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The effect of bone regeneration according to maintenance period of the non-resorbable membrane in rabbit calvarial defects

조선대학교 대학원

치의학과

김 형 석

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가토 두개골 결손부에서 비흡수성 차단막의
유지기간에 따른 골재생 효과

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ABSTRACT

The effect of bone regeneration according to maintenance period of the non-resorbable membrane in rabbit calvarial defects

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When the tooth loss is due to trauma or congenital abscence, often a ridge augmentation procedure is requested to correct the bone defect prior to implant placement.[2] Although many clinicians have tried GTR, they haven't sure about maintaing period of non-resorbable membrane used here such as PTFE.

The purpose of this study is to figure out how maintaining period of PTFE membrane used in GTR with autogeneous bone, heterogeneous bone and synthetic bone on rabbits' cranial defect effect on bone formation.

Eight adult New Zealand white rabbits were used in this study. Four defects were surgically made in their calvaria. Using a trephine bur, 4 'through and through' defects were created and classified into 4 groups, which were consisted of control(no graft), experimental group 1(autogeonous bone)and experimental group 2(deproteiniwed bovine bone:OCS-B®), experimental group 3(Xenogenic graft: MBCP). The defects were covered with PTFE membrane(Cytoplast®). Membranes were romoved after 1, 2, 4 and 8 weeks post-GBR in each 2 rabbits. And then, all rabbits were sacrificed, specimens were taken and observed histologically. The results were as follow:

1) After removing the membranes in a week, bone formation was not evident in a control group but the area was took place with only loose fibrous connective tissue. In group 1, thin bone formation and infiltration of connective tissue on the superficial layer were observed. Initial bone formation and infiltration of fibrous connective tissue were evident in group 2 and 3.

2) When the membranes were removed after 2 weeks of the experiment, bridge shaped bone formation was shown in control group but mostly connective tissue took place. More increased bone thickness was evident in group 1 and increased bone formation than first week was shown in group 2 and 3.

3) When the membranes were removed after 4 weeks, 2/3 of normal bone thickness was formed in control group still with infiltration of connective tissue. In group 1, regular bone formation with normal bone thickness were shown and in group 2 and 3, similar bone thickness to the normal one was evident.

4) After the removal of the membranes in 8 weeks, bone thickness formed in control group was increased than 4th week but could not reach normal bone thickness. In group 1, normal bone thickness was formed and similar bone thickness to that of normal one was observed in group 2 and 3.

5) After GBR, the membrane was removed in initial time, the usage of nonabsorbable membrane and autogenous bone resulted in the most favorable bone formation. When heterogeneous bone and synthetic bone were used, similarly favorable result was observed and in the group without any graft material showed the least bone formation.

6) In GBR, at least 4-week period of maintaining the membrane is required and when xenograft or synthetic bone is used more maintaining time than that of autogenous bone is needed for better bone regeneration. In the future, additional studies with more species and other graft materials will be needed and clinical studies based on this will also be required.

Ⅰ. *Introduction*

The successful use of osseointegrated implants in the treatment of complete or partial edentulism requires a sufficient quantity of available bone. Placement of dental titanium implants is a well-estabilished treatment modality in edentulous areas of the jaws.[1] However, when the tooth loss is due to trauma or congenital abscence, often a ridge augmentation procedure is requested to correct the bone defect prior to implant placement.[2] Guided bone regeneration (GBR) has become an acceptable method in clinical dentistry to facilitate augmentation of alveolar ridge defects, to promote implant wound healing, and to regenerate implant defects. The goal of GBR is to stimulate or at least facilitate the growth of new bone into the augmented site. Successful outcomes with the GBR technique require the fulfillment of certain biologic principles, namely wound stabilization, exclusion of competing tissues, and space maintenance.[3] To enhance the regenerative potentiality in GBR technique, a combination of bone fillers and the use of membranes seems to be an appropriate treatment preference. A variety of synthetic and naturally derived GBR barriers have been developed and tested with promising results.[4] The membranes are often used to create a space between the bone compartment and the overlying gingival flap. They are all supposed to prevent epithelial and connective tissue cells, which migrate more quickly than bone cells, from invading the area where angiogenesis and osteogenesis must take place.[5-7] Currently when GBR is performed, e-PTEE membrane is the most widely used one among non-resorbable membranes. However, e-PTEE membrane is lack of solidity so that the collapse of membrane was observed during healing period[8-11] or when it was exposed orally in early stage, it could result in infection from plaque deposition due to rough surface of the membrane.[12-14] Still, when e-PTEE membrane is used, it is suitable for soft tissues because it doesn't form inflammation or abscess. In addition, it is

