

CURRENT KNOWLEDGE AND FUTURE PERSPECTIVES OF BARRIER MEMBRANES: A BIOMATERIALS PERSPECTIVE

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Abstract:

Periodontal regenerations and bone augmentations are common procedures practiced on a daily basis worldwide. This had led to the introduction of a wide number of barrier membranes, all aiming at regenerating a sufficient amount of bone while being safe, cost effective and easy to handle. Membranes have different characteristics that may influence their clinical properties and the result obtained. The article aims at presenting an overview of the different barrier membranes commonly used in the oral surgery field, while shedding light on the new advances in the third generation membranes.

Keywords: Barrier membrane – periodontal regeneration – bone augmentation.

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CONNAISSANCES ACTUELLES ET PERSPECTIVES D'AVENIR DES MEMBRANES BARRIÈRES

Résumé

La régénération parodontale et les chirurgies d'augmentation osseuse sont des procédures courantes pratiquées quotidiennement dans le monde entier. Cela a conduit à l'introduction d'un grand nombre de membranes barrières, toutes visant à régénérer une quantité suffisante d'os tout en étant sûres, rentables et faciles à manipuler. Les membranes ont des caractéristiques différentes qui peuvent influencer leurs propriétés cliniques et le résultat obtenu. L'article vise à présenter un aperçu des différentes membranes barrières couramment utilisées dans le domaine de la chirurgie buccale, tout en mettant en lumière les nouvelles avancées des membranes de troisième génération.

Mots-clés: membrane - régénération parodontale - augmentation osseuse.

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Introduction

Periodontal regeneration requires the coordinated formation of new alveolar bone, dental cementum, and functionally oriented periodontal ligament interposed between these two tissues. These requirements pose particular issues that are unique to the periodontal tissues. These include: (a) the requirement for the coordinated formation of the three tissues of the periodontal ligament; (b) the potential role of bacterial contamination during healing; (c) the specific requirement for dental cementum formation, a tissue that is not seen in other parts of the body; (d) the requirement for coronal regeneration of tissues towards the overlying superficial tissues. [1].

It is believed that the placement of a subgingival barrier achieves the following:

- Epithelial cells are impeded from apically migrating and interfering with connective tissue-root surface interactions.

- The gingival connective tissue from the flap is excluded from healing sites.

- Progenitor cells from the periodontal ligament are favored to repopulate the coronal root surface facilitating formation of a new periodontium [2].

- The membrane creates a protected space for the organizing blood clot and prevents its collapse by the pressure from the tissue flap [3].

- Particulate grafts are separated from the surrounding tissues allowing for bone regeneration [4].

This phenomenon has been recognized as “compartmentalized healing” which permits exclusion of undesirable cell populations and accommodates the mitosis and chemotaxis of osteoprogenitor cells [3]. In order to achieve the abovementioned functions, many authors [5-7] described five main criteria a barrier membrane needs to fulfill : biocompatibility, cell exclusion, space maintenance, tissue integration and ease of use/ clinical manageability.

Faced with different membranes and bone replacement grafts, the clinician has a considerable number of combinations of biomaterials that can be used depending on the clinical situation and his personal experience.

The aim of this article is to present an overview of the most commonly used barrier membranes in the oral surgery field, helping the clinician make a better selection and shedding light on the new advances in the third generation membranes.

1. Non-resorbable membranes

Non-absorbable barriers were the first generation of barrier membranes developed and approved for clinical use. They maintain their structural integrity, and the essential features they possess for as long as they are left in the tissues. However, they require a second surgical procedure for their removal. This is accompanied by concerns over patient acceptance, time, cost, and possible morbidity associated with any surgical procedure [8]. Moreover, membrane exposure caused by variable amounts of flap sloughing during healing has been a frequent post-surgical complication associated with non-absorbable membranes.

1.1. Cellulose filters

In the first guided tissue regeneration attempts, Nyman et al. [9] used a bacterial filter produced from cellulose acetate as an occlusive membrane in 1982. Histologic examination showed regeneration of the alveolar bone and new attachment of new cementum with inserting periodontal ligament fibers. Although this type of membrane served its purpose, it was not ideal for clinical application due to reported exfoliation and premature removal.

