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THE EFFECT OF PLATELET RICH PLASMA IN BONE TUNNEL TENDON-BONE HEALING

KEMIK TÜNEL İÇI TENDON-KEMIK IYILEŞMESINDE TROMBOSITTEN ZENGIN PLAZMANIN ETKISI

MESUT ULUÖZ[1], SİNAN KARAOĞLU[2], CEVAT YAZICI[3], ÖZLEM CANÖZ[4]

[1] University of Health Sciences, Adana Faculty of Medicine, Department of Orthopedics and Traumatology, Adana, Turkey
[2] Acıbadem Kayseri Hospital, Department of Orthopedics and Traumatology, Kayseri, Turkey
[3] Erciyes University Faculty of Medicine, Department of Medical Biochemistry, Kayseri, Turkey
[4] Erciyes University Faculty of Medicine, Department of Pathology, Kayseri, Turkey

ABSTRACT

Introduction: In our study, we aimed to evaluate the effect of platelet-rich plasma (PRP) obtained from autologous blood on rabbit intra-tunnel tendon bone healing using biomechanical and histologic parameters.

Methods: The hind legs of 31 New Zealand albino rabbits were used in the study. After the extensor digitorum longus tendon of both hind legs was removed from the proximal attachment site, the same leg was placed in a bone tunnel opened in the tibia. In the P "platelet" group, PRP was injected into the tunneled part of the tendon, while in the K "control" group, the tunneled part of the tendon. In addition, each group was divided into two groups "six and twelve weeks old". After sacrification, the bone-tendon junction, which was removed together with the tibia and tendon, was pulled in a pulling device at a speed of 5mm/second. The machine recorded the maximal endurance force (ULF). Using these values, stiffness and energy absorption were calculated. Three specimens each from the sixth and twelfth groups were examined histologically.

Results: At 6.-12. weeks, all biomechanical parameters were higher than in the control group and the increase was significant in all three parameters at twelfth week and in two of the parameters (ULF, stiffness) at sixth week (p<0.05)

Conclusions: As a conclusion of the study, it was determined by biomechanical and histological examinations that PRP application positively enhanced healing in the intra-tunnel healing model created in the New Zealand albino rabbit. PRP application can be successfully used to accelerate tendon-bone healing.

Keywords: Anterior cruciate ligament, Platelet-rich plasma, Tendons

ÖZET

Giriş: Çalışmamızda otolog kandan elde edilen trombositten zengin plazmanın (TZP) tavşan tünel içi tendon kemik iyileşmesine etkisini, biyomekanik ve histolojik parametreler kullanılarak değerlendirmeyi amaçladık.

Yöntemler: Çalışmada 31 adet Yeni Zelanda tipi albino tavşanın arka bacakları kullanıldı. Her iki arka bacağın ekstensör digitorum longus tendonu proksimal yapışma yerinden alındıktan sonra, aynı bacak tibiada açılan kemik tünel içine yerleştirildi. P "trombosit" grubunda tendonun tünelde kalacak kısmına üç ayrı yerden insülin enjektörü ile TZP enjekte edildi, K "Kontrol" grubuna tendonun tünelde kalacak kısmına boş insülin enjektörüyle üç defa girildi. Ayrıca her grup kendi içerisinde "altı ve oniki haftalık olarak" ikiye ayrıldı. Sakrifikasyon işleminden sonra tibia ve tendonla birlikte çıkartılan kemik-tendon bileşkesi çekme cihazında 5mm/saniye hızında çekildi. Çekme işlemi, tendon, kemik-tendon bileşkesinden ayrılıncaya veya tendon kopuncaya kadar sürdürüldü. İşlem sırasında maksimum dayanma kuvveti (ULF) ve kopana kadar geçen süredeki uzama miktarı, makine tarafından kaydedildi. Bu değerler kullanılarak stiffness (katılık) ve enerji absorbsiyonu hesaplandı. Altıncı ve onikinci gruplardan üçer adet denek histolojik olarak incelendi.

