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The Effects of Platelet-Rich Plasma and Platelet-Rich Fibrin on Rabbit Auricular Cartilage Regeneration

Trombositten Zengin Plazma ve Trombositten Zengin Fibrin Yapılarının Tavşan Kulak Kıkırdağı Rejenerasyonu Üzerindeki Etkilerinin Karşılaştırılması

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ABSTRACT Objective: This study aims to examine the impact of platelet-rich fibrin (PRF) and platelet-rich plasma (PRP) on the repair of cartilage tissue. The objective is to discover if these materials effectively boost the healing ability of cartilage tissue. **Material and Methods:** The study consisted of 18 male rabbits from New Zealand, all of whom were adults and white in color. The rabbits were partitioned into three study cohorts, each consisting of six rabbits. The study group was partitioned into subgroups A and B, each consisting of three rabbits. Cartilage of 10×10 mm^2 was surgically removed from the ears of rabbits in all A subgroups. A 1 mm section of cartilage was removed from the outer edge of the excised cartilage to decrease its dimensions. The 8×8 mm cartilage acquired from the initial group was positioned in the exact location from whence it was extracted. Within all B subgroups, a section of cartilage measuring 10×10 mm^2 was extracted from the ears of rabbits. In the initial cohort, a volume of 2 milliliters of PRP was administered onto the mucoperichondrium at the site where the cartilage was excised. In the second group, PRF was applied to the site where the cartilage was excised. No intervention was conducted on the area where cartilage was removed in the third group. A scoring system was used to evaluate degenerative changes in microscopic cartilage analysis. **Results:** There was no significant difference between the groups in terms of cartilage healing. **Conclusion:** PRP and PRF don't improve healing of the cartilage tissue in ear.

Keywords: platelet-rich plasma; platelet-rich fibrin; rabbits; ear cartilage; growth factors

ÖZET Amaç: Bu çalışmanın amacı, trombositten zengin fibrin (TZF) ve trombositten zengin plazmanın (TZP) kıkırdak dokusunun onarımı üzerindeki etkisini incelemek ve bu materyallerin kıkırdak dokusunun iyileşme yeteneğini etkili bir şekilde artırıp artırmadığını araştırmaktır. **Gereç ve Yöntemler:** Bu çalışmaya 18 adet beyaz erkek Yeni Zelanda tavşanı dâhil edilmiştir. Tavşanlar her bir kohortta 6 tavşan olacak şekilde 3 gruba ayrılmıştır. Bu 3 grup da kendi içinde her biri üçer tavşan içerecek şekilde A ve B alt gruplarına ayrılmıştır. Tüm A alt gruplarında tavşanların kulaklarından 10×10 mm^2 kıkırdak eksize edilmiştir. Dışarıya çıkarılan kıkırdağın çevresinden 1 mm'lik kıkırdak eksize edilmiştir. Birinci grupta kalan 8×8 mm^2 kıkırdak TZP ile muamele edildikten sonra çıkarıldığı alana yerleştirilmiştir. İkinci grupta kıkırdak TZF ile muamele edildikten sonra çıkarıldığı alana yerleştirilmiştir. Üçüncü grupta ise kıkırdak herhangi bir muameleye tabi tutulmaksızın çıkarıldığı alana yerleştirilmiştir. Tüm B alt gruplarında tavşanların kulaklarından 10×10 mm2 kıkırdak eksize edilmiştir. Eksize edilen kıkırdak yerine yerleştirilmemiştir. Birinci grupta kıkırdağın çıkarıldığı alanda birbiri ile karşılıklı gelen mukoperikondrium üzerine TZP uygulanmıştır. İkinci grupta kıkırdağın çıkarıldığı alana TZF yerleştirilmiştir. Üçüncü grupta ise kıkırdağın çıkarıldığı alana bir müdahalede bulunulmamıştır. Mikroskobik kıkırdak analizinde dejeneratif değişiklikleri değerlendirmek için bir skorlama sistemi kullanılmıştır. **Bulgular:** Kıkırdak iyileşmesi açısından gruplar arasında anlamlı bir fark bulunmamıştır. **Sonuç:** TZP ve TZF'nin kıkırdak iyileşmesi üzerine etkisi yoktur.