reported that even though the membrane is exposed, normal bone remodeling in bone defect area is accomplished.[15]

The use of bone fillers underneath the membrane in larger defects has been advised because bone fillers not only support the membrane to maintain the created space, but they may also accelerate bone regeneration with their osteoconductive or possibly osteoinductive properties.[16-18] Grafting materials are autograft, synthetic grafts, allografts and xenografts. Autograft is considered the "gold standard" for grafting oral bony defects.[19,20]Grafting materials have been developed synthetically derived from corals or algae or produced from natural bone mineral.[21-23] Deprotenized bovine bone materials with high biocompatibility showed good clinical success and proven osteoconductive properties.[24-26] The development of calcium phosphate ceramics and other related biomaterials for graft involved a better control of the process of biomaterials resorption and bone substitution. Hydorxyapatite(HA) was possible to offer magnificent skeletal structure for newly formed bone to grow but it showed skeptical result in ability of regenerating. On the contrary, β-TCP proved to have the ability to form new bone in bone defect area around the teeth but its predictability in speed of resorption was low.[27-30] The study to figure out the most favorable compound ratio of HA and β-TCP was developed and it was reported that the higher ratio of HA than β-TCP promoted new bone formation in bone defect area. [31-33] These materials differ in composition and physical properties from each other and from bone and must be take in consideration for more efficient bone ingrowth at the expense of the biomaterials and to adapt to new development of dedicated biomaterials.[34] MBCP (Macroporous biphasic calcium phosphate) with a 60/40 HA/β-TCP weight ratio was global porosity (70%) and two different pore size (macropore size>100μm, micropore size<10μm). Of these, microporosity induces the deposition of bone crystal and makes angiogenesis and bone ingrowth possible. [35]

The purpose of the present study was histologically and histometrically to evaluate the effects according to the membrane application periods on GBR with non-resorbable membrane and graft materials (autograft, OCS-B, MBCP,) newly formed bone and newly formed bone remodeling process after removal of e-PTFE membranes and compared the effectiveness of e-PTFE membranes, with the use of autograft, OCS-B and MBCP graft, in bone regeneration.

Ⅱ. *Material and Method*

1. Surgical protocol

Eight New Zealand white female rabbits between 2.8 and 3.2 kg were included in this randomized, blinded, prospective study. Each rabbit was anesthetized with Zoletil 50® (10mg/kg, VIRBAC Lab, France) and Xylazine Hcl (Rompun®, 2.323mg/kg, Bayer, Korea).

The fur was shaved over cranium, which was prepared and draped in a sterile fashion. Incisions were made to the bony cranium and periosteum was reflected. By means of trephine bur(external diameter: 8mm, 3i, USA), four standardized 'through-through' bone defect were created with copious irrigation. The cranial defects were randomly grafted with autogenous bone(Experimental Group 1), OCS-B® (NIBEC, Korea: Group 2), MBCP® (PURGO, Korea: Group 3) and no graft(Control group). The defects were covered with nonresorbable PTFE membrane (Cytoplast®). The wound was closed with resorbable suture material (Surgifit®, AILEE, Korea). At the end of the surgical procedure, all animals received a single intramuscular injection of Gentamicin (5mg/kg, Daesung Microbiological Labs. Co. Korea) during 1 week. Membranes were removed after 1, 2, 4 and 8 weeks post-GBR in each 2 rabbits. And then, all rabbits were sacrified using phentobarbital (100mg/kg) intravenously at 8 weeks.