1.2. e-PTFE

Polytetrafluoroethylene is a fluorocarbon polymer with exceptional inertness and biocompatibility. It is non-porous, does not allow tissue ingrowth and does not elicit a foreign-

body reaction in tissue. Expanded polytetrafluoroethylene is a polytetrafluoroethylene subjected to tensile stress during manufacturing, resulting in differences in physical structure. It exhibits minimal inflammatory tissue reactions and has been used as vascular graft material for over 20 years [10, 11]. There are two configurations of e-PTFE membranes; trans-gingival and submerged [9].

The potential of these expanded polytetrafluoroethylene devices to support periodontal regeneration has been demonstrated in canine, non-human primate studies [5, 12, 13] and in different clinical settings [14-16]. In fact, treatment of intra-bony lesions with e-PTFE membranes demonstrated positive outcomes regarding clinical attachment level (CAL) gain and residual probing depth [17].

1.3. d-PTFE

The high-density PTFE (d-PTFE) is made of pure medical-grade and inert PTFE, which is non-expanded and non-permeable. These membranes have a porosity of up to one hundred times lower (0.2 μm) and are thinner (0.2-0.3mm) than the e-PTFE (around 1mm) membranes [18].

These characteristics eliminate bacterial infiltration into the bone augmentation site, which protects the underlying graft material and/or implant. Furthermore, primary soft tissue closure is not mandatory [19]. In fact, previous authors have reported that it completely blocks the penetration of food and bacteria, and thus, even if it is exposed to the oral cavity, it still acts as an appropriate membrane barrier, and the risk of infection remains lower than e-PTFE [20, 21]. When no primary closure is realized the full width of keratinized mucosa is preserved [20] and they can be removed easily by pulling on the membrane without lifting the mucosal flap, thus, not requiring a second surgery [22]. It is considered today the “gold standard” of non-resorbable membranes [23].

1.4. Titanium mesh / Titanuim-reinforced e-PTFE membranes

Titanium reinforced barrier membranes provide advanced mechanical support (increased tent-like effect), which allows a larger space for bone and tissue regrowth. This is of special importance when the defect morphology does not create an adequate space recognized as important requirement for achieving regeneration. However, their main disadvantages remain the increased risk of exposure due to their stiffness and a more complex secondary surgery to remove them [9, 24].

These membranes consist of a double layer of e-PTFE with a titanium framework interposed [3, 25]. Recent research has demonstrated the successful use of these membranes in vertical ridge augmentations and in the treatment of large defects in the alveolar process [26]. Some other studies reveal superior regenerative capacity [3] and less persistent inflammation when compared to traditional PTFE membranes [27].

1.5. Other non-resorbable membranes

Case reports have documented the use of rubber dam [16]. However the latter offers little rigidity to assure space maintenance, can be tedious to manipulate, and exhibits no tissue integration [8].

The use of a resin-ionomer barrier has also been reported [28]. It could have excellent space-making properties; however, it is difficult to fabricate in situ, have the potential to elicit local inflammatory reactions and its tissue integration properties, if any, are unknown [29].

Cobalt–chromium based alloy has also been suggested for guided bone regeneration (GBR). Although this alloy is known to be less biocompatible than titanium and titanium alloy, it has superior mechanical properties (e.g. stiffness and toughness). The potential use of CoCr alloy for GBR has been evaluated in a recent animal study but it has not yet been documented in any clinical report [30].

It appears that neither of the abovementioned materials fulfills yet the design criteria for a guided tissue regeneration device [31].

Today, as evidence of the effectiveness of bioresorbable membranes increases, non-resorbable membranes are losing importance in clinical practice and their use is increasingly limited to specific indications. Since the use of e-PTFE membranes has been documented to result in successful GBR therapy, results obtained using new materials should always be compared with results of e-PTFE membranes [26].

2. Resorbable membranes

Absorbable barriers do not require additional surgery for removal, which reduces patient discomfort, chair-side time and related cost, while eliminating potential surgery-related morbidity. They also offer the advantages of having better cost-effectiveness while causing less complication; they are quickly resorbed in case of exposure, thus eliminating the open microstructures that are prone to increased bacterial contamination [26, 32].

However, resorbable membranes offer limited control over the length of application because the disintegration process starts upon placement in the tissues, and the ability of each individual patient to degrade a particular biomaterial may vary significantly, particularly for materials requiring enzymatic degradation [8].

Several studies have compared bioresorbable membranes to non-resorbable membranes made of e-PTFE. In situations where no membrane exposures were noted, the results regarding the relative amount of bone formation were usually more favorable using the e-PTFE membranes compared to the bioresorbable ones [33]. This is mainly due to the better space-making capacity of e-PTFE and the lack of a resorption process and thus the absence of the resorption products that negatively affect bone formation.