Anahtar Kelimeler: Plateletten zengin plazma; plateletten zengin fibrin; tavşan; kulak kıkırdağı; büyüme faktörleri

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Cartilage is a form of connective tissue that is responsible for distributing loads within joints (known as hyaline cartilage), transferring loads between tendons and bones (known as fibrocartilage), and providing flexible support to exterior structures (known as elastic cartilage). Cartilages consist of chondrocytes and chondroblast cells, which are surrounded by an extracellular matrix made up of proteoglycans and collagen fibrils. However, the amount and structure of the extracellular matrix vary between different forms of cartilage.[1]

The auricle is composed of elastic cartilage and is covered by skin that conforms to the contours of the cartilage. The auricle's elastic cartilage, which is connected to the elastic cartilage of the external auditory meatus, consists of chondrocytes and a matrix that contains tightly woven elastic fibers. The perichondrium is histologically amorphous, but plays a crucial role in providing nourishment to the avascular cartilage through diffusion from a network of blood vessels. At this location, the lower layers of elastic cartilage cells combine with connective tissue. Within this region, there are small arteries and arterioles that are oriented in a plane that is parallel to the surface of the cartilage.[2]

The auricle is located on both sides of the head. Considering its prominent lateral position, it is exposed to blunt trauma quite frequently.[3]

Cartilage is a tissue that is active in metabolism, but it has a slow pace of both creation and destruction due to its low number of chondrocytes. Although these cells are active, their inherent ability to repair is restricted, and even slight damage can result in a gradual decline in functionality. The primary determinant for cartilage healing is the magnitude of the injury.[4]

The majority of studies on cartilage healing have mostly concentrated on damage to articular cartilage. Following superficial damage, chondrocytes in the vicinity of the affected tissue initiate cell division and expedite the production of the extracellular matrix. Typically, the recently produced matrix and dividing chondrocytes are insufficient to fully heal the defect. The root cause of this failure is the persistent disruption of matrix creation and cellular division. Treatment of osteochondral abnormalities varies depending on whether the damage is limited to the matrix or if there is a full rupture of the articular cartilage. The outcomes of healing and remodeling are intricately connected to the integrity of the underlying cartilage tissue. With a full-thickness injury, there is bleeding in the bone tissue beneath the cartilage, resulting in the formation of a hematoma at the injury site. Fibrin is produced in the hematoma and platelets adhere to collagen fibers and release various substances that affect blood vessels and promote the growth of tissues, including transforming growth factor-beta (TGF-β), platelet-derived growth factor (PDGF), bone morphogenic proteins (BMPs), insulin-like growth factors I and II (IGF-I, IGF-II). The growth factors that are involved in bone healing also have a significant impact on the healing process of cartilage.[4]

Platelet-rich plasma (PRP) is a widely recognized platelet concentrate that has been shown to stimulate cell growth, blood vessel formation, and collagen production. It also aids in the healing of cartilage and promotes the growth and production of cartilage cells and matrix. Extensive research has been conducted over the past decade, particularly in orthopedic literature, to examine the impact of PRP on joint cartilages and osteochondral disorders. The role of PRP in the repair of cartilage tissue is believed to be attributed to the presence of growth factors, including PDGF, vascular endothelial growth factor (VEGF), TGF-β, epidermal growth factor (EGF), and IGF-1. In addition to several contentious discoveries, literature demonstrates a general consensus on the beneficial impact of PRP in enhancing cartilage regeneration.[5,6]

Platelet-rich fibrin (PRF) is a platelet concentration derived immediately after centrifugation from autologous blood. There are no further activation processes necessary, and the release of growth factors from PRF can be continued over time.[7] PRF contains a substantial quantity of cytokines derived from platelets and leukocytes, including interleukin (IL)-1α, IL-4, IL-6, and tumor necrosis factor (TNF)-α. It also contains an autologous fibrin matrix that is rich in growth factors such as PDGF-AB, TGF β-1, IGF, EGF, and VEGF.[8]

Auricular cartilage reconstruction is still challaging today. Wang et al. in their *in vitro* study combined biocompatible and nondegradable elastic polyurethane with PRP and obtained higher cell distribution and higher cell density, induced higher level expressions of aggrecan and Type II collagen gene, increased content of newly developed glycosaminoglycans, and produced high-quality cartilaginous tissue, which stimulated chondrocyte proliferation.[9] Based on this idea, we aimed to investigate the effects of PRF and PRP on cartilage tissue repair and determine if these two materials significantly enhance cartilage tissue healing capacity. We also aimed to evaluate the healing capacity of cartilage implanted as autogenous graft.

