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Ear Cartilage Regeneration:

A Comparison of Free Perichondrial and

Periosteal Grafts

유리연골막 이식과 유리골막 이식의

귀연골재생능력 비교

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A thesis of the Degree of Master

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February, 2014

The Department of Plastic Surgery

Seoul National University

College of Medicine

Byung Jun Kim

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김 병 준

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Ear Cartilage Regeneration:

A Comparison of Free Perichondrial and

Periosteal Grafts

by

Byung Jun Kim

A thesis submitted to the Department of Plastic Surgery in partial fulfillment of the requirements for the Degree of Master of Science in Plastic Surgery at Seoul National University College of Medicine

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Abstract

Background

Ear cartilage is a good source for tissue support or augmentation in plastic and reconstructive surgery. However, the amount of ear cartilage is limited and excessive use of cartilage can cause deformation of the donor site. To minimize the loss of cartilage, the potential of periosteal chondrogenesis was investigated in an ear cartilage defect model.

Materials and Methods

Twelve New Zealand White rabbits were used in the present study. Four sections of ear cartilage defect were created on the ear of each rabbit bilaterally, between the central artery and marginal veins. Skin flaps measuring 12×12 mm^2 were elevated and 10×10 mm^2 auricular cartilage defects were created including the perichondrium. The defects were covered with perichondrium (group 1), periosteum taken from the calvarium (group 2), or periosteum taken from the tibia (group 3), whereas no coverage was made in a control group (group 4). All animals were sacrificed 6 weeks later, and the results were investigated both, macroscopically and microscopically.

Results

Significant chondrogenesis occurred only in the perichondrial graft group, whereas osteogenesis, instead of chondrogenesis was seen in the periosteal graft groups. There was no statistical difference in the amount of osteogenesis or chondrogenesis between groups 2 and 3. Group 4 showed fibrous tissue accumulation in the defect area.

Conclusion

Periosteal grafts showed weak chondrogenic potential in an ear cartilage defect model; instead, they exhibited osteogenesis, and showed the same clinical activity irrespective of their embryological origin.

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Introduction

Ear cartilage is widely used as a source for tissue augmentation or support in aesthetic or reconstructive surgery. Conchal cartilage has its unique characteristics of a concave shape with solid but elastic properties, while donor site can be repaired with minimal visible scar; therefore it is widely used for eyelid reconstruction, nasal tip augmentation, columellar strut, or chondrocutaneous composite graft to correct short nose deformity. (1-3)

However, the amount of ear cartilage is limited and alternative sources are required for wide defect coverage. A cartilage allograft is an attractive substitute, considering the weak antigenicity and low oxygen demand of cartilage, but absorption and contour irregularity in the long term limits its clinical usefulness. Tissue engineering could be another option, but the properties of cartilage are not fully understood, and the long-term clinical outcome has not been elucidated.

There have been reports of successful cartilage regeneration using periosteal grafts. Most of these studies are confined to hyaline cartilage regeneration in the knee joint using periosteum from the tibia. However, the head and neck environment differs from that of joint space in anatomy and physiologic property, with its relatively robust blood supply and less movement or tension. Furthermore, because periosteum from calvarium can be harvested in the same field with head and neck surgery; it is more reasonable to use pericranium than periosteum from the tibia.

In the present study, we investigate the possibility of elastic ear cartilage regeneration with free grafts of perichondrium and periosteum of different embryologic origins: periosteum from tibia (endochondral ossification), and periosteum from calvarium (intramembranous ossification). To the best of our knowledge, no study has yet directly compared the chondrogenic potential of periosteum from different origins for regeneration of elastic cartilage.

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Materials and Methods

Twelve 12-week-old male New Zealand White rabbits weighing 2000-2500g were included in the present study. All procedures were performed under the approval of the Institutional Animal Care and Use Committee (IACUC) of SNUH (Seoul National University Hospital) (IACUC number 13-0164). All animals were observed for at least 1 week preoperatively, to provide an accommodation period and to screen any systemic impairment.

A cocktail of 15 mg/kg zolazepam tiletamine (Zoletil®, Virbac France) with 5 mg/kg xylaxine hydrochloride (Rompun®, Bayer Germany) was administered in the quadriceps femoris muscle of the rabbits to achieve anesthesia. Intramuscular injection of 30 mg/kg cefazolin (Chong Kun Dang, Korea) was also performed to prevent wound infection. The fur on the auricle, scalp, and right medial tibia was removed with an electric shaver. Skin was prepared to provide aseptic condition during the procedure.