Absorbable materials used for guided tissue regeneration (GTR) or guided bone regeneration (GBR) devices fall into two broad categories: natural products and synthetic materials [8].

2.1. Natural products

Natural membranes are made of collagen or chitosan. Successful treatment following the use of such barrier materials have been demonstrated, but the results of studies vary [34].

2.1.1. Collagen barriers

Collagen constitutes almost one third of all protein in the body and is a major constituent of natural extracellular matrix. It is (a) physiologically metabolized, (b) chemotactic for fibroblasts and neutrophils, (c) hemostatic, (d) a weak immunogen and (e) a scaffold for migrating cells [8, 35].

There are two major types of collagen used in the manufacturing of membranes, type I and type III, usually derived from different bovine and porcine tissues (e.g. tendon, dermis, and small intestine). When exposed to the oral cavity, periodontal pathogens (*Porphyromonas gingivalis* and *Bacteroides melaninogenicus*) are capable of producing collagenase, an enzyme that can lead to premature membrane degradation. Collagen membranes are often used with bone grafting material or extra-stabilization with mini-screws and tacks to compensate for their lack of space-making ability [36].

2.1.1.1. Cross-linking of collagen barriers

Collagen membrane goes through the process of cross-linking, which involves the multiplication of natural occurring connections between the collagen molecules, in order to enhance its mechanical properties [37]. This process makes the membranes more rigid (increased tensile strength) and decelerates enzymatic degradation process [38]. Many authors suggested that the use of cross-linked collagen membranes brought many benefits to guided tissue regeneration (GBR) [36].

2.1.1.2. Membrane architecture and thickness

Membranes of greater thickness, arranged in several layers, show greater barrier ability and remain for longer time in tissue; they decompose slowly and can enable better bone defect ossification. The second layer achieves a reduction of micro movements and improves its stability. The vascularization of the double layer membrane was not impaired by its increased thickness since the transmembranous formation of blood vessels is essential for collagen resorption [31, 39].

2.1.2. Chitosan based barriers

Chitosan is natural polymer derived from partial de-acetylation of chitin. The latter material exists in crustacean shells (i.e. that of shrimp and crab) and has a role analogous to that of collagen in higher animals [40]. Chitosan possess important material properties, including biocompatibility, biodegradability, low immunogenicity, and a bacteriostatic effect. These characteristics make this material suitable to be used in guided tissue regeneration (GTR) techniques.

Although there is evidence indicating that chitosan-based membranes promote bone regeneration in experimental bone defects and are suitable materials for GBR, no significant papers describing the clinical results were found in the literature [41].

2.1.3. Cargile membrane

Cargile membrane is derived from bovine intestine and is processed and chromatized in a similar manner to gut suture material. It is reported to resorb in 30-60 days [2]. The literature contains a paucity of information assessing the efficacy of these membranes. Investigators reported limited results and difficult handling characteristics [42]. They concluded that cargile membranes did not appear to be the optimal biodegradable material for GTR [2].

2.1.4. Cortical lamina

The cortical lamina is a cortical bone matrix made of carbonated nanocrystal bone minerals and collagen of natural heterologous origins. It is described as osteoconductive, resorbable, biocompatible, hygroscopic and can function as a carrier for certain medication and drugs [43]. The fine model becomes flexible after hydration and can be shaped [44] and adapted to the defect morphology creating, once fixated with osteosynthesis screws, a semi-rigid covering to the underlying graft [45]. This property is particularly useful when it is necessary to obtain a space making effect in aesthetic areas [46].

The collagenated porcine barrier has been described to have a slow resorbability (approximately 5 to 6 months) [47], not requiring re-entry, maintaining the desired volume for bone formation due to its mechanical properties and plastic consistency thus facilitating the handling, and a second intention healing in case of exposure [48]. Thus, is particularly indicated in regenerations with risks of exposure because its consistency and plasticity allow a second intentions healing of the wound.

2.1.5. Oxidized cellulose

Oxidized cellulose mesh, a plant-based product, is a commercially available resorbable hemostatic dressing that converts to a gelatinous mass upon incorporating blood. It has been used as a guided tissue regeneration device [49]. In vivo and in vitro studies have demonstrated that the material resorbed without harmful effects and may possess antibacterial properties. It appears to offer limited, if any, space provision and/or maintenance, cell exclusion and has not been investigated histologically for regenerative outcome [8].

