



Membranes for the Guided Bone Regeneration

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Abstract

Many kinds of membrane have been used for the guided bone regeneration (GBR) technique. However, most membranes do not fulfill all requirements for the ideal membrane for the GBR technique. Among them, collagen membrane has been most widely used. However, its high price and weak tensile strength in wet condition are limitations for wide clinical application. Synthetic polymers have also been used for the GBR technique. Recently, silk based membrane has been considered as a membrane for the GBR technique. Despite many promising preclinical data for use of a silk membrane, clinical data regarding the silk membrane has been limited. However, silk based material has been used clinically as vessel-tie material and an electrospun silk membrane was applied successfully to patients. No adverse effect related to the silk suture has been reported. Considering that silk membrane can be provided to patients at a cheap price, its clinical application should be encouraged.

Key words: Membrane, Bone, Silk, Collagen, Polymer

Introduction

In recent decades, guided bone regeneration (GBR) procedures have been commonly performed to repair bone defect due to pathologic lesions or to augment alveolar bone for dental implant treatment[1]. In the GBR procedure, the role of barrier membrane is crucial for proper bone regeneration. It can prevent in-growth of soft tissue to the bone defect, and maintain the defect space during bone tissue regeneration. To achieve maximum bone regeneration, GBR membrane should have several characteristics, including (1) biocompatibility; (2) proper stiffness for space maintenance; (3) prevent epithelial cell migration; and (4) appropriate resorption time after proper bone re-

generation[2].

Many tissue engineering studies have been conducted for development of an ideal GBR membrane from various natural and synthetic sources. Clinically, collagen membrane and expanded polytetrafluoroethylene (ePTFE) membrane have been widely used for the GBR procedure. Numerous clinical studies with these membranes have demonstrated their clinical usefulness. However, these membranes still have limitations in terms of ideal characteristics of GBR membrane.

In the clinical aspect, the indications for GBR membrane have increased. GBR membrane has mainly been used for bone augmentation surgery[3]. Recently, GBR membrane has been used for mandibular third molar extraction[4] or

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periodontal flap surgery[5]. GBR membrane is also used for treatment of peri-implant bone loss[6]. Although the indications for GBR membrane have increased, its clinical application has not shown a rapid increase. The main obstacle for its wide clinical application may be its high price. In this article, commercially available GBR membranes are selectively reviewed. In addition, silk materials are reviewed as GBR membrane. The limitations of each material and the future perspective are also discussed.

Collagen

Collagen membrane is a representative absorbable GBR membrane. Commercially available membranes are shown in Table 1. Collagen, the major constituent of connective tissue, is a structural component. It showed excellent biocompatibility when applied in tissue engineering[7]. Type I and III collagens derived from porcine, bovine, and human were mainly used in production of GBR membrane[8]. Thus, its antigenicity should be eliminated through specific chemical processes.

Rapid degradation is another disadvantage of collagen materials. To overcome rapid degradation, cross-linking treatments using glutaraldehyde, formaldehyde, or enzyme were performed depending on commercial products[9,10], which can control the absorption times of the collagen membrane during the bone regeneration period. However,

some fixatives, such as glutaraldehyde, can be cytotoxic[11]. In general, the surface of collagen membrane is modified for acceleration of tissue integration (Fig. 1).

In clinical use, collagen membrane generally has less stiffness compared with non-absorbable membrane such as ePTFE or titanium mesh[12]. Thus, the space maintaining ability was lower than that of ePTFE or titanium mesh. The collagen membrane can be used for labial or buccal bone augmentation procedure combined with autogenous block bone graft[13]. Therefore, the bone graft has frequently accompanied the collagen membrane application during the GBR procedure[14]. The complication ratio of

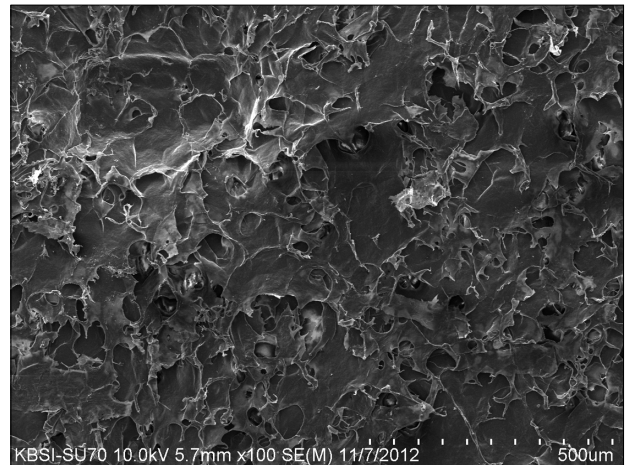


Fig. 1. Scanning electron microscopic view of collagen membrane.