2. Histology and Histometric Procedures

The block sections, including the experimental sites, were fixed in 10% buffered formalin solution for 2 weeks, and decalcified in 10% formic acid decalcifying solution(Fisher Scientific, Tustin, CA) during 4 months. It was embedded in paraffin and cut into 6μm thickness. The sections were stained with H&E and observed by optical microscope.

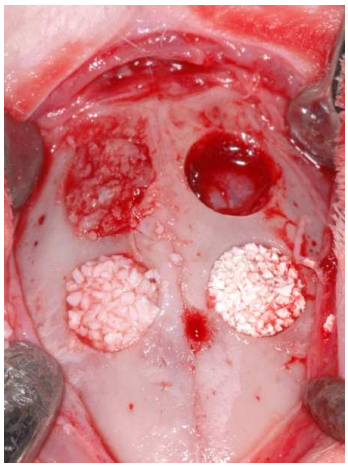

Fig. 1. Photograph of the surgical sites.

Ⅲ. *Results*

1. Control group (No grafting)

In the group removed membrane after 1 week, bone window barely showed bone formation and it was healed with connective tissues. In the group removed membrane after 2 weeks, a little bone formation was appeared from the lateral part of bone window and the rest was healed with connective tissues. In the group with removal of membrane after 4 weeks, the thickness of general bone formation in bone window was less than adjacent natural bone. In the group which maintained the membrane until 8 weeks, likely the group of 4 weeks, incomplete, less bone formation than adjacent natural bone was evident and the rest was healed with connective tissues.

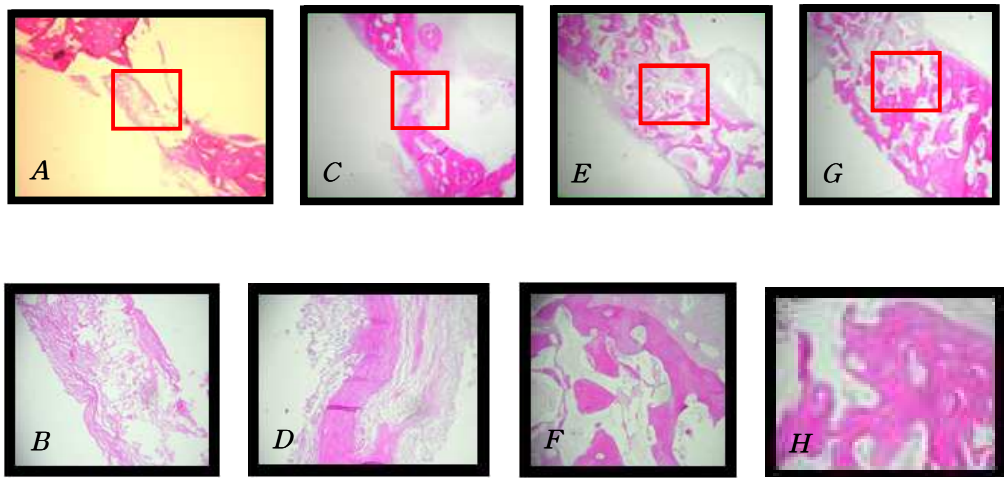

Fig. 2. Histological images of control group. Membranes were removed after 1 (A, B), 2 (C, D), 4 (E, F) and 8-weeks (G, H) of GBR. (A, C, E, G-magnification×50;B, D, F, H-magnification × 100)

2. Group 1 (Autogenous bone)

In the group removed the membrane after a week, original bone thickness was recovered but a little connective tissue proliferation in the center of grafted area was observed. In the group of 2 weeks, similar aspect was evident. In the group which maintained the membrane more than 4 weeks, bone formation in the center of the grafted area was shown and the thickness of bone was formed as much as adjacent one. Additionally, combination of autogenous bone and newly formed bone was accomplished.