Bulgular: Altıncı ve onikinci haftalarda biyomekanik parametrelerin hepsi kontrol grubuna göre yüksek bulundu ve onikinci haftadaki üç parametrenin tamamında, altıncı haftadaki üç parametrenin ikisinde (ULF, katılık) yükseklik anlamlıydı. (p<0,05)

Sonuç: Çalışma sonucunda Yeni Zelanda tipi albino tavşanda oluşturulan tünel içi iyileşme modelinde TZP uygulamasının, iyileşmeyi olumlu şekilde arttırdığı biyomekanik ve histolojik incelemelerle belirlendi. TZP uygulaması, tendon-kemik iyileşmesini hızlandırmak için başarıyla kullanılabilir.

Anahtar Kelimeler: Ön çapraz bağ, Trombositten zengin plazma, Tendon

INTRODUCTION

The injury of anterior cruciate ligament rupture (ACLR) is a well-known knee injury that can occur when the knee joint is stressed accounting for around 80% of all sports-related knee injuries (1,2). The treatment often requires reconstruction surgery in which autograft tendons are widely used. Among the alternatives, bone-patellar tendon-bone (BTB) and four-strand hamstring tendon (HT) are the most commonly preferred ones. One of the advantages of HT which makes the technique a more favorable choice, is having lower rates of donor site morbidity compared to BTB

Corresponding Author: Mesut Uluöz, Kışla Mah. Seyhanpark Evleri B blok Kat:8 No:16 Yüreğir/ADANA
E-mail: mesutuluoz@hotmail.com
ORCID: 0000-0003-0319-3832

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cases. However, the increased healing duration of the tendon to the bone inside the tunnel, which prolongs the rehabilitation period is a significant downside of the method (3,4). Aiming to speed up the healing process various materials and methods have been used including bone morphogenetic protein-2 (BMP-2), bone morphogenetic protein-2 gene transfer, bone morphogenetic protein-7 (BMP-7), bone growth factor mixture (BGF), periosteum, bone marrow stromal cells, bone marrow, and periosteum and a decrease in the duration was observed. The ease of application, cost, and availability have caused some of these products and methods to be less preferred, and recently the use of growth factors found in platelets has become more frequent (5-14). Platelet-rich plasma (PRP), which involves abundant amounts of growth factors in a concentration of platelets exceeding 1.0 × 106 platelets/μl is shown to improve bone tissue restoration and is presently used in ACLR reported in numerous studies with inconsistent results (15-16). The aim of this study was to demonstrate the effectiveness of local PRP application on tendon histology and mechanical properties in procedures where in-tunnel bone tendon healing is expected, such as ACL surgery, by injecting PRP into the surgical field.

METHODS

Ethics

The study was approved by the Ethics Committee of the Faculty of Medicine of the Erciyes University (12/11/08 No: 08/62) and the study permit was obtained from the Experimental and Clinical Research Center of Erciyes University. A total of 31 female, adult, New Zealand albino rabbits were provided from the Experimental and Clinical Research Center of Hakan Cetinsaya Experimental and Clinical Research Center. The study was conducted in accordance with the principles of the Care and Treatment Guidelines. (www.nap.edu/catalog/5140.html).

Study Design and Subjects

The number of rabbits in this animal experiment study was determined by “sample size analysis” and 31 female rabbits were selected for the study. Since the female of these rabbits is larger, female rabbits are preferred for surgery. Rabbits were kept in rooms with a temperature of 24 Cº and a humidity of 45%. They were fed with 150 g of artificial feed and 100 ml of water daily. The rabbits used in the study were randomly divided into two groups. Group A: The group sacrificed 6 weeks after the surgical procedure. Group B: The group sacrificed 12 weeks after the surgical procedure. The hind legs of the subjects were used in the study. Group A consisted of 15 and Group B consisted of 16 subjects. Three rabbits from each group were randomly separated for histological study, while the remaining were planned to undergo biomechanical tests.