Table 1. Summary of commercially available membrane for guided bone regeneration

Product	Manufacturer	Biodegradation	Crosslinking	Raw materials
AlloDerm	BioHorizons	Yes	Not presented	Acellular dermal matrix human skin
Bio-Arm	ACE Surgical Supply Company	Yes	Yes (formaldehyde crosslinking)	Porcine type I collagen
Bio-Gide	Geistlich	Yes	No	Porcine type I, III collagen
Biomend	Zimmer Dental	Yes	Yes (glutaraldehyde crosslinking)	Bovine type I collagen
Cytoblast RTM collagen	Osteogenics Biomedical	Yes	Not presented	Bovine type I collagen
Guidoss	Nibec	Yes	Yes	Porcine type I collagen
OSSiX plus	OraPharma	Yes	Yes (sugar based crosslinking)	Porcine-based collagen
OsseoGuard Flex	BIOMET 3i	Yes	Yes	Bovine type I, III collagen
EZCure	Biomatlante	No	Yes	Porcine-based collagen
Lyoplant	B. Braun Melsungen AG	Yes	No	Bovine collagen
Rapiderm	Dalim medical	Yes	Not presented	Porcine type I collagen
Rapigide	Dalim medical	Yes	Not presented	Porcine type I collagen
Surederm	Hans GBR	Yes	Not presented	Human skin tissue
Cytoflex (open membrane TEF guard)	Unicare biomedical	No	No	Micro-porous, PTFE membrane
Cytoplast (Ti-250 or Ti-150 Titanium-Reinforced)	Osteogenics biomedical	No	No	High-density PTFE membrane
Cytoplast TXT200	Osteogenics biomedical	No	No	High-density PTFE membrane
Gore-TEX	W. L. Gore and Associates	No	No	ePTFE membrane
Open-tex	Purgo	No	No	High-density PTFE (100%) membrane

PTFE, polytetrafluoroethylene; ePTFE, expanded polytetrafluoroethylene.

the collagen membrane has been lower in the GBR procedure. Premature exposure of the collagen membrane shows severely compromised amounts of bone regeneration[15].

Synthetic Polymers

Aliphatic polyesters such as polylactic acid (PLA), polyglycolic acid (PGA), poly(ϵ -caprolactone), and polydioxanone have been used for production of synthetic polymers[16]. Synthetic polymers have traditionally been used for the plate and screw systems in orthopedic surgery[17]. In dentistry, the PLA membrane was first used for periodontal tissue regeneration[18]. After that, various GBR membranes, for example, Guidor (Sunstar Americas Inc, Chicago, IL, USA), Resolut (W.L. Gore & Associates Inc., Newark, NJ, USA), Atrisorb (Atrix Laboratories Inc., Fort Collins, CO, USA), Epi-Guide (Kensey Nash Corp., Research Triangle Park, NC, USA), and Biomesch (Samyang Corp., Seoul, Korea) have been commercially available.

The PLA polymer showed a slower hydrolysis rate compared with the PGA polymer in the human body[19]. For proper degradation of polymer, PLA polymer has mainly been combined with the PGA polymer as a copolymer; these polymers degrade by enzymatic hydrolysis[20]. Thus, Poly(lactic-co-glycolic) acid (PLGA) has mainly been used in dentistry for synthesis of GBR membrane[21]. The compositional change of PLGA affects the hydrolysis rate and mechanical strength of the GBR membrane[22]. Synthetic

polymer membranes showed less inflammation when applied in the GBR procedures[23]. In addition, it can also be used as a carrier for drug delivery[24]. Compared to collagen membrane, when using the synthetic polymer membrane, there is no possibility of cross infection and less limitation of its production. As most synthetic polymer is poorly bio-degradable, it should be removed after bone regeneration. Synthetic polymer is usually encapsulated by the fibrotic capsule[25]. Without incorporating bio-active molecules, synthetic polymer membrane itself does not have osteoinduction ability[26]. Therefore, compared to collagen membrane, new bone formation in the bony defect was lower[12].

