tissue ingrowth, exhibits minimal inflammatory tissue reaction, formed when dPTFE subjected a tensile stress and used as a vascular graft material. ePTFE membrane has been modified by incorporation of titanium reinforcements, set between two layers of ePTFE, resulting in identical surface properties and better mechanical strength. Gore-Tex periodontal membrane has two structural designs, a coronal open microstructure collar, and a cell- occlusive apical portion. Collar promotes tissue ingrowth, support wound stability and inhibit epithelial migration is 1 mm thick, low density (0.2 g/ml) and 90 % porous (100-300 µm between nodes). Apical portion, serving as a space provider for regeneration as well as a barrier towards the gingival flap is 0.15 mm thick, higher density (1.5 g/ml) and 30 % porous (<8 µm between nodes). Gottlow et al. [9] in 1986 showed new attachment formation in human periodontium by ePTFE membrane in 3 months. Cortellini et al. [10] in 1993 showed periodontal regeneration of human intrabony defects by ePTFE membrane in 6 months. Murphy [11] in 1995 showed minor post-operative healing complications of ePTFE membrane as pain, purulence, swelling and tissue sloughing with an incidence slightly higher than conventional periodontal surgery. Other non-absorbable membranes are RUBBER DAM, RESIN/GLASS-ionomer barrier and COMPOSITE barrier. Rubber dam and resin/glass-ionomer barriers do not fulfill design criteria for GTR membrane. A composite membrane (BioBrane) [12] is made from knitted nylon fabric mechanically bonded onto a semipermeable silicone membrane and coated with collagen peptides have been evaluated in animals but gives mixed results in terms of regenerative potential.

Absorbable barriers:

Absorbable barriers are biodegradable, hence do not require their removal which reduce patient discomfort and eliminate surgery related complications. Absorbable membrane's disintegration process starts immediately after placement in the surgical site and their rate of disintegration vary from individual to individual, hence there is no control over length of application. Minabe [13] in 1991 reported that absorbable barriers should maintain their in vivo structure at least 4 weeks for biological rationale of GTR. Due to their biodegradable nature absorbable barriers elicit tissue reactions which influence wound healing and regeneration. Absorbable barriers can be natural or synthetic:

Natural absorbable barriers:

COLLAGEN shows hemostatic activity, attracts and activates neutrophils, fibroblasts, interacts with various cells during tissue remodelling and wound healing, and low immunogenicity which make collagen an attractive biomaterials. Collagen is obtained from animal sources as bovine skin, tendon, intestine, ox cecum or rat tail. Isolation and purification are done by two ways, either enzymatic preparation of soluble collagen or chemical extraction of fibrillar collagen. After isolation and purification, collagen is processed by several means to make gels, sponges, filaments, membranes etc. for specific uses [14]. The most common processing is cross-linking by aldehyde treatment and other procedures which results into reduced toxicity, immunogenicity, water absorption, solubility, susceptibility to enzymatic degradation, and increased tensile strength and biodegradation time.

Implanted collagen is enzymatically degraded by macrophages and PMNs, their resorption rate vary depending on sources and modifications of collagen. Collagenase enzyme initiates resorption of membrane at specific site into fragments which denaturate and become gelatines. Gelatine is degraded by gelatinase and other enzymes into amino-acids. Porphyromonas gingivalis produces collagenase, if membrane exposed during healing, uncontrolled degradation take place, resulting in unfavourable outcome. Although, injectable collagens induce anticollagen antibodies and possible transmission of bovine spongiform encephalopathy from infected bovine products, US FDA determines that collagen devices are safe. Avitene is a microfibrillar collagen hemostatic barrier derived from bovine corium, has been evaluated histologically in humans which showed no more effective than control group. Avitene was difficult to use before and after wetting with saliva or blood. Collistat is another collagen hemostatic

barrier also resulted in regeneration similar to control group. These two materials were mostly resorbed in 3 days, and completely resorbed in 7 days after implantation [15]. Bio- Guide is bilayer porcine collagen membrane. Biomend is a bovine Achilles tendon, semi- occlusive (pore size 0.004 µm) membrane, resorbed in 4-8 weeks. Rat- tail collagen membrane resorbed in 4 weeks, and when exposed resorbed in 5 days. A chronic inflammatory infiltrate was present around the membrane but completely disappeared after resorption. Cargile membrane is procured from bovine intestine (ox cecum) in a manner similar to chromic gut suture. A canine model histological study revealed that it provides limited inhibition of apical migration of epithelium, and resorbed in 4 weeks post-surgery. Oxycel is a oxidised cellulose mesh hemostatic dressing material has been used as a GTR membrane which resorbed in 4 weeks of implantation. Histological study showed that it is well tolerated in soft tissue but delayed healing in bone tissue due to acidic natur[16]. Paroguide is a collagen membrane enriched with chondroitin sulfate, showed no signs of inflammation and regeneration of PDL, cementum and alveolar bone, verified by histologically. LAMINAR BONE, a 300-500 µm thick strip of cortical bone, processed in a manner similar to DFDBA has also been used as a GTR membrane with particulate DFDBA, but limited information is available as resorption time [17]. DURA MATER, consists of irregular network of collagen fibers, obtained from cadavers can be used as GTR membrane. It was resorbed in 6 weeks, bone formation observed along material but risk to acquire Creutz-feldt-Jakob disease not only for recipient but also for operator may present [18]. CONNECTIVE TISSUE GRAFT may consider as collagen based barrier has been used as natural barrier for GTR in mandibular class II furcation [19]. AUTOGENOUS PERIOSTEUM can be used as a periosteal graft barrier for treatment of class II furcation involvements in lower molars [20]. Type I collagen membrane derived from calf PERICARDIUM and cross-linked by diphenylphosphorylazide has been evaluated for GTR which showed significant inflammatory reaction, resorbed in 2 weeks and has week regenerative potential [21].