Flap elevation

Four skin flaps measuring 1.2×1.2 cm^2 were designed on the posterior aspect of both ears between the central artery and marginal veins, taking care not to interfere with the vessels. The flap design was easily made using a film template of the same size. Semi-permanent markings of the flap design were added using a micro-tattoo machine (Digital-Pro, BOMTECH, Korea) (Figure 1). Lidocaine 2% (Huons, Korea) was injected over the perichondrium plane on the anterior and posterior aspects of the ears to make a clear dissection plane and to facilitate flap elevation. Epinephrine was not used to avoid vasoconstriction, which can affect flap viability and cartilage regeneration. A skin incision was made along the marked line, except on the proximal side, and then proximally-based skin flaps were elevated over perichondrium plane using a #15 blade and sharp scissors. Meticulous care must be taken during the flap elevation because it is important not to include the perichondrium in the flap to avoid the interference of remnant perichondrium. A square of ear cartilage measuring 1.0×10 cm^2 was removed,

including the perichondrium on both sides.

Preparation of free grafts

This study was designed such that each rabbit belonged to all 4 groups to reduce sample size and to minimize differences in the environment between samples. The skin flap was located on the widest area between the central artery and marginal vein. Furthermore, the sites of 4 groups were randomly distributed to minimize bias caused by location. The defect area of cartilage was covered with perichondrium (group 1), periosteum from the calvarium (group 2), periosteum from the tibia (group 3), and no coverage was made in the control group (group 4) (Figure 2).

Group 1 (perichondrial graft)

Perichondrium was harvested from the ear cartilage after skin flap elevation. A careful incision was made on the perichondrium measuring $1.0 \times 10 \text{ cm}^2$, and then the perichondrium of the posterior side was elevated from the ear cartilage. A piece of ear cartilage of the same size, including perichondrium of anterior side, was removed. The free perichondrial graft was re-attached in situ over the ear cartilage defect using non-absorbable suture (7-0 Nylon, Johnson and Johnson, USA) (Figure 3).

Group 2 (periosteal graft taken from the calvarium)

A midline incision was made on the scalp of the rabbit, followed by supra-pericranial dissection. The pericranium measuring $1.0 \times 10 \text{ cm}^2$ was harvested from the parietal side of the cranium, and the donor site was closed using non-absorbable suture (5-0 Nylon, Johnson and Johnson, USA). The pericranium was attached on the posterior aspect of the ear cartilage defect in the same manner as for group 1. The cambium layer was facing the anterior side, whereas the fibrous layer was facing the posterior flap side (Figure 4).

Group 3 (periosteal graft taken from the tibia)

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Periosteum was harvested from the proximal and antero-medial aspect of the right tibia. The outline of the tibia along with the incision line was designed on the surface, followed by incision and supra-periosteal dissection. Periosteum measuring 1.0×10 cm^2 was harvested, and the donor site was closed after meticulous hemostasis. The periosteum was attached on the ear cartilage defect in the same manner as for Groups 1 and 2.

Group 4 (control)

In the control group, the cartilage defect was made by the aforementioned method, and then the skin flap was closed over the cartilage defect with no additional intervention.

After all graft procedures were completed, the skin flap was closed. The surgical wound was treated with antibiotic ointment (Terramycin®, Pfizer USA), and then opened during the follow-up period. Meloxicam 2mg/kg was administered to alleviate postoperative pain. The results were investigated at 6 weeks after the experiment. All animals were sacrificed using potassium chloride (KCl) injection in the marginal vein.

Macroscopic evaluation

Gross inspection was performed to detect any wound problems such as infection or dehiscence. The character of regenerated tissue was evaluated qualitatively regarding hardness, thickness, and the relationship between newly formed tissue and surrounding normal cartilage. Skin flap dimensions were calculated to investigate the effect of wound contraction. The outlines of the flaps were drawn using transparent paper, and the dimension of the flap was measured using the Image J software program. Image J is a Java-based image analysis program that can be downloaded from the website (http://imagej.nih.gov/ij/). The change in flap area was evaluated as a ratio: change in the flap dimension divided by the original flap size [(original flap - final flap) / original flap].