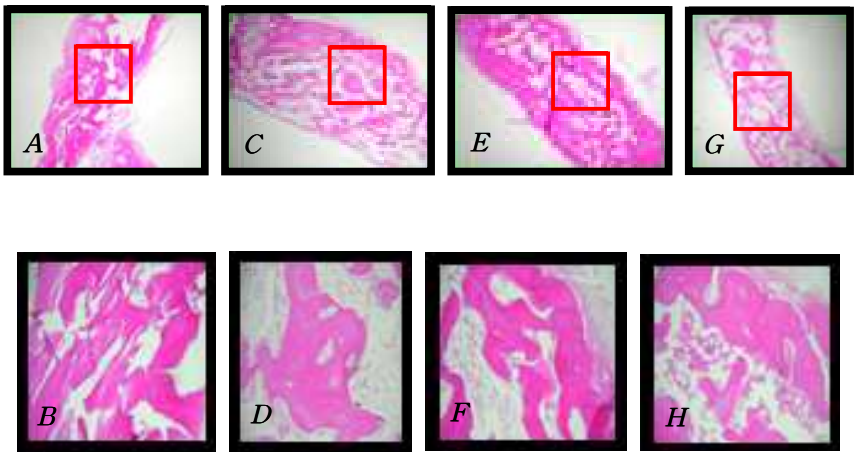

Fig. 3. Histological images of experimental group I . Membranes were removed after 1 (A, B), 2 (C, D), 4 (E ,F) and 8-weeks (G, H) of GBR. (A, C, E, G-magnification×50; B, D, F, H-magnification × 100)

3. Group 2 (OCS-B)

In groups removed the membrane after 1 week, 2weeks and 4weeks, the bone thickness maintains similar to the adjacent natural bone but connective tissue in the upper center of grafted area was observed. In the group maintained the membrane till 8 weeks similar bone thickness to the adjacent natural bone was formed without the infiltration of connective tissue. Graft material didn't absorbed and new bone was formed around it.

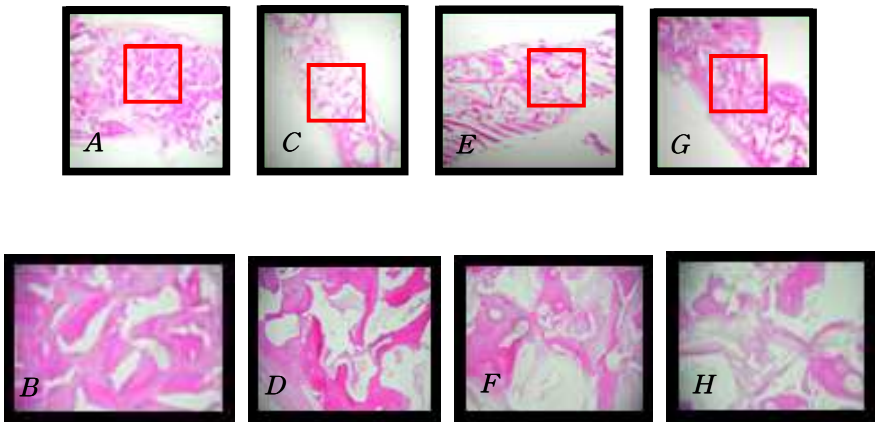

Fig. 4. Histological images of experimental group II . Membranes were removed after1 (A, B), 2 (C, D), 4 (E, F) and 8-weeks (G, H) of GBR. (A, C, E, G-magnification×50; B, D, F, H-magnification × 100)

4. Group 3 (MBCP)

In groups with removal of membrane after a week, 2 weeks and 4 weeks, they maintained less than group 2 but similar to natural bone like group 2 but connective tissue in the upper center of the grafted area was observed. In the group maintained the membrane until 8 weeks, similar thickness of bone formation to adjacent natural bone was evident.