Synthetic absorbable barriers:

Synthetic absorbable barriers are manufactured from organic aliphatic thermoplastic polymers, most commonly used material are poly α-hydroxy acids which include POLYGLYCOLIC ACID (-O- CH_2-***(O)***C-)n and POLYLACTIC ACID (-O-CH(CH_3)-(O)C-)n and their copolymer, POLY GLYCOLIDE-LACTIDE. Poly α-hydroxy acid is degraded by hydrolysis into products that are metabolized to CO_2 & H_2O through citric/Kreb's cycle. The degradation rate depends on pH, mechanical strain, enzymes, bacteria, cross-linking, composition and addition of glycolide or lactide. Poly glycolic acid degrades fastest and poly lactide is most stable. Half-life of 100 % poly lactide is decreased from more than 6 months to 2 weeks

for the 25:75 poly glycolic acid: polylactide copolymer, and to 1 week for 50:50 poly glycolic acid: poly lactide copolymer. When these polymers persist for long periods (4-6 years) can elicit late localized foreign-body type reaction, histologically characterized by presence of cells, mostly foamy macrophages with intracellular fragments of poly lactide. Hydrolysis results into release of monomers (lactic & glycolic acid), dimers and oligomers. Although high concentration of degradation products may be toxic, sufficient biocompatibility was reported in vitro. The toxicity of acidic hydrolytic by-products may be due to localized pH decrease and themselves due to pH-independent toxic effects, as osteolytic effects & inhibitory effects on osteogenesis, when these polymers degrade rapidly. Guidor matrix barrier is double layered, made of poly lactic acid containing both L-&D-lactic acid enantiomers and a citric acid ester (acetyl-tributyl citrate). External layer has large rectangular perforations, 400-500 /cm^2 which allow integration of overlying gingival flap, results into limited gingival recession. Internal layer has small circular perforations, 4000-5000 /cm^2 and outer spacers to ensure a space between barrier and root surface. The coronal portion of internal layer contains a coronal bar to provide a seal between barrier and tooth. Between outer and internal layers, there are internal spacers to create a space into which tissue can grow. Coronal portion of interspace contains a biodegradable suture to fasten the barrier to tooth. Animal studies showed complete resorption in 6-12 months and maintain its barrier function for at least 6 weeks. The degradation process involves foreign-body reaction characterized by macrophages and multinucleated giant cells, observed after 3 months post- surgery [22]. Resolut regenerative material is a composite contains an occlusive membrane of glycolide and lactide copolymer and a porous web structure of bonded glycolide fiber. Occlusive part serves cell exclusion, porous part serves tissue integration while stiffness of membrane serves space maintenance function. To secure barrier to tooth, it is supplied with a poly caprolate coated poly glycolic acid suture. It is as effective as non-absorbable membrane and absorb in 5-6 months. Vicryl periodontal mesh is a tightly woven mesh of poly glactin 910, a copolymer of glycolide and L-lactide (90/10 molar ratio). Coronal margin contains a suture made from poly glactin 910 to anchor barrier to tooth. It can lose integrity in 2 weeks and resorb in 4 or more weeks. A modified poly glactin 910 membrane, coated with bovine type I & III collagen, resorb in 1-3 months has been evaluated in recession treatment [23]. Atrisorb barrier is prepared chair side contains 37 % flowable poly lactide polymer dissolved in 63 % N-methyl-2-pyrrolidone, by weight. When polymer is exposed to 0.9 % saline solution in cassette, an irregular shape barrier is formed which cut and trimmed into desired shape & size with 600-750 µm thick. It has modest adhesion property, place into defect by gentle pressure without suturing. It is completely absorbed in 6-12 months. POLYESTER is a 300 µm thick sheet of 50: 50 poly glycolide: poly lactide copolymer,

histologically evaluated after 3 months surgery in humans failed to prevent apical migration of epithelium or any regenerative effect [24]. POLYURETHANES are organic polymers contain urethane group (-NH-CO-O-)n, resist degradation for at least 8 weeks even in presence of infection and inflammatory reaction [25]. Epi-Guide is made from poly lactic acid, has 3 layers designed to prevent migration of epithelium and fibroblasts. It resists degradation for 20 weeks and fully resorbed in 6-12 months. Mempol is made from POLY DIOXANON (PDS) is bilayer, first layer is unpermeable, covered with PDS loops 200 µm long on gingival side to integrate with connective tissue. Efficacy is similar to Guidor.

GTR membrane in future:

The future will see membranes that maintain safety (biocompatibility) with improved efficacy (performance) which will be possible through several modifications as alteration of surface properties, incorporation of adhesion molecules, proteins, peptides, antimicrobial agents, basic salts for low pH associated polymeric membranes, growth factors and differentiation factors to ensure predictable regenerative outcome in defects and clinical situations that remain a challenge today.

Conclusion:

The use of GTR membranes can lead to significant periodontal regeneration with formation of alveolar bone, cementum and inserting periodontal ligament fibers, although complete regeneration has never been reported.

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