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Microscopic evaluation

Rectangular specimens measuring approximately 20×5 mm^2 were harvested in the middle of the flap including both the defective and the normal side, fixed with 10% formalin for more than 48 hours, and embedded in paraffin after washing in flowing water for at least 24 hours. Tissue sections, 5μm thick, were made along the longitudinal axis and then stained with hematoxylin and eosin. The amount of regenerated cartilage, measured using Image J, was divided by the predicted area of the cartilage defect to estimate the cartilage regeneration ratio, calculated as regenerated cartilage amount (N)/predicted defect area (D). The cartilage defect predicted area can be calculated by multiplying the average the thickness of both defect margins by the defect length (10mm) (Figure 5).

Statistical analysis

Statistical evaluation was performed using the SPSS$^{®}$ (version 19; SPSS Inc., Chicago, IL, USA). A generalized estimating equation was used to evaluate the degree of chondrogenic difference among the groups.

Results

Of the 12 rabbits in this study, 11 were evaluated 6 weeks after the experiment. One rabbit died as a result of an accident related to anesthesia.

Macroscopic evaluation

There were no surgical complications such as wound infection, dehiscence, or hematoma. In group 1, the newly formed tissue had a thickness and stiffness similar to the surrounding normal cartilage tissues and fused well with them. In groups 2 and 3, regenerated tissues showed a relatively bumpy surface with a yellow to brownish color, which fused with the surrounding normal cartilage, but was thicker and hard like bony tissue. In the control group, the defect area was hollow without sufficient regenerated cartilage tissue.

Wound contraction ratio was estimated using the flap dimension change compared with the original flap dimension. Group 2 (0.32 ± 0.10) and group 3 (0.38 ± 0.10) showed more wound contraction compared with group 1 (0.26 ± 0.10 and group 4 (0.29 ± 0.09), but it was not statistically significant.

Microscopic evaluation

Cartilage tissue regeneration was seen in group 1 and it fused well with surrounding normal cartilage. However, the thickness of the regenerated cartilage was uneven compared with the normal side, and complete maturation of the cartilage was not obtained. The cartilage regeneration ratio in group 1 (0.97 ± 0.60) was greater than in group 2 (0.10 ± 0.11), group 3 (0.08 ± 0.09), and group 4 (0.08 ± 0.14) which was statistically significant (p=0.004), but there were no differences between groups 2, 3, and 4 (Figure 6).

In groups 2 and 3, a paucity of elastic cartilage was observed in the vicinity of the normal cartilage tissue. Instead, newly formed osteon was observed in the middle of the defect (Figure 7). The bone regeneration ratio, calculated by the aforementioned method, was 2.10 ± 1.97 in group 2 and 2.92 ± 4.17 in group 3, but no osteogenesis was observed in groups 1 and 4. There was no statistically significant difference in the osteogenesis or chondrogenesis between groups 2 and 3.

6

Discussion

Elastic cartilage is composed of collagen fibers and abundant elastic fibers in a solid matrix. The elastic fibers provide great flexibility to cartilage, which can endure repeated bending forces and it is found in elastic structures with soft movement, such as ear, epiglottis, and the Eustachian tube. The elastic, but durable, properties of ear cartilage enables variable uses in plastic and reconstructive surgery. However, because the amount of ear cartilage is limited, many studies have been conducted on chondrogenesis.

Except for alloplastic and tissue engineering methods, a perichondrial graft is the first option for regeneration of cartilage tissue. Perichondrium contains multipotent stem cells, which differentiate into chondroblasts. (4, 5) This technique is used in a limited manner in knee joint cartilage regeneration with a maximal chondrotrophic environment. (6, 7)

Periosteum is also known to bear a chondrogenic potential when favorable environments for chondrogenesis are provided. It can be harvested more easily and in greater amounts than perichondrium. Periosteum is composed of 2 layers; the cambium layer facing the bone cortex contains osteoprogenitors, preosteoblasts, osteoblasts, and other precursor cells, and the outer fibrous layer is attached to the muscular structure. (8) It originates from perichondrium, and chondrocyte precursor cells in the cambium layer are thought to be a source for chondrogenesis in a chondrotrophic environment. (9)