MATERIAL AND METHODS

All of the procedures were approved by the Kırıkkale University Animal Experimentation Local Ethics Committee (date: February 24, 2011; no: 11/193) and were carried out in accordance with the principles of the Declaration of Helsinki. In the study, eighteen 9-12 months old (3,500-4,500 g) adult white New Zealand male rabbits were used. The rabbits were housed in suitable cages at a temperature of 22±20 C under 12 hours dark and 12 hours light conditions. The nutritional needs of the subjects were met regularly with standard laboratory feed and water. First, the rabbits were divided into 3 study groups with 6 rabbits in each group. Each study group was divided into subgroups A and B with three rabbits in each subgroup. The right and left ears of the rabbits were included separately, and a total of 6 ears were evaluated in each subgroup. PRP was prepared according to Cellular Mask Advanced (RegenACR®, Switzerland) system. For the preparation of PRP, 8 mL of blood was collected from the central auricular artery of rabbits into a 10 mL citrated tube provided in the kit and centrifuged at 3,100 rpm for 9 minutes. For the preparation of PRF, 8 mL of blood was collected from the central auricular artery of rabbits into a 10 mL tube containing no anticoagulant and centrifuged at 3,000 rpm for 10 minutes. After centrifugation, the PRF accumulated in the center of the tube was collected.

In all A subgroups, 10x10 mm^2 cartilage was excised from the ears of rabbits. 1 mm cartilage was excised from the periphery of the excised cartilage to reduce its size. The 8x8 mm cartilage obtained in the first group was placed in the area where it was removed and fixed with sutures. 2 mL of PRP was injected into it. In the second group, the 8x8 mm cartilage obtained was treated with PRF and placed in the area where it was removed and fixed with sutures. In the third group, the cartilage was placed in the area where it was removed without any treatment and fixed with sutures.

In all B subgroups, 10x10 mm^2 cartilage was removed from the ears of rabbits. In the first group, 2 mL of PRP was applied on the mucoperichondrium in the area where the cartilage was removed. In the second group, PRF was placed in the area where the cartilage was removed. In the third group, no intervention was performed on the cartilage removal area. The schematic planning of the study groups was given in Figure 1.

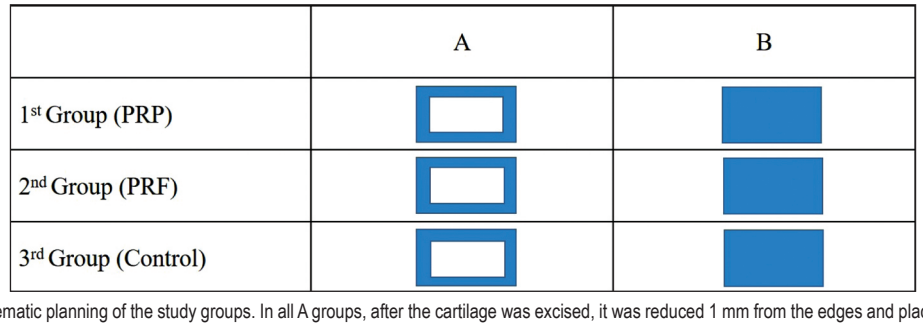

FIGURE 1: The schematic planning of the study groups. In all A groups, after the cartilage was excised, it was reduced 1 mm from the edges and placed as an autologous graft in the same area. In Group B, no autologous grafting was performed, only cartilage excision was performed.
PRP: Platelet-rich plasma; PRF: Platelet-rich fibrin.

Groups 3A and 3B were considered as control groups.

All rabbits were sacrificed at the end of the 3-month follow-up period by administration of lethal dose of pentobarbital.

The removed ear cartilages were stained with Haematoxylin & Eosin. Each specimen was evaluated for mucosal inflammation, mucosal ulceration, cartilage damage, and cartilage regeneration. Parameters were evaluated semiquantitatively:

0=normal intact cartilage,

1=minimal chondrocyte loss,

2=marked loss of chondrocytes in the damaged area, the damaged area is obvious,

3=fibrous and osteoid tissue formation in the damaged area in addition to chondrocyte loss,

4=fibrous cartilage and osteoid tissue-like structures between the cartilage ends in the damaged area,

5=fibrous and osteoid tissue between the cartilage ends, excluding cartilage tissue.