PRP Preparation

The ear for blood collection was shaved and wiped with xylol. 10 cc of blood was collected in 10 cc EDTA tubes by using a 24 G intraket. As a technique for obtaining platelet-rich plasma, Yokota described was used (17). The blood taken from the rabbit ear vein was first centrifuged for 10 minutes at 1500 rpm and the plasma remaining on top was taken with the buffy coat and generally separated from the red blood cells. Then the plasma was spun at 2000 rpm for 10 minutes and the platelet-poor part on top was separated. The plasma remaining at the bottom was spun again at 2500 rpm and the lowest part of 1/3 was accepted as PRP, which corresponded to approximately 1.5 cc. While the platelet concentration rate in PRP was 3.66±1.29 times higher than the whole blood platelet concentration rate before the intervention, a 3.93±0.95-fold increase was achieved in the group planned for sacrifice at the end of the 12th week. All these procedures were performed under sterile conditions.

Surgical Technique

All rabbits were fasted for four hours before the operation. Xysilazine HCL (Rompun®-Bayer Pharmaceuticals San. Turkey) and 10 mg/kg I.M (intramuscular), 40 mg/kg I.M ketamine (Ketalar®-Eczacıbaşı İlaç San. Turkey) was performed for induction of general anesthesia. This procedure provided anesthesia for about 30 minutes. The operations were performed by two orthopedicians under sterile conditions. After general anesthesia, a tunnel was opened manually using a K wire in the tibia metaphysis and the extensor digitorum longus tendon was prepared. Into the left knee using an insulin syringe PRP was injected from three different points aiming to provide that two-thirds of the PRP was preserved inside the tunnel. Then, the tendon was passed through the tunnel and sutured to the surrounding soft tissue medially; the remaining part of the PRP was given inside the tunnel. In order to ensure that the tendon was exposed to the same trauma in the right knee, the part that would remain inside the tunnel was entered in the same way with an empty insulin syringe from the corresponding symmetrical three marks. The tendon was passed through the tunnel and sutured to the surrounding soft tissues medially. No restraint was applied to the animals after the operations and the animals were allowed to move freely in the cage. The rabbits in group A were sacrificed at the end of the 6th week and the ones in group B at the end of the 12th week. After the sacrifice procedure, the bone was removed in making sure that the tendon-bone junction was not damaged. Three pairs of specimens were separated from each group for histology. The remaining materials were placed in refrigerators at -20 Cº to be stored until the biomechanical measurement day (18). The specimens separated for biomechanical tests were labeled as P and K, with P indicating the PRP-injected tissue and K for the control sample. The labels were numbered 6 and 12 indicating the time the sample was obtained. For example, P6 belongs to the tissue of the PRP-injected subject which was sacrificed at the end of the 6th week, and K12 indicates the sample of the control subject sacrificed at the end of the 12th week.

Biomechanical measurements

In the study, the Instron® 4411 (Instron Corp.®-England) tensile machine was used. The tensile machine laboratory temperature was fixed at 20 ºC and the humidity rate was fixed at 56%. The specimens, which were previously removed from the cooler and thawed at room temperature, were placed in the tensile device. The preload of the device was set to one Newton (N). Ten cycles of stretching and relaxing up to one N were performed and "preconditioning" was accepted as achieved, the tendon-bone complex was stretched at a speed of five mm/s until the breaking point. The ultimate load failure (ULF), energy absorption, and stiffness values formed during the process were recorded in a digital environment.

Histological examinations

The blocks to be histologically examined on a rotary microtome (Microm, HM 360, Germany) 5-7 µm sections were taken. Sections stained with Hematoxylin-Eosin, Mallory Trichrome and alcian blue method; generalized bone and tendon morphology, structure of the tendon-bone junction and tendon healing process evaluated. Histologic examinations were performed under a microscope at 40x magnification.

Statistical analysis

Statistical calculations were performed using the SPSS package program. The variables used in the study were examined using the Kolmogorov-Smirnov distribution test which showed that the variables were normally distributed. The "unpaired student's t" test (a test of significance between two means) was used in the comparison between the samples obtained at the end of the 6th and the 12th week. The mean and standard deviation were used in presenting the continuous variables. The "p" value less than 0.05 was accepted as significant.

RESULTS

A total of 31 rabbits were divided into four groups. Group A included 15 subjects treated with PRP and were sacrificed at the end of the 6th week and Group B with 16 control cases sacrificed at the end of the 12th week.

Biomechanical analysis results

The analysis of the ULF, hardness, and energy absorption values of the subjects that were treated using PRP showed that although all recorded values were higher in the P12 group, a statistically significant difference occurred for hardness.