Previous studies revealed that periosteal grafts had chondrogenic potential equal to that of perichondrial grafts when they were grafted into joint space. O'Driscoll SW et al. reported positive results of periosteal grafts on chondrogenesis and maintained that lower oxygen pressure, repetitive movement, and young age are important factors, along with other minor contributes for chondrogenesis of periosteal grafts. (10, 11) Ulutas et al. reported a comparable cartilage regeneration using periosteal grafts compared with perichondrial grafts in an ear cartilage defect model. (12)

However, in the present study, chondrogenesis of periosteal grafts was poor compared with perichondrial grafts irrespective of their embryologic origin. This result corresponds with

previous reports, including recent research showing no significant chondrogenesis of periosteal grafts in the long term even though they were applied with chondro-inductive growth factors. (13) Sari et al compared the chondrogenic potential of perichondrial and periosteal grafts that were wrapped on themselves and transplanted under the abdominis fascia in rabbits, and could not find any mature cartilage formation from the periosteal grafts. (14) Poussa at el designed 2 different models to analyze chondrogenesis from periosteal grafts; one was inserted between the perichondrium and cartilage, which provided an avascular milieu, and the other was transplanted between 2 skin layers. In the former, neo-cartilage was observed, and the latter showed bone formation within 1 week without chondrogenesis. Insufficient circulation in the recipient bed was thought to be an important precondition for chondrogenesis from periosteal grafts. (15)

The sub-dermal plane under the skin flap is thought to have a different environment compared with joint space for chondrogenic factors. Synovial fluid in the joint space contributes an avascular environment while providing growth factors. The chondrogenesis observed by Ulutas et al. in the periosteal grafts could have resulted from insufficient perichondrium removal. Remnant perichondrium contained in the skin flap could serve as a source of chondrogenesis. . Indeed, at the beginning of our pilot study, we experienced considerable chondrogenesis in the control group when we did not achieve meticulous perichondrium removal.

It is known that embryologic bone formation occurs in 2 ways; endochondral ossification in long bones is generated through a cartilaginous intermediate, while intramembranous ossification in flat bones is formed without a cartilaginous intermediate. (8) Previous studies have shown that periosteal grafts have different osteogenic potential according to the donor site. (16, 17) In general, periosteum taken from endochondral ossification bone such as tibia showed superior osteogenicity over those from intramembranous ossification bone such as calvarium or rib. However, no studies have been conducted regarding the chondrogenic capacity of periosteum from different donor sites. In the present study, there was no significant difference in chondrogenesis and osteogenesis between periosteal grafts from calvarium and tibia.

To the best of our knowledge, this is the first report that directly compares the chondrogenic potential of perichondrium, periosteum of intramembranous origin, and periosteum from endochondral origin in an elastic cartilage defect model. Cartilage regeneration by periosteum

was increased when it was treated with basic fibroblast growth factor, transforming growth factor beta, a mixture of growth factors using platelet-rich plasma, or adipose-derived stem cells. (18-20) In vitro expanded chondrocytes mixed with various growth factors can positively affect the regeneration of cartilage, which could be elucidated in a future study.

Conclusion

Periosteal chondrogenesis was not seen in an ear cartilage defect model. It can be inferred that cartilage regeneration by periosteum can be induced in a well-organized hypoxic environment. The clinical function of periosteum is thought to be the same regardless of the embryological origin. Therefore, preserving perichondrium during the grafting procedure is required for cartilage regeneration. Future study of chondrocytes and growth factors may contribute to our knowledge of periosteal chondrogenesis.

