A Space-maintaining Resorbable Membrane for Guided Tissue Regeneration

a report by

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Introduction

The use of guided tissue regeneration techniques to treat periodontal defects is now commonplace. The protocol employs barrier membranes to regenerate periodontal ligament, cementum and bone by excluding the faster growing soft tissue cells from the defect space. Clinical studies have widely demonstrated superiority of this treatment modality over traditional open flap debridement techniques.1–2

A variety of membranes are available in the marketplace, starting from non-resorbable polytetrafluoroethylene (PTFE) membranes to resorbable collagen and polylactide (PLA) polyglycolic acid (PGA)-based membranes, all of which exhibit satisfactory clinical outcomes.3–5

Tatakis et al.6 have referred to a set of design requirements that need to be met for a periodontal membrane to be effective. In short, these are biocompatibility, cell exclusion, space maintenance, tissue integration, ease of use and biological activity. The failure of a device in one or more of these criteria may be the reason for unsatisfactory performance in the regeneration of periodontal defects. Most of the membranes currently available have incorporated these criteria into their design to varying degrees.

Nevertheless, none of the first-generation membranes exhibits a truly optimal design, satisfying all the criteria. Two of the design criteria mentioned have been particularly hard to meet so far. They are space maintenance and biological activity. A membrane that features optimal space maintenance has to be stiff, so that it will not collapse over the defect it spans. This is particularly true if no graft materials are used in the defect to support the membrane mechanically from underneath. If a membrane collapses into the defect space, the potentially regenerated volume is reduced and will not allow optimal clinical outcome. The membrane should be stiff enough to withstand the pressures exerted by the overlying flaps and to withstand external forces like mastication, until the blood clot building underneath the membrane has matured enough to support it.

This stiffness, on the other hand, would not allow good clinical manageability or ease of use, as a stiff membrane cannot be contoured easily to a three-dimensional-defect – it would have sharp corners that may perforate the gingival tissues and membrane immobilisation could be difficult due to its spring-back effect. Therefore, there has been a trade-off between these criteria to present date.

The second criteria that has not been satisfied by the membranes of the first generation is that of biological activity. Some pre-clinical research is underway in which membranes in combination with growth factors are evaluated,7–9 with encouraging results. The growth factors are added to accelerate the regeneration of periodontium and lead to faster healing. Undoubtedly, the future belongs to these devices. However, it is yet unclear whether such devices will become available to the end user in the near future, simply because of the high cost of growth factors and the fact that these

require a lengthy regulatory process before they can be marketed for a specific clinical application. This is the impetus for devices that exhibit biological activity without the use of growth factors.

Inion Inc., a medical device company specialising in the development and manufacture of resorbable implants, has concentrated its periodontal membrane development on closing these design gaps. In the following section, the new Inion GTR™ Biodegradable Membrane System and how it addresses all design aspects will be discussed.

**Space Maintenance and Ease of Use**

The idea was to conceptualise a membrane that is soft only as long as it needs to be soft, during the insertion phase. After insertion, when the membrane contacts saliva, the membrane turns stiff within minutes. This allows the surgeon to spare the use of a bone grafting material, provided the defect is not too large. There would only be a blood clot in the defect space and that is suggested to provide optimal regeneration conditions for periodontal ligament, cementum and bone.

This two-stage membrane characteristic is obtained by the use of a plasticising agent, which temporarily softens the membrane matrix and leaches out slowly after the membrane is placed, thus rendering the membrane material stiff again. During the insertion phase the material is soft and a little stretchy or rubbery, but not as weak as collagen materials. This facilitates the safe and precise trimming of the membrane, easy insertion and the formation of a good seal between the root of the affected tooth and the membrane, hindering the intrusion of soft tissue cells into the space. In the soft stage the membrane shows adequate contourability and the shape given is ‘conserved’ when the membrane stiffens up. The stiffening can be accelerated by flushing with sterile water, thus accelerating the release of the plasticiser. Moreover, the rubbery membrane material possesses enough tear strength to be immobilised with sutures. It is easy to form a seal between the root of the affected tooth and the membrane by using a suture sling around the tooth. The pliability of the material helps to strictly appose the membrane to the tooth when pulled tight with the suture. The elimination of a residual gap will help exclude soft tissue cells from the defect and therefore increase the success rate.

Another fast way to immobilise the membrane is to use the Inion GTR Biodegradable Tacks. These can be inserted without membrane dislocation immediately after pilot holes are drilled through the membrane into the bone. The tack kit is provided with six tacks, a sterile drill and a single-use tack applicator, eliminating any preparatory work for the physician.