STATISTICAL ANALYSIS

Frequency and percentage distributions of the data were given. Since the data did not fit the normal distribution, the Mann-Whitney U test was used for independent group comparisons. In more than two independent groups, the Kruskal-Wallis H test with correction was used for variables that were not normally distributed.

When examining the difference between the groups, 0.05 was used as the significance level and it was stated that there was a significant difference between the groups if $p<0.05$, and there was no significant difference between the groups if $p>0.05$.

RESULTS

Six rabbits in each group, a total of 18 subjects were followed-up for 3 months postoperatively and the study was completed. All of the subjects tolerated the anesthesia protocol. In the postoperative follow-up, no hematoma or infection requiring intervention at the wound site was found in any of the subjects.

A scoring system was used to evaluate degenerative changes in microscopic cartilage analysis. When Groups 1, 2, and 3 were analyzed, no statistically significant difference was observed between the groups in terms of score values (H=0.425, p=0.808). Although there was no statistically significant difference, it was observed that the score values were lower in the 2nd group (PRF group). Score changes among groups were given in Table 1. When all A groups were compared with each other, no significant difference was obtained between the groups in terms of cartilage healing (H=1.030, p=0.597). When all B groups were compared with each other, no significant difference was obtained between the groups in terms of cartilage healing (H=0.467, p=0.792).

ANALYSES OF THE 1st GROUP (PRP)

There was no statistically significant difference between A/B groups in terms of score values (H=15.5, p=0.670). Although there was no statistically significant difference, it was observed that the score values were lower in Group A. Results were given in Table 2.

ANALYSES OF THE 2nd GROUP (PRF)

There was no statistically significant difference between A/B groups in terms of score values (H=13.5, p=0.445). Although there was no statistically significant difference, it was observed that the score val-

TABLE 1: Score changes among groups.

		Group							Kruskal-Wallis test	
		n	Mean	Median	Minimum	Maximum	SD	Mean rank	H	p value
Score	Group 1	12	3.8	4.0	2.0	5.0	1.2	19.54	0.425	0.808
	Group 2	12	3.4	3.5	2.0	5.0	1.4	17.00		
	Group 3	12	3.7	4.0	2.0	5.0	1.4	18.96		
	Sum	36	3.6	4.0	2.0	5.0	1.3			

SD: Standard deviation.

TABLE 2: In the 1st group (PRP group) distribution of score values between A/B groups.

		Group						Mann-Whitney U test	
		n	Mean	Median	Minimum	Maximum	SD	Mean rank	H	p value
Score	A	6	3.83	4.00	2.00	5.00	0.98	6.08	15.500	0.670
	B	6	3.83	4.50	2.00	5.00	1.47	6.92		
	Sum	12	3.83	4.00	2.00	5.00	1.19			

PRP: Platelet-rich plasma; SD: Standard deviation.

ues were lower in Group A. Distribution of score values between A/B Groups were given in Table 3.

ANALYSES OF THE 3rd GROUP (NO BIOMATERIAL APPLIED ON CARTILAGE)

There was no statistically significant difference between A/B groups in terms of score values (H=9.5, p=0.149). Although there was no statistically significant difference, it was observed that the score values were lower in the A group. Distribution of score values between A/B groups were given in Table 4.

HISTOPATHOLOGICAL FINDINGS

1A (PRP A) group: In this group, it was observed that no new cartilage tissue was formed between the two cartilage pieces, instead acidophilic osteoid tissue was formed in the damaged area. Osteoblasts were observed around the gaps formed in the osteoid tissue. In some preparations, a fibrous cartilage-like structure different from normal fibrous tissue was observed. In some cartilage incision sites, no inflammation was observed and loose connective tissue was observed. Histological findings of Group 1A were shown in Figure 2.

2A (PRF A) group: In this group, osteoid tissue was observed around the damaged cartilage areas. Chondrocytes that shrunk and lost their function were observed in the areas with cartilage damage. Histological findings of Group 2A were shown in Figure 3.

3A (Control) group: In this group, tissue loss was observed in the interposed cartilage piece. Chondrocytes were found to shrink and lose their function, but matrix formation and a limited number of chondrocytes were observed around the interposed cartilage. Histological findings of Group 3A were shown in Figure 4.

1B (PRP B) group: In this group, fibrous cartilage-like structure was observed in the areas where

TABLE 3: In the 2nd group (PRF group) distribution of score values between A/B groups.