The subgroup comparison of the subjects sacrificed at the end of the 6th week (Group A) showed a similar presentation of higher recorded values for all three parameters of the rabbits treated using PRP (P6). In detail, in comparison to K6, P6 subjects were 39% more successful in ULF, 66% more successful in hardness, and 34% more successful in energy absorption. The statistical analysis findings, on the other hand, showed that except for energy absorption results, the ULF and hardness scores were significantly different (Table 1).

Table 1. Analysis results of parameters of group A (subjects sacrificed at the end of the 6th week)

	Right (Control)	Left (PRP)	t	p
ULF (N)	31,69± 7,66	44,13± 7,76	3,86	0,001
Energy Absorption	10,35 ± 6,46	13,85 ±4,92	1,48	0,151
Hardness (N/mm)	8,07± 3,84	13,29 ± 2,92	3,74	0,001

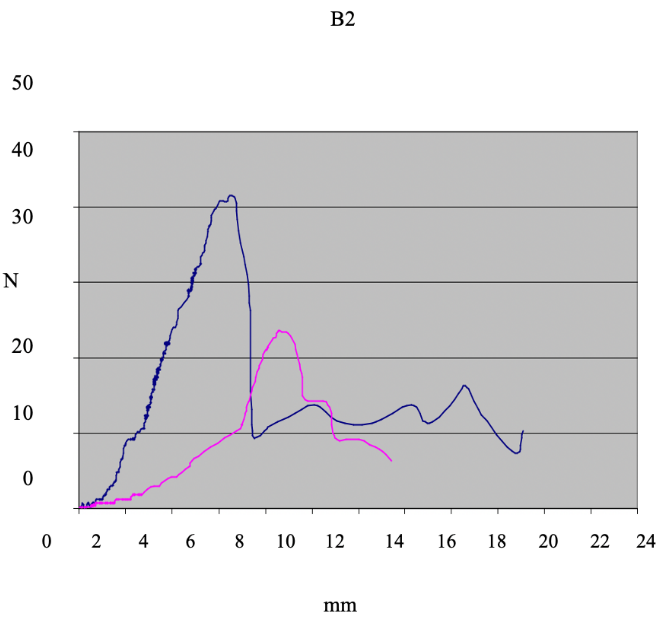
The rabbits treated with PRP of Group B presented similar but increasingly higher values. P12 subjects were 84% more successful in ULF, 149% more successful in hardness, and 101% more successful in energy absorption. The difference in the findings was statistically significant for all three parameters (Table 2). The effectiveness of PRP is seen in the force-extension curve of the second rabbit which was sacrificed at the end of the 12th week. (Graph 1).

Table 2. Analysis results of parameters of group B (subjects sacrificed at the end of the 12th week)

	Right (Control)	Left (PRP)	t	p
ULF (N)	28,89± 17,14	55,30± 0,97	3,38	0,002
Energy Absorption	6,93 ± 5,08	14,49 ± 4,80	3,89	0,001
Hardness (N/mm)	8,13± 4,67	20,17 ± 7,62	4,85	0,000

Histological Examination Results

In the histological assessment of the Group A subjects, there was a significant increase in vascularization in P6, while irregular fibrous tissues were observed in K6. The thickness of the fibrovascular connective tissue at the bone-



Graph 1. Force-extension curve of subject 2 (Group B, blue: P12, pink: K12)

tendon interface was less organized in the control cases than in the PRP. In both groups, collagen fibrils were mostly arranged parallel to the tendon-bone axis, but especially in the PRP group, the presence of perpendicular ones (similar to Sharpey fibers) was noted. In the histological assessment of the Group B rabbits, the cartilage tissue in the transition area on the right side was narrow and irregular, however, there was wide and regular cartilage tissue in the tendon-bone transition area in the PRP group. At the end of the 12th week, it was observed that the bone growth into the tendon and the restructuring process in the PRP group developed faster than in the control group, and a thinner intervening connective tissue was observed. In the PRP group, it was determined that the bone trabeculae were better integrated with the tendon. Besides, the cartilage layer connected to the bone tissue by the transition zone and the collagen fibrils perpendicular to them were clearly noticeable. (Figure 1)