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Figure Legends

Figure 1. Surface marking of flap design on the posterior side of rabbit ears. The inner square (1.0 × 1.0cm^2) indicates the area of the cartilage defect, and the outer square (1.2 × 1.2 cm^2) indicates the flap margin. The arrow in the middle indicates the central artery, and the arrowheads indicate the marginal veins bilaterally.
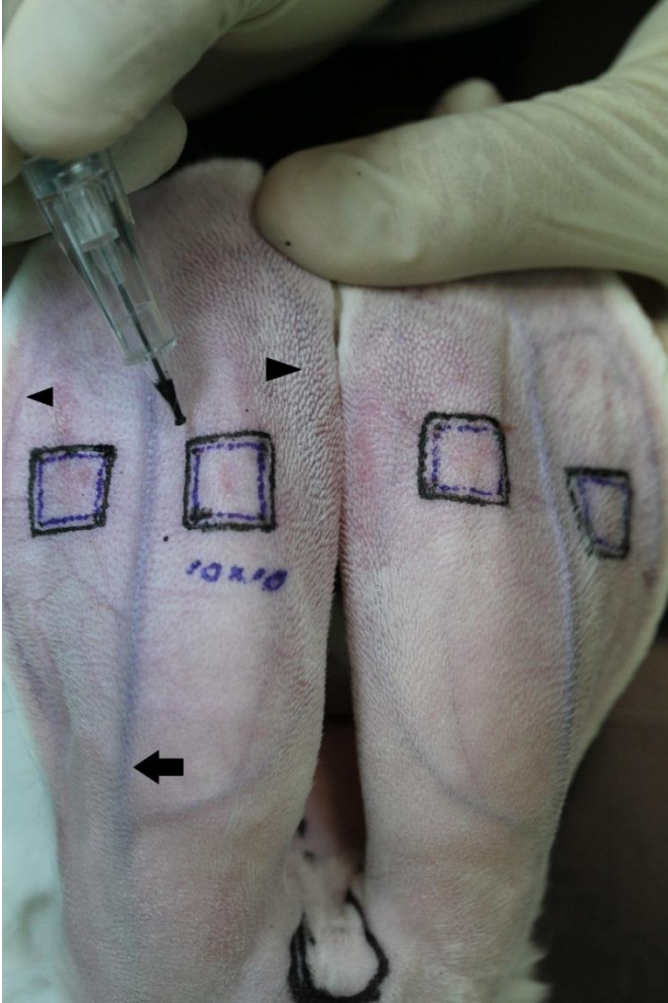
Figure 2. Skin flaps are elevated, and grafts are covering the cartilage defect: from left to right, periosteum taken from tibia, periosteum taken from cranium, perichondrium, and control.

Figure 3. Schematic drawings of group 1. Perichondrium on the posterior side is elevated from cartilage, and then re-attached in-situ. Cartilage including the perichondrium on the anterior side is removed. (Ant., anterior; Post., posterior)
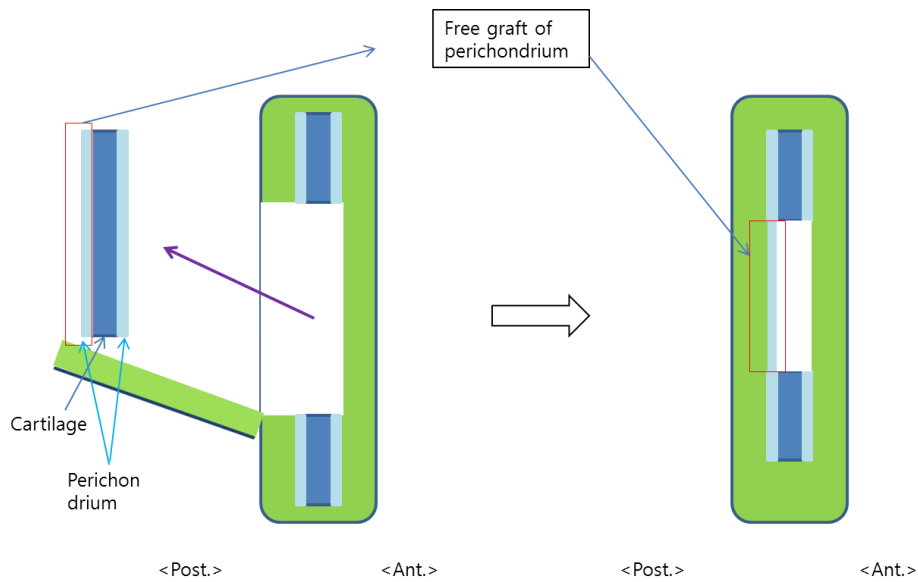