		Group						Mann-Whitney U test	
		n	Mean	Median	Minimum	Maximum	SD	Mean rank	H	p value
Score	A	6	3.17	3.00	2.00	5.00	1.33	5.75	13.500	0.445
	B	6	3.67	4.00	2.00	5.00	1.51	7.25		
	Sum	12	3.42	3.50	2.00	5.00	1.38			

PRF: Platelet-rich fibrin; SD: Standard deviation.

TABLE 4: In the 3rd group (No biomaterial applied on cartilage) distribution of score values between A/B groups.

		Group						Mann-Whitney U test	
		n	Mean	Median	Minimum	Maximum	SD	Mean rank	H	p value
Score	A	6	3.17	3.00	2.00	5.00	1.33	5.08	9.500	0.149
	B	6	4.17	5.00	2.00	5.00	1.33	7.92		
	Sum	12	3.67	4.00	2.00	5.00	1.37			

SD: Standard deviation.

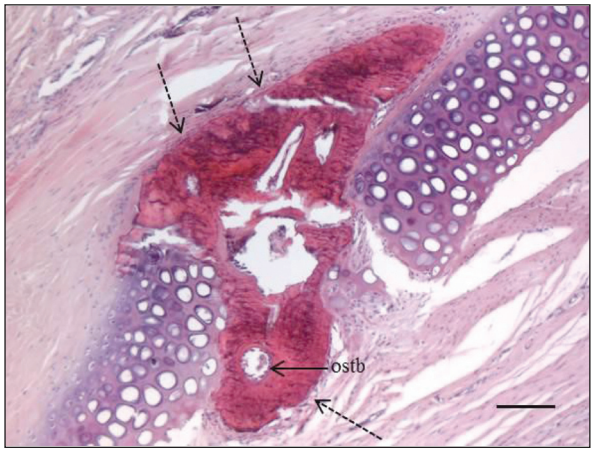

FIGURE 2: Osteoid-like tissue is observed between cartilage fragments. The spaces between the osteoid tissue are lined by a single row of osteoblasts (black arrow). The density of osteoid-like myxomatous tissue is high enough to separate the cartilage ends (dashed arrow), ostb=osteoblast, Haematoxylin & Eosin staining, bar=140 µm.

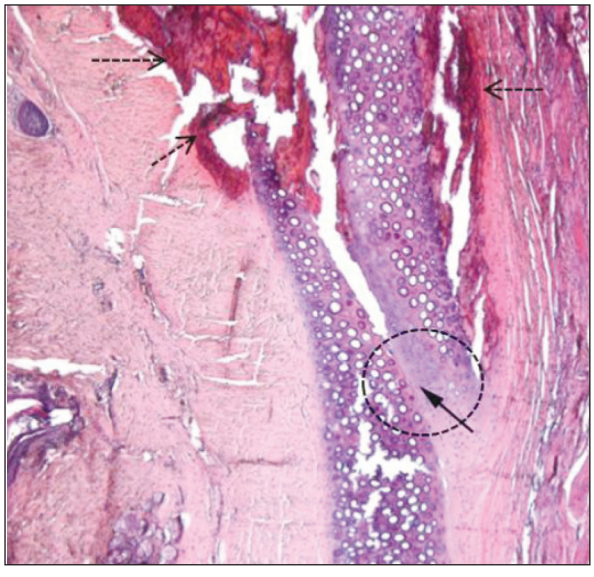

FIGURE 3: Limited cartilage adhesion and attachment areas (arrows) are seen on the cartilage incision line. It is observed that the two tissues are attached to each other and fusion is observed. Osteoid tissue is seen around the cartilage (dashed arrows). Haematoxylin & Eosin staining, bar=140 µm.