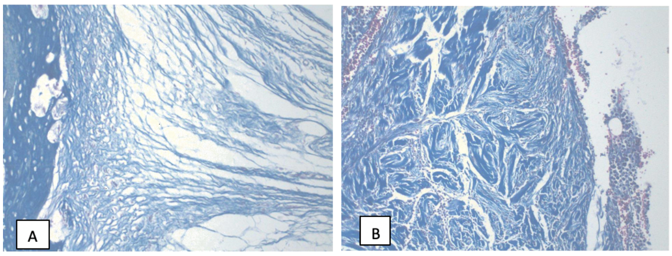


Figure 1. 12th week light microscope alcian blue staining images, A: PRP group B: Control group

DISCUSSION

This experimental study, which tested tendon-bone healing biomechanically and histologically, found significant differences in parameters in both areas.

After reconstruction surgeries using hamstring or patellar tendons, the tunnel area is the area where the graft strength is weakest until complete bone-tendon or bone-bone healing occurs within the bone tunnel. Therefore, its movement is partially restricted until healing is achieved. Rehabilitation procedures should be started as early as possible to prevent complications due to long-term immobilization such as muscle atrophy, joint contractures, and reflex sympathetic dystrophy, to regain joint range of motion and to ensure early return to daily activation. Such goals may be possible with quality and rapid bone-bone or bone-tendon healing. Tunnel healing is the osteointegration of the tendon to the bone, basically a tenodesis phenomenon. It has been shown that the use of PRP in rotator cuff repair has positive clinical results (19). Our study also helps provide a histological and biomechanical basis for such studies. Additionally, our study may not be interpreted for cases including only the anterior cruciate ligament, but also for cases where the basic principle is based on the tenodesis, including but not limited to tendon transfers or tendon repairs that are torn from the junction. Based on the results of our findings, the recovery period can be shortened and rehabilitation can be started earlier in surgeries require tendon-bone healing.

In recent years, the use of hamstring tendons as autografts in anterior cruciate ligament reconstruction surgery has increased. Many methods have been introduced using this graft to support the bone-tendon healing process, involving periosteum wrapping of the tendon-bone junction; application of purified bone marrow, BMP-2, BMP-7, bone growth factor, and BMP- 2 gene transfer (5-7,10,12). The literature focused on the positive effects of growth factors on healing have clearly demonstrated the improved effects. However, despite all these promising effects, the supply of growth factors is difficult and the economic cost is high. Thus, the use of growth factors is limited. In fact, these factors play a partial role in the wound-healing cascade and affect each other in harmony, increasing and decreasing at different times in tissue healing. In this context, instead of giving these factors one by one, using platelets that contain all these factors may mimic the natural process and increase effectiveness.

The factors contained in platelet-rich plasma have positive effects on chemotaxis, cell proliferation, angiogenesis, extracellular matrix formation, and remodeling (20). A study conducted by Rozman (21) in 2007 supports most of these effects, but considering that remodeling begins in the 26th week, it was suggested that growth factors cannot remain active for such a long time and therefore cannot play an active role in remodeling. There are also examples of research conducted at more frequent intervals (2, 4, 8, 12, and 24 weeks), such as the study by Rodeo et al. (22), but similar studies in the literature show that significant biomechanical and histological changes in the bone-tendon healing process occur between the 6th and 8th weeks postoperatively and that there are no sharp changes in healing after this period (23).

Anderson et al. (24) applied bone growth factor to the bone-tendon junction in a rabbit model to accelerate bone-tendon healing and reported statistically significant ($p<0.001$) 85% higher average ULF values in the first eight weeks compared to the control group. In our study, the ULF values at the end of the 6th and 12th weeks were significantly higher in the PRP group

than in the control cases. The findings indicate that a 39% higher average ULF value was reached in the sixth week and 84% higher at the end of the 12th week. However, it is important to note that the parameters of stiffness and energy absorption were not assessed in the study by Anderson et al. The stiffness and energy absorption levels of a tendon are as important as its strength at the moment of rupture (ULF). Tendons exposed to a force undergo an elongation process, and the ratio of this force to the amount of elongation in the tendon is called stiffness and its unit is N/mm. Studies conducted focusing on the matter report that repaired tendon stiffness values do not reach normal tendon values (25). Therefore, the higher the study hardness value, the closer it is to normal it is expected to be. In our study, hardness was significantly higher in the PRP group than in the control group at the end of the 6th and the 12th weeks.