Figure 4. Schematic drawings of groups 2 and 3. The cambium layer of the periosteum is facing toward the cartilage defect area. (Ant., anterior; Post., posterior)
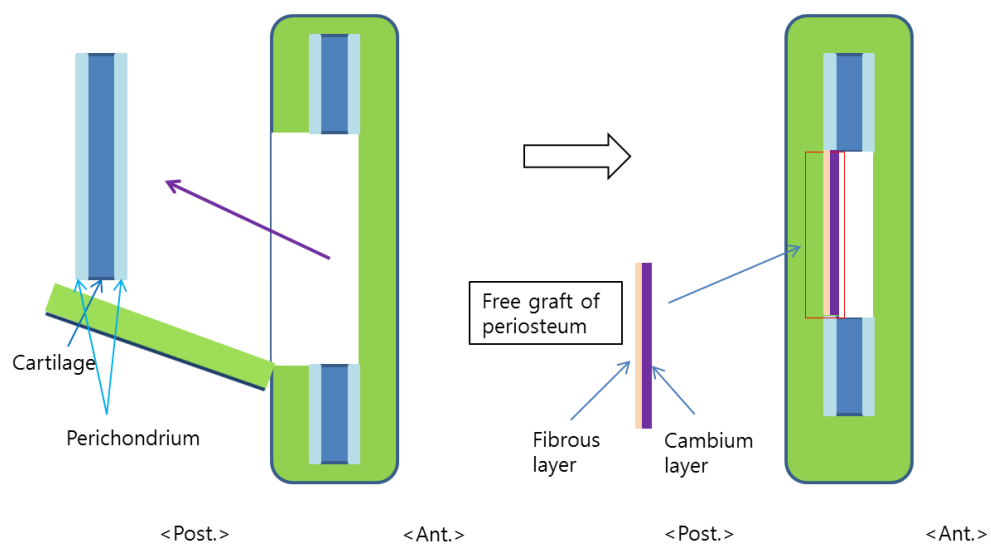