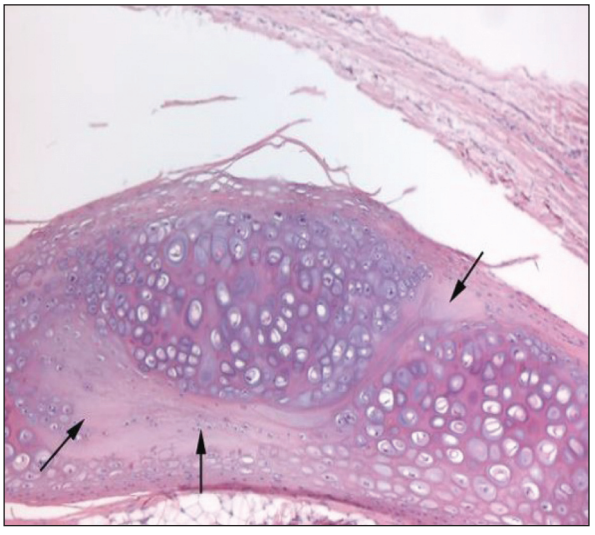

FIGURE 4: Matrix formation and a limited number of chondrocytes are seen between the graft cartilage and the main block cartilage (arrows), Haematoxylin & Eosin staining, bar=140 µm.

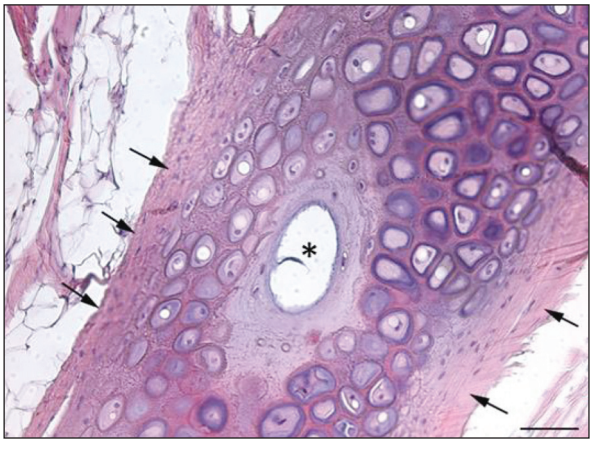

FIGURE 5: In this specimen, enlarged lacunae (*) can be seen in addition to chondrocyte loss in the areas adjacent to the cartilage incision sites. Thickening of the perichondrium around the incision line is observed. Haematoxylin & Eosin staining, bar=140 µm.

the cartilage was removed in some specimens. Loss of chondrocytes was also observed. In some specimens, fibrous tissue was found to fill the space between the cartilages. Histological findings of Group 1B were shown in Figure 5.

2B (PRF B) group: In this group, cartilage cells were observed to shrink and lose their function in the damaged areas of the cartilage.

3B (Control B) group: In this group, acidophilic osteoid tissue and occasional fibrous and fibrocartilage-like tissues were observed to fill the removed cartilage area. Cells resembling chondrocytes rather than osteocytes were observed in the lacunae formed in the osteoid tissue. The most severe reaction was observed in this group. Osteoblasts were observed around the gaps formed in the osteoid tissue. In some sections, chondrocyte loss was observed in the incision lines.

DISCUSSION

Cartilage tissue is used as graft material in many operations such as mentoplasty, enophthalmus correction, cranioplasty, repair of thoracic cage defects and repair of herniations, especially in nasal aesthetic and functional surgery and tympanoplasty with cartilage graft.[10] Various methods are used in the repair of cartilage defects. The use of autogenous, homologous, heterologous cartilage, use of biomaterials, use of perichondrial flaps and grafts, use of secondary vascularised perichondrial flaps are some of them. Autogenous grafts have many advantages such as not causing foreign body reactions, not being allergic and not being carcinogenic.[11] However, damage to the donor tissue and resorption of the cartilage graft over time are the disadvantages of autologous cartilage grafts. The most feared complication is bowing, especially in costal grafts. The fact that the cartilage of the ear is more fragile than the cartilage of the septum, especially in elderly patients, makes shaping difficult.[12]

Unlike many other tissues, anaerobic metabolism is observed in cartilage tissue. Therefore, it withstands hypoxic condition during transplantation better than other tissues.[13] While cartilage grafts are widely used to maintain structural integrity and restore volume, one of the biggest concerns associated with cartilage grafting is the slow reduction in volume and the unexpected rates of viability of these grafts. Bulam et al. examined the effect of PRP on cartilage grafts on rabbit ears and concluded that PRP injected subcutaneously had no effect on graft viability.[6] In our study, histomorphological evaluation showed that all cartilage grafts that were replanted were viable, but no effect of PRP and PRF on catrilage viability was observed. Unlike our study, Beriat et al. reported that IGF-1 had a positive effect on the viability of cartilage grafts.[14]

Göral et al. wrapped the sliced cartilage grafts from rabbit ears with PRF, oxidized regenerated cellulose and fascia and reported that the group wrapped with PRF showed better viability than the group wrapped with oxidized regenerated cellulose. They found no significant difference between the other groups, one of which was the control group.[8] Since there was no significant difference between the control group and the PRF group, it is not possible to say that PRF has a positive effect on graft viability or cartilage healing, just like in our study.