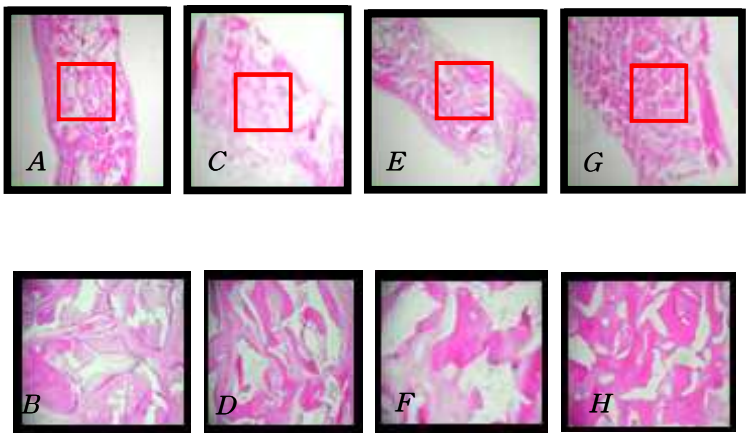

Fig. 5. Histologicalimagesof experimental group III . Membranes were removed after 1 (A, B), 2 (C, D), 4 (E, F) and 8-weeks (G, H) of GBR. (A, C, E, G- magnification×50; B, D, F, H-magnification × 100)

IV. Discussion

In the past decade, the use of barrier membrane became a clinically well-documented and successful procedure.[36,37] The placement of a rigid barrier membrane created a secluded space adjacent to a bone surface. The barrier impeded cells originating from the surrounding soft tissues to invade the created space that becomes gradually filled with newly formed bone[38]. To date, a prolonged membrane application period has been regarded as ideal for the maturation of newly formed bone except for the occurrence of infection. Thus, it has been proposed that long-term membrane application periods such as 6 to 10 months and 4 to 6 weeks are suitable for GBR operation and GTR operations, respectively. However, recent studies have pointed out the disadvantages of long-term application of membranes to newly formed bone such as the induction of pronounced bone atrophy underneath the membrane[39] and the immaturation of newly formed bone at the time of 11 months post GBR.[40] When GBR is performed, bone graft materials are used to secure the regenerating area with membrane. Autogenous bone is widely known as the most ideal bone material[41] but it requires secondary surgery on donor sites and longer operation time. In addition it could result in infection, postoperative pain, paresthesia or scar and it also limit the size of graft fragment and the ratio of resorption is not stable.[42] Therefore, substitutes for autogenous bone is widely introduced deproteinized bovine bone mineral (DBBM) is a xenogenic graft material that has been widely used as a bone substitute in implant dentistry and in periodontology[43]. DBBM has osteoconductive properties as it promotes cellular adhesion, wound healing and the formation of new bone tissue. It has a physical- chemical structure similar to that of human cancellous bone, in terms of its calcium phosphor index (2.03) and its isomeric crystalline dimensions.[44] Several authors recommend the use of bovine apatite in GBR techniques with both resorbable and nonresorbable membranes.[45]

Xenogenic grafts like (deproteinized bone) has problem in genetic graft antigen so many studies focused on how to minimalized the immune reaction by treating the bone diversely. The difference of bone conduction can be shown according to the amount of apatite crystals or carbons. In hence, the degree of bone conduction is improved if degree of apatite crystal is low and the amount of carbon is abundant..[46-47]Graft material used in this study, OCS-B is reported when bone graft material undergo low-temperature treatment its physical, chemical characteristic is similar to those of apatite in human bone.[48] Another graft material used in this study, MBCP, is synthetic bone produced by mixing HA whose activity is low and stable and β-TCP whose activity is high. It is reported that calcium and phosphorous ions released with gradual resorption of bone graft material play the role of growing seed of newly formed bone.[27] In the study of Daculsi et.al., they reported that mixture of 60% of HA and 40% of β-TCP is MBCP and the ratio is the most ideal as bone substitute. It also has multi-porous structure which can make it easier for new bone to grow and to be calcificated.[49]

The necessity for prolonged application periods remains questionable. The present study has demonstrated by light microscopy and histometrical changes in newly formed bone and the effects of membrane removal on the maturation of newly formed bone.