2.1.6. Alginate-based membranes

Alginate is a natural biocompatible polysaccharide that can be obtained from brown seaweed and achieves a similar structure to extracellular

matrices when crosslinked to hydrogels. It has a slow degradation rate and may last several months upon implantation [18].

Although there is evidence indicating that alginate-based membranes promote bone regeneration in experimental bone defects and are suitable materials for GBR, no significant papers describing the clinical results were found in the literature [41].

2.1.7. Human-derived membranes

2.1.7.1. Laminar bone

Laminar bone, a 300- to 500- μ m-thick strip of cortical bone (from calvarium region), processed in a manner similar to demineralized freeze-dried bone allografts (successive removal of lipoproteins), has also been used as guided tissue regeneration device, in conjunction with a particulate demineralized freeze-dried bone allograft. Limited information is available on other aspects (such as resorption time) of this material, although it has been reported that it might not be easy to use [50].

2.1.7.2. Acellular dermal allografts (ADM)

ADM is a bioresorbable grafting material from cadaver skin that has been obtained from tissue banks. The material (mainly of type-I collagen) has undergone a process of de-epithelialization and de-cellularization to eliminate the targets of rejection response, leaving an immunologically inert avascular connective tissue. They have been successfully used for the treatment of third degree burns and are currently used as a membrane barrier, for mucogingival defects, for formation of attached gingiva and as a biologic bandage after osseous resection [9].

2.1.7.3. Human pericardium, dura mater and amnion-based membranes

Lyophilized multilayered amniotic membrane preserves the structural and mechanical properties of the amnion ECM and has good flexibility in adjusting the thickness and mechanical properties. This particular membrane has been suggested to promote bone growth whilst limiting fibrous tissue invasion [31, 51].

Dura mater, consisting of an irregular network of collagen fibers, is obtained from cadavers. Clinical reports suggest that dura mater has limited potential to support periodontal regeneration. Moreover, use of cadaveric dura mater may represent a risk to acquire Creutzfeldt-Jakob disease not only for the recipient, but for the operator as well [8].

2.1.7.4. Platelet-concentrate membranes derivatives

Platelet-concentrate membranes are natural autologous membranes developed through venous blood collection and centrifugation protocol and/or freezing cycles. The biggest drawback of these membranes is the short resorption time (generally 10 days). Thus, it would be most useful when combined with other grafting materials to take advantage of its healing properties rather than serving as an inherent barrier membrane for GTR or GBR [52, 53].

2.2. Synthetic products

These synthetic resorbable membranes are based on different variants of polyesters (PGA poly-lactic acid, PLA poly-lactic acid, PCL poly-caprolactone) and their copolymers. These are natural metabolites of the body, which are eliminated through the Krebs cycle as carbon dioxide and water [54] (52). These materials are biocompatible, but by definition they are not inert since some tissue reactions and inflammatory response may be expected during degradation [55].

2.2.1. PGA and PLA membranes

PGA and PLA are manufactured by catalytic polymerization of the monomers and are widely used for sutures and drug controlled-release devices [2, 8].

The main advantages of these types of polymeric membranes are their manageability, processability, tuned biodegradation, and drug-encapsulating ability. However, their degradation might elicit a strong inflammatory response, leading to resorption of the regenerated bone [31]. In humans, biopsy specimens of PLA screws used

for bone fixation demonstrated that the material persists for approximately four to six years [56].

At present, there are limited and contradictory data regarding the efficacy of polylactic acid to facilitate regeneration. Additional research is needed to clarify the potential of this material [2].

2.2.2. PUR membranes

Polyurethanes are organic polymers containing the urethane group, encompassing a variety of materials with diverse properties [28]. These membranes did not result in significant regeneration compared with control and some clinical complications were described (probable exfoliation of the membranes during early healing) [8].

2.2.3. Calcium sulfate

These barriers are composed of medical-grade calcium sulfate and can be placed over the bone grafts for clot stabilization and to exclude undesirable tissue. They provide a source of calcium in the early mineralization process and aid particle retention. Calcium sulfate dissolves in approximately 30 days without an inflammatory reaction, and it does not attract bacteria or support infection [9].