Manafi et al. also prepared 2 types of cartilage grafts from rabbit ear cartilages, one piece and sliced, and applied PRP to these grafts. They found that chondrocyte regeneration was higher in both types of graft groups to which PRP was applied. However, since the comparison in this study was made only by looking at the number of nucleated lacunae, it is controversial to comment on functionality.[15]

Liao et al. prepared autologous grafts sliced from rabbit ear cartilages and applied PRP to the grafts. They found no significant difference in graft viability between the PRP-treated group and the non-treated group.[16] Therefore, it is not possible to say that PRP and PRF have a positive effect on cartilage healing or autologous grafts based on the general literature.

In a study by Verwoerd et al., it was shown that the perichondrium develops high amounts of cartilage with different morphology and growth potential from the original septal cartilage in response to trauma.[17] In a study by Haberal Can et al., it was found that the response of the perichondrium to trauma was not only new cartilage formation but also ossification.[18] In our study, osification as well as fibrous cartilage development was observed in response to trauma in histomorphological evaluation. Haberal Can et al. argued that working under the perichondrium during surgical intervention may prevent this bone formation, but our study has shown that even if the cartilage tissue is intervened by working under the perichondrium, high amounts of bone tissue formation can be observed at the cartilage damage sites. Nevertheless, before reaching this conclusion, it should be kept in mind that even minimal perichondrium damage may occur during surgery.[18]

Ossification in the ear cartilage was first demonstrated histopathologically by the Polish anatomist Bochdalek in 1866. Later in 1899, Wassmund demonstrated ossification of the ear cartilage on plain radiography in a patient.[19] There are few cases of ossification in the ear cartilage have been shown. In

these cases, the most common cause of ossification was cold-related trauma.

Studies have reported that growth factors such as PDGF, TGF-β, IGF, and EGF are secreted from α-granules of platelets. These growth factors increase collagen synthesis. It is thought that the increase in collagen synthesis increases resistance in soft tissue and initiates callus formation in bone tissue.[20-22] Growth factors, especially TGF-β, basic fibroblast growth factor, and BMP have been proven to play an active role in cartilage healing.[23]

In a study by Petrera et al., tissue culture was prepared with chondrocytes isolated from metacarpophalangeal joints of cattle. Tissue cultures were supported with fetal bovine serum and PRP. In the comparison of these two tissue cultures, it was observed that more cartilage tissue was obtained in the cultures supported with PRP.[24] In our study, no significant difference was found between the PRP group and the control group and it was concluded that PRP had no positive effect on cartilage healing.

Kazemi et al. created defects in the femoral condyles of dogs in a study. They applied PRF on these defects in one group and left the other group untreated. At the end of the study, it was observed that the healing was significantly higher in the PRF group.[25]

In our study, unlike the above studies, neither PRP nor PRF had a positive effect on cartilage healing.

CONCLUSION

In cartilage healing, scar tissue consisting of compact connective tissue instead of new cartilage tissue is seen in diffusely damaged areas and rarely in small areas. Therefore, minimal resection of cartilage tissue should be performed during surgery to reduce scar tissue. Since PRP does not seem to have any effect on cartilage tissue healing, its application will not be beneficial. PRF does not seem to have any effect on cartilage tissue healing, so its application will not be beneficial.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ceren Karaçaylı, Mustafa Kazkayası;* ***Design:*** *Ceren Karaçaylı, Mustafa Kazkayası;* ***Control/Supervision:*** *Ceren Karaçaylı, Mustafa Kazkayası, Rahmi Kılıç;* ***Data Collection and/or Processing:*** *Ceren Karaçaylı, Mustafa Kazkayası, Siyami Karahan;* ***Analysis and/or Interpretation:*** *Ceren Karaçaylı, Siyami Karahan;* ***Literature Review:*** *Ceren Karaçaylı, Mustafa Kazkayası;* ***Writing the Article:*** *Ceren Karaçaylı;* ***Critical Review:*** *Ceren Karaçaylı, Rahmi Kılıç.*

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