In the present study, various bone fillers were examined in membrane-covered defects in the calvarium with regard to new bone formation and degradability. This study confirms previous reports that, with the placement of barrier membranes, bone fillers enhance the potential for bone regeneration in surgically created defects. In this study, after certain periods, in each group used autogenous bone, OCS-B, and MBCP bone formation was completed though the amount was different.

Here, bone forming ability of several bone graft materials with the effect of bone formation according to the time of removal of membrane when GBR was performed was studied. As a result, when autogenous bone was used, after 4 weeks and

when xenograft, synthetic bone was used, after 8 weeks, normal bone thickness was recovered without infiltration of connective tissue. Because of faster bone formation in the center of bone window, it is considered that at least 4 week-period of maintaining the membrane is required for bone formation.

Ⅴ. *Conclusion*

In this study, we formed bone window in rabbits crania and compared the amount of bone formation in groups of grafting autogenous bone, deproteinized bovine bone, heterogeneous bone, HA/TCP synthetic bone, and in the group without anything to be grafted. Following results were obtained.

1) After removing the membranes in a week, bone formation was not evident in a control group but the area was took place with only loose fibrous connective tissue. In group 1, thin bone formation and infiltration of connective tissue on the superficial layer were observed. Initial bone formation and infiltration of fibrous connective tissue were evident in group 2 and 3.

2) When the membranes were removed after 2 weeks of the experiment, bridge shaped bone formation was shown in control group but mostly connective tissue took place. More increased bone thickness was evident in group 1 and increased bone formation than first week was shown in group 2 and 3.

3) When the membranes were removed after 4 weeks, 2/3 of normal bone thickness was formed in control group still with infiltration of connective tissue. In group 1, regular bone formation with normal bone thickness were shown and in group 2 and 3, similar bone thickness to the normal one was evident.

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6) In GBR, at least 4-week period of maintaining the membrane is required and when xenograft or synthetic bone is used more maintaining time than that of autogenous bone is needed for better bone regeneration. In the future, additional studies with more species and other graft materials will be needed and clinical studies based on this will also be required.

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Table 1. Histometrically evaluation of control group. Membranes were removed after 1 week, 2week, 4 weeks, 8 weeks