Among the synthetic polymers, ePTFE has been widely used as a GBR membrane (Fig. 2). The ePTFE membrane is used with autogenous bone grafting for GBR[27]. In cases of autogenous bone grafting, premature exposure of ePTFE membrane does not influence the clinical outcome[27]. Immediate implant installations after tooth extraction and augmentation with ePTFE membranes have predictable results[28]. However, contamination of ePTFE membrane has shown unfavorable results. Infection is a serious risk factor for arterio-venous PTFE grafts[29]. The extent of bacterial contamination of the ePTFE membrane is an indicator of the long-term success of the GBR procedure[30].

Silk

Silk, a macromolecule produced by *Bombyx mori*, has

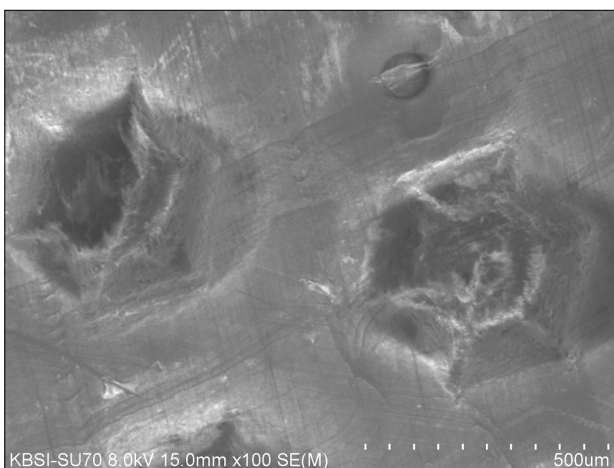


Fig. 2. Scanning electron microscopic view of expanded polytetrafluoroethylene membrane.

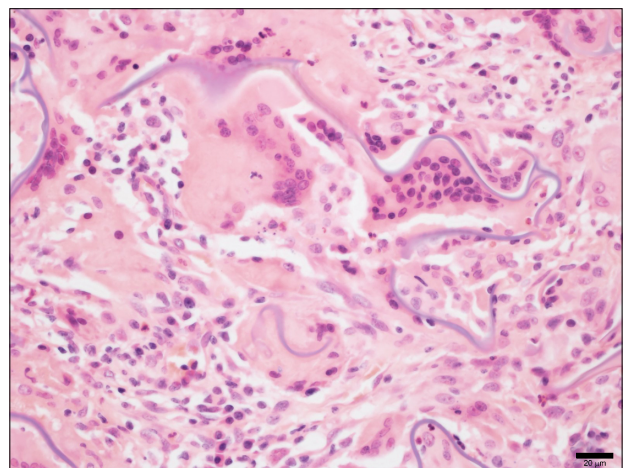


Fig. 3. Foreign body giant cells were attached to the silk implants (H&E, $\times 200$).

been used as a suture material in the medical field for a long time[31]. In particular, silk fibroin, a structural protein of silk material, has high biocompatibility and less foreign body reaction[32]. Silk fibroin has a fibrous structure and sericin is an adhesive for the silk fibroin. Silk fibroin has been investigated as a scaffold for bone grafts[33], artificial dura[34], wound dressing[35], or vessel[36]. Among commercialized silk-based materials, there is artificial tympanic membrane[37].

Silk fibroin usually induces a foreign body reaction when it is implanted into the bone defect (Fig. 3). If the silk fibroin is degraded by acid treatment, its molecular weight can be decreased below 1 kDa[38]. This low molecular weight silk protein can increase alkaline phosphatase activity and collagen synthesis in MG63 cells[38]. Use of this low molecular weight silk protein with platelet-rich-fibrin can increase bone regeneration in the rabbit calvarial defect model[39] and peri-implant bone defect model[40]. Silk membrane has still not been commercialized for the GBR procedure. However, several recent studies have reported on its potential application as a membrane for the GBR procedure[41-44].

Silk membrane can be produced by different methods of methods, including electrospun technique[44], casting technique[41,43], and simple separation technique[45]. Regardless of the production method, silk fibroin membrane showed favorable bone regeneration and less inflammation in the rat or rabbit calvarial defect model[41-45]. Electrospun silk membrane for the GBR technique was introduced by a team at Seoul National University in 2005[44]. The electrospun technique is proper for use in