15

Figure 5. Cartilage regeneration ratio: regenerated cartilage area divided by predicted defect area.
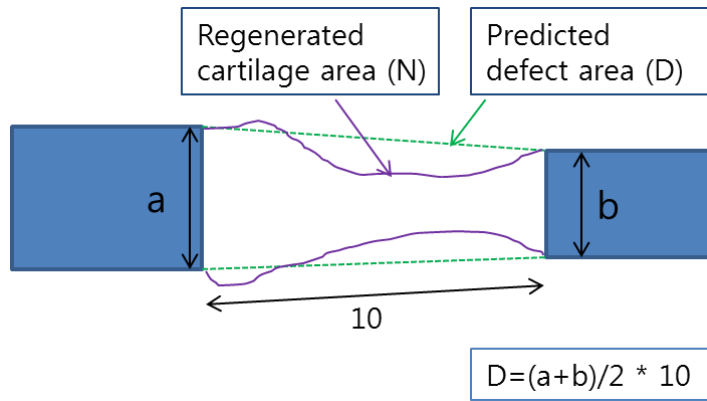
Figure 6. Neo-cartilage tissue was regenerated into the cartilage defect area in group 1. The arrow indicates the junction between normal cartilage and neo-cartilage. Neo-cartilage tissue is thinner than the normal side. Hematoxylin and eosin; magnification, x 40.
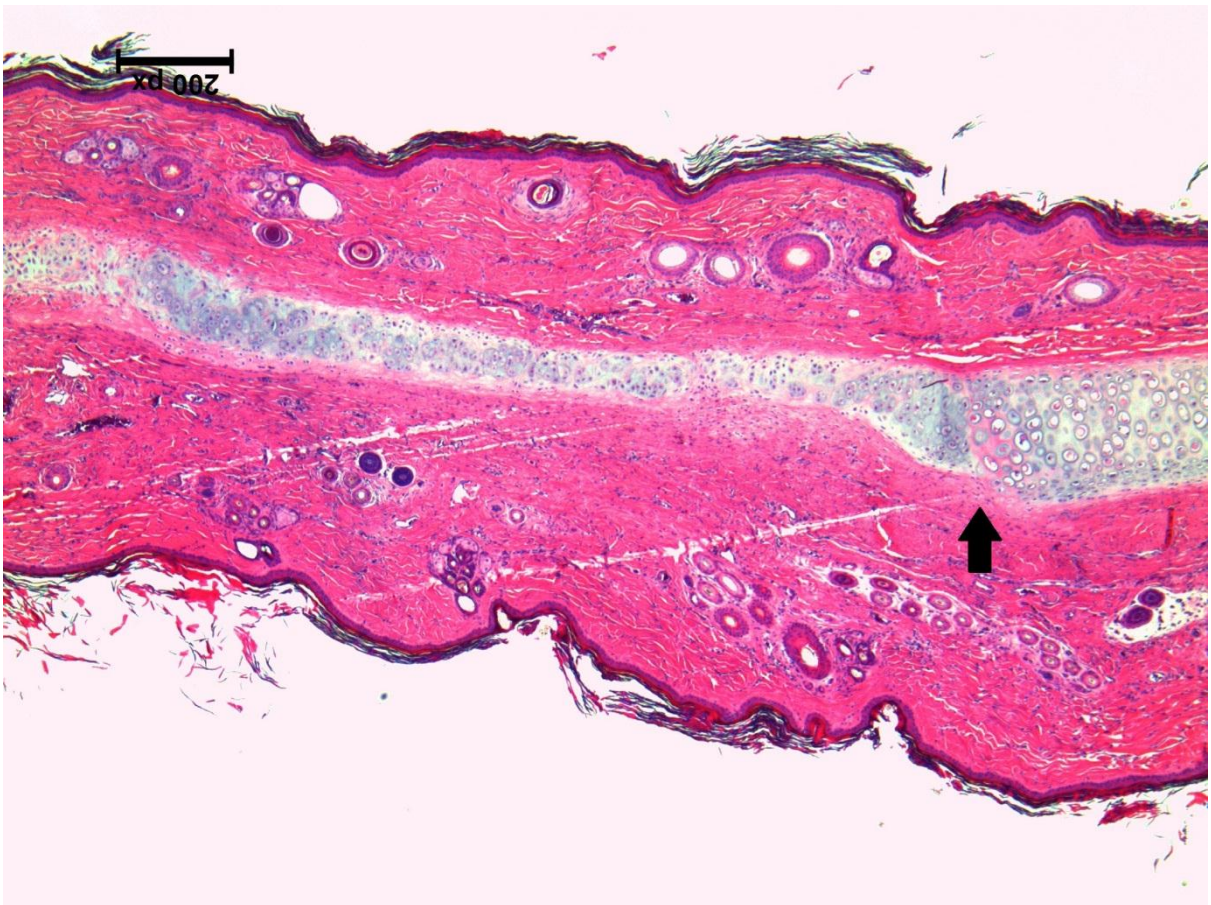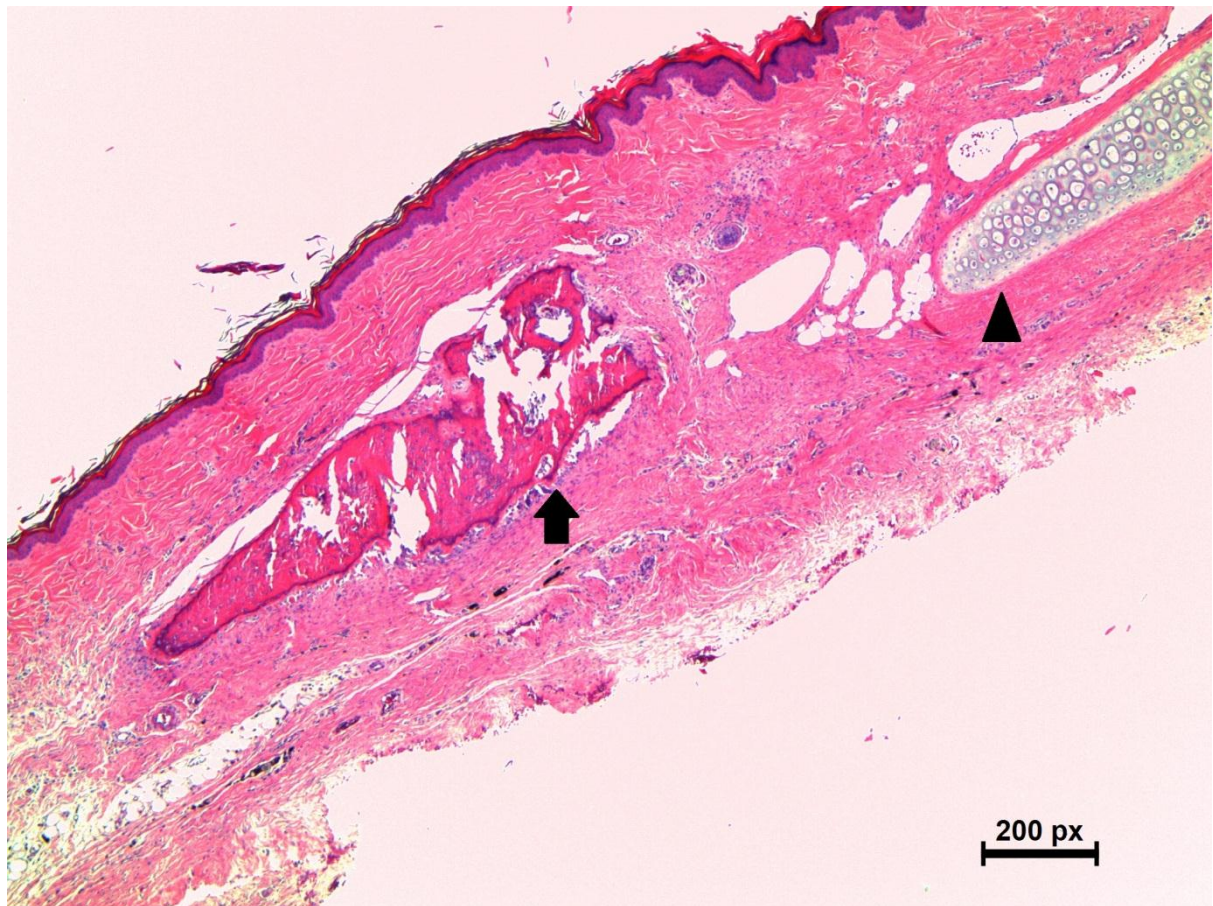
Figure 7. Osteogenesis was observed in group 3 on the anterior side of the periosteal graft, toward which the cambium layer is facing. There was no chondrogenesis in the periosteal graft groups. The arrow indicates neo-bone tissue, and the arrow-head indicates normal cartilage tissue. Hematoxylin and eosin; magnification, x 40.