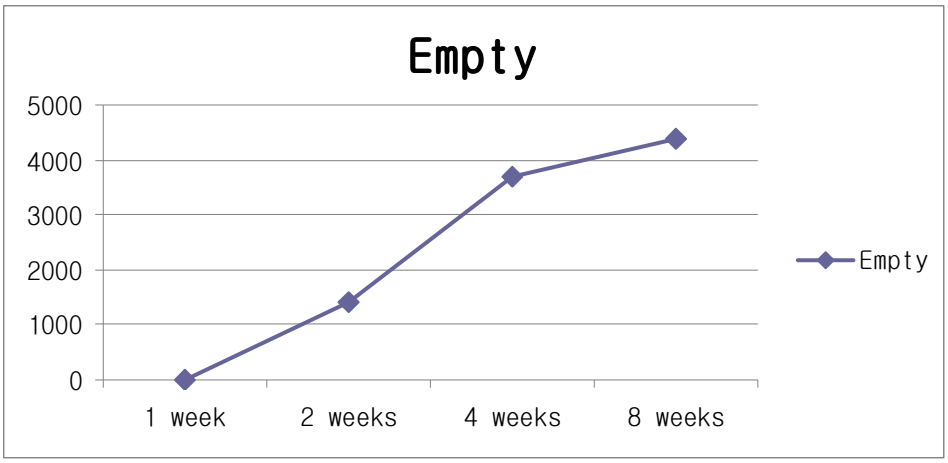


Table 2. Histometrical evaluation of experimental group I

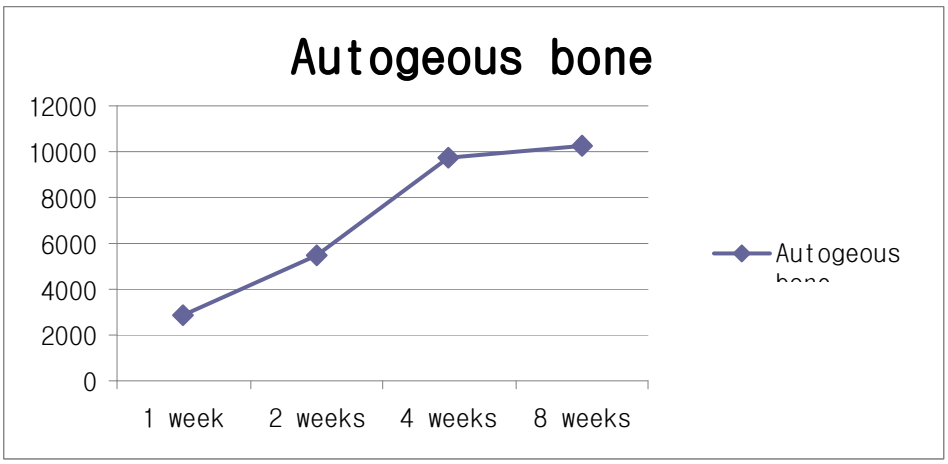


Table 3. Histometrical evaluation of experimental group II

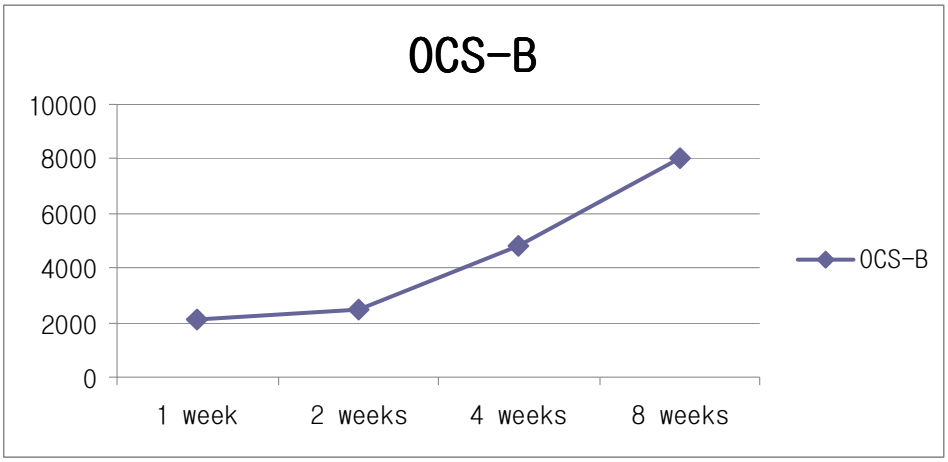
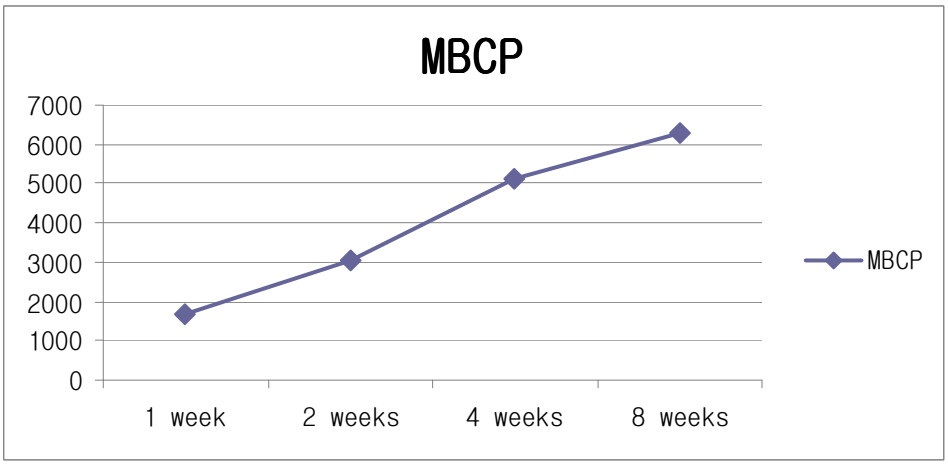