In an *in vitro* test the membrane was exposed to a watery solution and its tensile strength behaviour was measured after different exposure times. After one minute of exposure in the solution, the membrane shows about double its initial strength, reaching its ultimate strength after approximately 30 minutes immersion in water.

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Tissue Integration and Cell Occlusivity

One of the prime requirements for guided tissue regeneration barriers is occlusivity. It means that the barrier membrane has to be impermeable for epithelial cells; otherwise, these faster growing cells would populate the wound space and inhibit the regeneration of periodontium. This inhibition of epithelial migration should be provided for the time span the periodontal defect needs to heal (at least). This timespan was researched to be at least four weeks, but as healing depends greatly on a variety of patient related factors, this duration can be significantly longer. The Inion GTR membrane provides a barrier function of at least eight to 12 weeks and thus allows sufficient time for regeneration while at the same time allowing re-entry of the site should this be necessary. After that time period, the membrane starts to disintegrate and resorb gradually.

Effective exclusion of epithelial cells will occur if a tight seal is formed between the membrane and bony borders of the defect or the tooth root. Otherwise, epithelial cells can migrate through the membrane–bone gap into the wound space and compromise the clinical result. In addition, the membrane outer surface must allow for soft tissue integration so that retraction of soft tissue over the membrane (membrane exposure) can be avoided. The ‘bioseal’ forming between the membrane and the full thickness soft tissue flap also reduces the chances of bacterial infection and wound failure. Equally important, the inside of the membrane must incorporate structural elements to allow the blood clot forming underneath the membrane to be stabilised. Only then can it mature uncompromised and develop into tissue regenerating the periodontium. The Inion GTR membrane exhibits a surface structure that allows epithelial cells as well as blood cells to adhere. Figure 2 shows an scanning electron microscope (SEM) photograph of the 3-D globular surface structure. It needs to be noted that the roughness is not through and through but extends only on the surface layer.

In vivo tests in a cranial rabbit model showed close incorporation of epithelial cells into the membrane surface after four weeks. The incorporation with no signs of exfoliation was determined by stained histological cross-sections (ref poster)

Biocompatibility

The Inion GTR membrane and tack materials were carefully selected to combine strength, toughness and degradation features. They are processed in such a way that none of the material characteristics are negatively influenced.

The proprietary compounds and resulting devices were independently tested according to internationally recognised standards and were found to possess excellent biocompatibility. Moreover, polymers made from identical building blocks were used safely already for decades in resorbable suture materials, sports medicine devices and craniofacial implants.

In an in vivo degradation study, membranes were implanted in the mandibles of sheep and histologically analysed after six and 12 months. After follow-up, the membranes were resorbed to a great degree and the surrounding tissues showed no signs of irritation or sterile abscesses.

After serving as a barrier for periodontal regeneration, the membrane gradually resorbs and is completely cleared from the body in one to two years. This eliminates the need for a removal surgery. Degradation takes place by hydrolysis and metabolisation in which the breakdown products are carbon dioxide and water.

One of the further advantages of this material is that it is fully synthetic and not of animal or human origin and therefore does not bear the risk of disease transmission.

Biological Activity

The plasticiser used to soften the membrane is a biocompatible substance called N-2-methyl-pyrrolidone (NMP). When the membrane is implanted, it leaches out of the membrane and dissipates into the surrounding tissues. Pre-clinical studies suggest that this substance, when used in small doses, stimulates bone growth.

The membrane was used to cover artificially created defects in the skulls of rabbits, compared with a competitive product and with empty control defects. After a four-week healing period, the defects covered with the Inion GTR membrane showed 79% defect fill versus 61% defect fill and 31% defect fill for the competitive membrane and the control, respectively. Results were verified by a cell line test with NMP present. This yielded a 2.5-fold increase in the ALP
activity of MC3T3-E1 cells (concentration-dependant). MC3T3-E1 cells resemble osteoblasts and therefore represent similar activity. Furthermore, the mineralisation of these cells was enhanced 1.5-fold over controls as determined by staining after four weeks of incubation.

This phenomenon can be explained by the hypothesis that the NMP activates autogenous bone morphogenic proteins (BMPs), which naturally occur in the wound space. As NMP is a hydrophilic solvent, the activation of it may be explained through solubilisation of normally hardly soluble BMPs. The NMP-activated proteins would then lead to a faster maturation of preosteoblasts into osteoblasts consequently accelerating bone and tissue formation.

These results were presented by Dr Franz Weber from the University of Zürich at the Annual Conference of the International Association of Dental Research in March 2004, Honolulu, USA. Further research on this topic is on-going.