국문초록

배경

귀 연골은 미용 및 재건성형분야에 걸쳐 연부조직을 보충하거나 지지해주기 위한 목적으로 다양하게 이용되고 있다. 하지만 귀 연골의 양이 제한되어 있으며 많은 양을 채취할 경우 공여부의 변형이 오는 문제점을 유발할 수 있다. 연골재생을 위한 다른 대안을 찾아볼 필요가 있으며, 이번 연구에서는 귀 연골 결손모델을 이용하여 골막의 연골재생능력을 평가하고자 한다.

재료 및 방법

총 12마리의 토끼를 대상으로 실험을 진행하였다. 토끼 귀의 중앙동맥과 변연정맥 사이에 각각 한 부위, 양쪽 귀에서 총 네 부위에서 귀 연골 결손부를 인위적으로 만들었다. 귀 후방부에서 1.2 x 1.2 cm 크기의 피부 피판을 든 후 1.0 x 1.0 cm 의 연골을 연골막을 포함하여 제거하였다. 세 개의 실험군과 한 개의 대조군을 임의로 배정하여, 결손부위를 같은 크기의 연골막, 두개골막, 경골막으로 각각 덮어주었고 대조군에서는 별다른 조치 없이 피부 피판을 덮어주었다. 6주 후에 토끼를 희생시키고 육안과 현미경으로 결과를 분석하였다.

결과

연골막 이식을 시행한 군이 두개골막, 경골막을 이식한 군과 대조군에 비해 통계적으로 유의하게 높은 연골재생능력을 보였다. 반면 골막 이식을 시행한 두 그룹에서는 골 재생이 일어난 것을 관찰할 수 있었다. 두개골막, 경골막을 이식한 그룹의 골재생과 연골 재생에서 통계적으로 유의한 차이는 없었다. 대조군에서 는 섬유조직이 증가된 소견을 보였다.

결론

귀연골 결손 모델에서 골막이식은 연골재생에 적합하지 않았으며 골재생이 일어남을 확인할 수 있었다. 골막은 발생학적인 차이에 관계 없이 동일한 임상적인

역할을 하는 것으로 나타났다. 적절한 귀연골 재생을 위해서는 반드시 연골막이 있어야 함을 알 수 있었다.

주요 단어: 연골생성, 골막, 연골막, 탄성연골, 연골재생