The energy absorption value is the amount of energy absorbed by the tendon-bone complex until rupture, in other words, the result value of the parameter will be parallelly increased to the higher amount of force the tendon can handle. In our study, energy absorption was significantly higher in the PRP group than in the control group at the end of the 6th and the 12th weeks. In the study conducted by Lyras et al. (26) in 2009 on the effect of PRP in patellar tendon ruptures, ULF, stiffness, and energy absorption were assessed and on the 14th day, a high average of 72.2% in ULF, 53.1% in stiffness, and 39.1% in energy absorption was observed. In a study conducted with quadriceps tendon graft, the need for painkillers, the time to use crutches, and the time to reach the target joint range were found to be reduced in the PRP group. Such effects may also contribute to early inflammation (27).

Histologically, an irregular, thin cartilage formation was observed at the tendon-bone transition in the control group, while a regular and thicker cartilage layer was encountered in the PRP group. Rodeo et al. (22) examined bone-tendon healing in dogs histologically and biomechanically and concluded that the endurance of the bone-tendon junction is increased in parallel to the formation of new bone tissue, and the maturation and mineralization of the recovery tissue. Similar results were observed in the study conducted by Arnoczky et al. (23). In both studies, the bone-tendon junction that was subsequently formed differed from the natural structure histologically. Histologically the natural structure is an ideal attachment form with its four-layered transition feature in addition to important biomechanical properties. In the structure, since the tension in the tendon is distributed equally to the entire attachment area through the fibrous cartilage, excessive load is prevented from being applied to a single region increasing the total durability of the entire junction. The literature lacks studies describing accurate formation of the natural structure that is formed in a short time along the entire tunnel histologically. In the study conducted by Shino et al. (28) in dogs, in addition to early findings regarding healing of the tissue, a four-layered natural structure was partially observed between 30 and 52 weeks after implantation. In our study, the regular, thick cartilage tissue formed between collagen fibers and bone at the end of the 12th week in the PRP group presented similar properties to the four-layered transition in the natural tendon-bone junction. The finding is also parallel to the results with significant differences in the biomechanical study, since a narrower, irregular cartilage layer was observed in the control group, with predominantly fibrous tissue was observed in the recovering tissue. Although the regular cartilage tissue seen in the PRP group in our study was not encountered in some studies conducted using a similar model with using periosteum, successful results have been reported (7,8).

Limitations

The structure we subjected to biomechanical testing is not a homogeneous tissue; it is a complex consisting of tendon, tendon-bone junction, and bone parts. In our study, the complex was evaluated as a whole without isolating any parts. In other words, the complex's structural tensile properties were examined and the properties of the isolated healing tissue (material properties) as a homogeneous tissue were not assessed. In order to analyze the material properties much more sophisticated laboratory devices with high resolution and speed cameras and marking systems are required. Since our study is an extra-articular study model, it may be interpreted to a wide range of surgical models based on tenodesis.

Another limitation of our study is that the surgical field was not in contact with joint fluid and histologic scoring could not be performed.

CONCLUSION

In surgical procedures based on in-tunnel tendon healing, such as anterior cruciate ligament or tendon transfer, local application of PRP can contribute to graft integration and durability both biomechanically and histologically. The application of PRP can improve surgical success by allowing early, aggressive rehabilitation.

Ethics Committee Approval: Ethics approval was obtained from Faculty of Medicine of the Erciyes University.

Informed Consent: No need.

Authorship Contributions: Idea/Concept: SK, Design: SK,MU, Supervision: SK, MU, Data Collection or Processing: MU,SK,CY, Analysis or Interpretation: MU,CY, ÖC, Literature Search: SK, MU, Writing: SK,MU, Critical Review: SK, MU, CY, ÖC, Fundings: -, Materials: SK, MU.

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