3. An outlook into the future: the third generation membranes

As the concept of tissue engineering has developed, third-generation membranes have evolved, not only acting as barriers but also as delivery devices to release specific agents such as antibiotics, growth factors, adhesion factors, etc., at the wound. Briefly they may be considered into the following subdivisions [55].

3.1. Functionally graded and multilayered membranes

A novel functionally graded membrane (FGM) was designed and fabricated via multi-layering e-spinning [57]. The FGM consists of a core-layer (CL) and two functional surface-layers (SL) interfacing bone (nanohydroxyapatite, n-Hap) and epithelial (metronidazole, MET) tissues. The CL comprises a neat poly (D,L-lactide-co-

caprilactone)(PLCL) layer surrounded by two composite layers composed of a gelatin/polymer ternary blend (PLCL:PLA:GEL).

3.2. Antibacterial properties

Some antimicrobials, like tetracycline for example, which have anti-inflammatory, fibroblast stimulatory properties and collagenase-inhibiting properties, may improve the regenerative response because of these properties, even in the absence of a bacterial challenge. Thus integrating these antimicrobials into the membranes can prolong their degradation time [55].

The incorporation of metronidazole benzoate (MET) to the layer interfacing the epithelial tissue has been developed to reduce the amount of anaerobic Gram-negative bacteria such as *Porphyromonas gingivalis* and anaerobic spore-forming Gram-positive bacilli [53].

Other investigators have also focused on the successful incorporation of tetracycline hydrochloride and metronidazole benzoate (MET) into various membranes [58].

Incorporation of 25% doxycycline into a GTR membrane, which was composed of polyglycolic acid and polylactic acid, would seem to have a beneficial effect on periodontal bone regeneration in dogs [55].

3.3. The incorporation of nanotechnology in GTR

The coating or incorporation of nano-particles has been shown to improve other functional characteristics of the membranes such as stiffness, bioactivity, drug and antimicrobial delivery and protein or molecules carriers [36]. (34)

Studies have demonstrated that the addition of nano-carbonated hydroxyapatite (nCHAC) improved both the biocompatibility and the osteoconductivity of the membrane. The authors demonstrated that calcium phosphate nanoparticles played a significant role in terms of improving membrane bioactivity and facilitating early cell differentiation [55].

3.4. Barrier membranes with Growth Factors release

Growth and differentiation factors modulate the cellular activity and provide stimuli to cells to differentiate and produce matrix toward the developing tissue. They influence tissue repair and disease, including angiogenesis, chemotaxis and cell proliferation; and control the synthesis and degradation of extracellular matrix proteins. The targeted delivery of these proteins is the focus of substantial research [8].

Growth and differentiation factors currently believed to contribute to periodontal and alveolar ridge augmentation include platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I and II), transforming growth factor beta (TGF- α and - β), fibroblast growth factor (α - and β -FGF), and bone morphogenetic proteins (BMPs 1-15). Recombinant human BMP-2 (rhBMP-2) has been found to exhibit very high osteogenic activity in experimental and clinical studies [26].

It was also found that PDGF-BB loaded PLLA membrane might potentially enhance guided tissue regenerative efficacy in rat calvarial defects. Despite a long history of preclinical evaluation with promising results, the routine use of growth factors as therapeutic agents for periodontal regeneration is not a reality yet [55].

3.5. Membranes as a stem cell therapy vehicle (Cell sheets)

The principle of stem cell therapy is the isolation of mesenchymal stem cells from bone marrow stroma or dental tissues, expansion of cell numbers *ex vivo*, and reimplantation of cells into the wound seeded into a suitable porous scaffold material or other matrix material, including collagen matrices, β -TCP, and combined β -TCP–extracellular matrix scaffolds [1]. Relying on stem cell therapy, either as cell sheets and/or using the GTR membranes as cell carriers may allow better outcomes and a more predictable regeneration of functional periodontium. However, utilizing stem

cells in combination with barrier membranes remains to be investigated further [1].

Conclusion

It is clear that the “ideal” membrane for use in periodontal regenerative therapy has yet to be developed. Based on a graded-biomaterials approach, it can be hypothesized that a biologically active, spatially designed and functionally graded nano-fibrous material that mimics closely the native extracellular matrix could succeed as the next generation of GTR/GBR membranes for periodontal tissue engineering [57].

Until then, since every membrane offers both advantages and disadvantages, a barrier should be selected based on a thorough understanding of the benefits and limitations inherent to the materials in relation to the functional requirements in the specific clinical application [32].

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