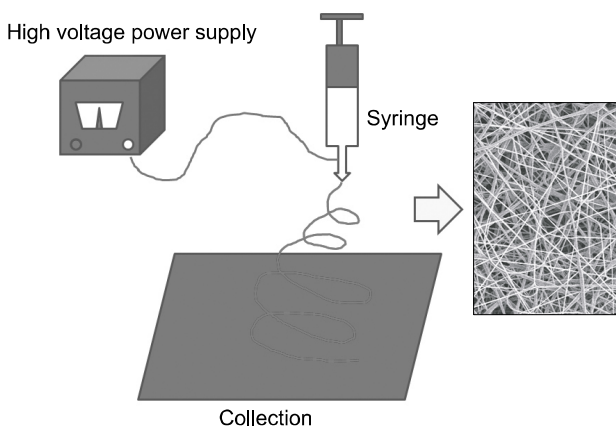


Fig. 4. Schematic drawing of the electrospun technique.

mass production (Fig. 4). In testing for patients it showed generally acceptable results[46,47]. However, the setting up and operating cost for the electrospun facility was higher than that for collagen membrane production (data not shown).

Silk membrane can be produced by casting technique[41,43]. Using this technique, a transparent silk membrane can be produced[43]. Similar technique has been used for production of the artificial tympanic membrane[48]. When compared to the unfilled control, this film type membrane showed higher new bone formation[43]. The silk membrane is surrounded by thin fibrotic tissue and very low inflammatory reaction around the silk membrane (Fig. 5). However, it is brittle in dry state. In wet condition, it has very low suture tensile strength. Therefore, the vacuum package is required to prevent breakage of the membrane. Although this film type membrane can be produced at two thirds the price of the available collagen membrane, the handling difficulty may be an obstacle to its wide application.

Recently, silk membrane is produced by a simple separation method[45]. The cocoon of *Bombyx mori* has a multi-layered structure[49]. These layers can be separated by shear stress. The thickness of the separated layer can generally range from 0.02 to 0.5 mm[49]. Separated layer has a thin fibrous network (Fig. 6). In dry condition, the silk membrane has similar tensile strength to the collagen membrane (Fig. 7). However, the tensile strength of this silk



Fig. 5. Film type silk membrane was encapsulated by fibrotic tissue. Below the silk membrane, new bone formation was observed (H&E, $\times 100$).

membrane is higher than that of collagen membrane or ePTFE membrane in wet state[45]. New bone formation is also comparable to that of collagen membrane[45]. In a previous report, PLGA barrier membrane did not show statistically greater new bone formation than negative control, but the collagen membrane did[50]. Silk membrane and collagen membrane show higher new bone regeneration compared to ePTFE membrane[45]. Foreign body giant cells were observed around the silk membrane, but the inflammatory reaction was minimal and new bone formation was observed below the silk membrane (Fig. 8). Unlike other collagen membranes, this silk membrane can be stored at room temperature. It can be sterilized by ethylene oxide gas, autoclave, or irradiation (data not shown). Thus, overall production cost will be much lower

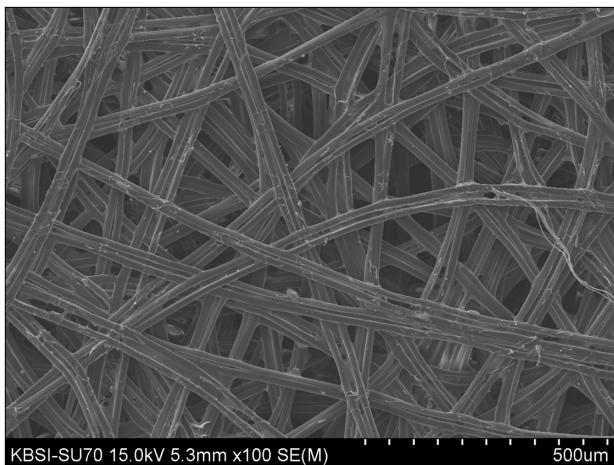


Fig. 6. Scanning electron microscopic view of silk membrane.

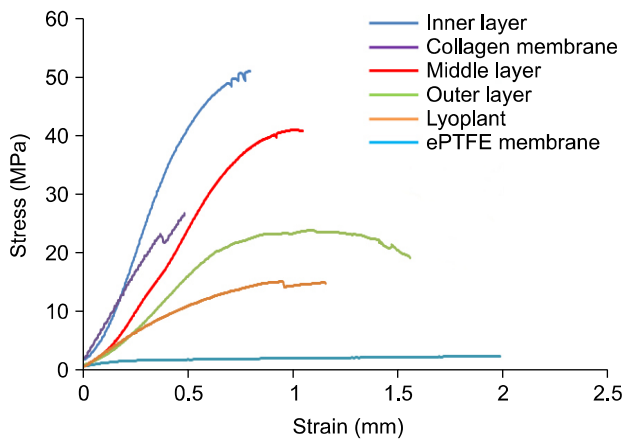


Fig. 7. The stress-strain curve of each membrane. It was measured in the dry state. Silk membranes were separated according to inner, middle, and outer layer. ePTFE, expanded polytetrafluoroethylene.

than that of other types of membrane. However, there has been no data on its clinical application.