Table 4. Histometrical evaluation of experimental group III



국문초록

가토 두개골 결손부에서 비흡수성 차단막의 유지기간에 따른 골재생 효과

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외상 또는 선천적으로든 광범위하게 결손된 치조골에서 이상적인 임플란트의 식립을 위해서는 골유도재생술이라는 술식이 필요로 하게 된다. 비록 많은 임상가들이 골유도재생술을 시행하지만, 이때 사용된 PTFE와 같은 비흡수성 차단막의 유지 기간에 대해서는 확신을 갖을수가 없었다. 이 실험의 목적은 토끼의 두개골 결손부에서 자가골, 이종골, 합성골등을 이용한 골유도 재생술에서 사용된 PTFE 차단막의 유지기간이 골형성 효과에 어떤 영향을 미치는지에 대해서 알아보고자 함이다.

이 연구에서는 8마리의 가토가 사용되었다. 트레핀 버를 이용하여, 그들의 두개골에 4개의 골결손부를 인위적으로 형성하였다. 각각의 결손부는 4개의 군: 대조군(이식재를 사용치 않은 군), 실험 1군(자가골), 2군(OCS-B), 3군(MBCP)으로 구분하였다. 결손부들은 비흡수성 차폐막인 e-PTFE membrane(Cytoplast)로 덮혀졌다. 차폐막은 골유도재생술 시행 후, 1주, 2주, 4주 그리고 8주째에 각 2마리씩 제거되어졌다. 그리고 나서 모든 가토는 희생되어지고 표본들은 조직학적으로 관찰되어졌다.

그 결과는 다음과 같다:

1) 1주 후 제거 시, 대조군에서는 골 형성은 보이지 않고 소성 섬유성 결합조직으로만 채워져 있으며,
1군에서는 얇은 골 형성과 표층에 결합조직의 침습을 볼수 있었다. 2군,3군에서는 약간의 골 형성이 보이면서 섬유성 결합조직의 침습을 볼 수 있었다.

2) 2주 후 제거 시, 대조군에서는 약간의 골형성 가교형태가 보이지는 거의 결합조직으로 채워져 있음이 보였고, 1군에서는 좀 더 증가된 골형성 두께를 보이고, 2군과 3군에서는 1주 때보다 약간 증가된 골 형성모습을 볼 수 있었다.

3) 4주 후 제거 시, 대조군에서는 정상 골의 약 2/3정도의 골형성 두께를 보이나, 여전히 결합조직의 침습이 보였다. 1군에서는 정상적인 골 양상과 두께를 보였고, 2군과 3군에서는 거의 정상 골과 비슷한 골 두께를 보였다.

4) 8주 후 제거 시, 대조군에서는 4주 때보다는 증가되었으나 정상 골의 두께에 미치지는 못하고, 1군에서는 정상 골의 두께를 보이며, 2군과 3군에서도 정상 골의 두께를 보였다.

5) 골유도재생술 시행 후, 차폐막을 초기에 제거했을 때, 비 흡수성막과 자가골을 사용 시 가장 양호한 골 형성을 보였고, 그 다음이 이종골과 합성골이 비슷하게 양호한 결과를 나타냈고, 아무 이식재도 사용하지 않은 것이 골 형성이 가장 적었다.

6) 골유도 재생술 시행 시, 이식재의 종류와 상관없이 차폐막은 최소한 4주간의 유지기간이 필요하며, 자가골보다 이종골, 합성골 사용 시 더 많은 유지기간을 필요로 한다.

(별 지)

저작물 이용 허락서

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논문제목	한글 : 가토 두개골 결손부에서 비흡수성 차단막의 유지기간에 따른 골재생 효과				
	영문 : The effect of bone regeneration according to maintenance period of the non-resorbable membrane in rabbit calvarial defects				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집·형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함.
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5년으로 하고, 기간종료 3개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함.
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1개월 이내에 대학에 이를 통보함.
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함.

동의여부 : 동의(○) 반대( )

2008년 2월 일

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조선대학교 총장 귀하