In addition, silk is an excellent drug carrier. Several candidate drugs can be incorporated into the silk membrane. Antiseptic drugs such as tetracycline[51] and 4-hexylresorcinol (4HR)[42] were combined on the silk membrane for better bone regeneration. Tetracycline has been incorporated into other types of grafts. Tetracycline incorporated bone graft materials generally showed more bone formation than those without[52,53]. As tetracycline can hold the calcium ion, localized free calcium ion can be elevated in the presence of tetracycline. It can activate osteoblast and new bone formation[54]. 4HR is a chemical chaperone and a dormancy inducer for the microorganism[55]. 4HR inhibits transglutaminase-2[56] and nuclear factor- κ B pathway[57]. 4HR can also inhibit calcium oscillation[58] and diacylglycerol kinase pathway[59]. Therefore, 4HR may activate osteoblast and macrophage. 4HR incorporated dental implant[60] or bone graft[61] showed higher bone formation, but its action is dose-dependent. 4HR also accelerates the bio-degradation of grafts[59]. If silk membrane should be degraded within a couple of weeks, 4HR incorporated silk membrane may be used.

Commercialization of Silk Membrane

In recent decades, silk materials have been widely stud-

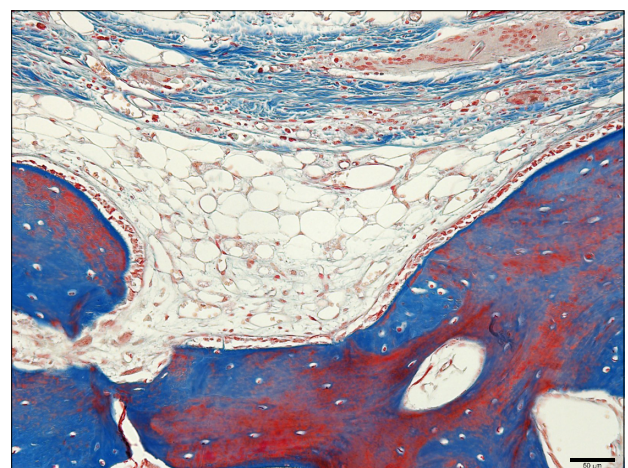


Fig. 8. New bone formation below silk membrane. Foreign body giant cells were attached to the silk membrane, but the inflammatory reaction was not severe (Masson trichrome stain, $\times 100$).

ied for dental and medical application. However, only film type silk membrane has been approved as a substitute for the tympanic membrane by the Korean Food and Drug Administration. In addition, the silk tympanic membrane is not widely used due to the imbalance between the cost for production and the price suggested by the health insurance. In the case of the tympanic membrane, most patients are healed naturally without artificial membrane. Only severely injured patients may need the artificial tympanic membrane. Therefore, its clinical application may be limited.

Unlike the silk tympanic membrane, silk membrane produced by simple separation method does not require the degumming process[46]. Therefore, there was no risk of residual bio-hazard salts that were added during the degumming process. However, separation itself should be done manually; it was very labor intensive work. The size of the silk membrane produced by simple separation[45] is dependent on the cocoon size. Therefore, a large sized membrane cannot be produced by use of this technique. Thus, this silk membrane cannot be used for covering maxillary sinus wall defect or cystic cavity wall defect. Despite these limitations, this new silk membrane can be widely used for covering small sized intra-oral defect such as extraction socket, periodontal defect, and peri-implant defect. As the silk material is classified as a non-biodegradable material[32], the clinical method for the silk membrane is generally in accordance with that of small sized ePTFE membrane. Compared to vessel tie silk material, the silk membrane for GBR, located mainly in the submucosal layer, can be easily removed. Whether it can be used for an open-membrane technique like collagen membrane is not clear. It should be tested in the clinical application.

Conclusion

There have been numerous patients who potentially need the GBR membrane. However, the cost for using the membrane is a main obstacle for its wide applications. When the silk membrane produced by simple separation method is commercialized, its price will be much lower than that of any other currently available types of membrane. Development of better material is a vital component of public health care.

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