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Comparative Histopathological Evaluation of Platelet-Rich Plasma Injection and Autologous Blood Injection to Temporomandibular Joint: A Pilot Experimental Study

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Abstract

Background: Chronic recurrent TMJ dislocation adversely affects patients' lives. Various surgical and non-surgical methods have been used for treating recurrent TMJ dislocation. Some non-surgical methods include physiotherapy, occlusal splint, and avoidance of activities causing large-mouth- opening, and autologous blood or Platelet- Rich Plasma- injection to the Temporomandibular Joint (TMJ).

Objectives: This experimental study aimed to compare the histopathological evaluation of Platelet-Rich Plasma (PRP) injection and autologous blood (AB) injection to the Temporomandibular Joint.

Methods: This experimental study was conducted in an animal lab affiliated to the Gazi University of Medical Sciences, Ankara, Turkey, in 2016. Bilateral TMJs from 12 young New Zealand White rabbits were assessed in the study. The animals were divided into two experimental groups with equal numbers (n = 6) including PRP and AB injection groups. For the experimental groups, 1 mL was injected into the upper joint space and 0.5 mL to the pericapsular tissue. The injections were administered unilaterally. Moreover, 1 mL of isotonic saline was injected into the contralateral sides of TMJ upper joint space and 0.5 mL into the pericapsular tissue to serve as controls for both groups. One month after the experimentation, the animals were sacrificed, and histological analyses were performed for fibrosis and tissue reactions.

Results: Collagen fibers and adipose tissue production in the retrodiscal ligament were more in the PRP group than in the AB group. According to the fibrosis classification, similar fibrotic changes were observed in the AB and PRP-injected tissue samples compared to controls. No cartilage degeneration was seen in either of the two groups.

Conclusions: Considering the limitations of this study, PRP injection may be an alternative to AB injection for treating chronic mandibular dislocation. Clinicians could safely use the PRP injection technique to increase the success rate of the treatment.

Keywords: Adipose Tissue, Autologous Blood, Chronic, Collagen, Joint Dislocations, Ligaments, Mandible, Occlusal Splints, Platelet-Rich Plasma, Rabbits, Temporomandibular Joint

1. Background

Hypermobility or dislocation of temporomandibular joint (TMJ) is a non-self-limiting displacement of the condyle outside of its physiological position, between the glenoid fossa and the posterior part of the articular eminence (1). Although various classification schemes have been reported, the most common classification divides the dislocations into acute, chronic, and chronic recurrent dislocations, as described by Adeyeke et al. and Rowe and Killey (2, 3). Acute dislocations are often self-limiting, without any adverse long-term sequelae or recurrent problems. They may lead to a predilection toward chronic dislocation or chronic recurrent dislocation (1). Chronic dislocations include acute dislocations that are not self-limiting but progressive without treatment, as well as, chronic recurrent dislocations in which individuals may experience multiple, recurrent dislocations when doing daily activities. Chronic recurrent dislocations may create a signifi-

cant interference in the patient's daily life and can be distressing physically and emotionally (1).

The etiologic factors of chronic recurrent TMJ dislocation include the laxity of TMJ ligaments, weakness of the TMJ capsule, unusual morphology and size of the eminence, muscle hyperactivity or spasm, trauma, and abnormal chewing movements that do not allow the condyle to translate back into the normal position (4). Other etiologic factors of TMJ dislocation include the use of antiemetics and phenothiazine exerting extrapyramidal effects, systemic diseases such as rheumatoid arthritis, and psychogenic/neurological disorders associated with TMJ dislocation (5, 6).

Chronic recurrent TMJ dislocation adversely affects the patients' lives due to the painful environment it creates and its interference with the health-related quality of life (7). Recurrent TMJ dislocation may cause internal derangement by injuring the disk, the capsule, and the ligaments (8, 9).

Various surgical and nonsurgical methods have been used for treating recurrent TMJ dislocation. They include physiotherapy, occlusal splint, and avoidance of activities causing large-mouth-opening (4, 10, 11). Some conservative techniques have been used for treating chronic recurrent dislocations, such as the injection of sclerosing agents and autologous blood (AB) into the pericapsular tissues of the TMJ and botulinum toxin to the muscles of mastication (12). Nonsurgical methods are not always successful. Therefore, surgical methods such as capsular plication reduction, augmentation of articular eminence, temporal tendon scarification, lateral pterygoid myotomy, and condylectomy may be used for treating chronic TMJ dislocation (4).

Although recurrent TMJ dislocation was successfully treated with an AB injection into the TMJ by some clinicians, this technique did not gain popularity (13, 14) until recently that it was re-established by Machon et al. and others (4, 15, 16). Gulses et al. reported that the injection of AB could develop fibrotic changes in the capsule and retrodiscal ligament of TMJ in the pig model (17).

Platelet-rich plasma (PRP) is the product of whole-blood centrifugation, which contains more concentrated platelets than the baseline whole-blood values. Platelets are the cellular components of plasma having several growth factors (18). These growth factors strengthen tendons and ligaments by stimulating fibroblast proliferation and collagen synthesis. We hypothesize that PRP injection to rabbit TMJ induces more collagen synthesis than AB injection does.

2. Objectives

The purpose of this study was to conduct a comparative histopathological evaluation to determine whether the injection of PRP induces more fibrotic changes than AB injection does.

3. Methods

The study was approved by the Animal Experimentation Ethics Committee of the Gazi University in Ankara, Turkey (approval date/number/city/country: 04.02.2016/G.Ü.ET-16.004/Ankara/Turkey), in 2016. Six subjects were required in each group to detect a clinically significant difference with a power of 80% and a significance level of 5%. The experimental subjects included bilateral TMJs from 12 male New Zealand White rabbits aged approximately one-year-old and weighing 2.5 - 3.0 kg. We used only the minimum number of animals required to produce scientifically reliable data. Before the study, the general health of rabbits were monitored for seven days. The animals were maintained in standard individual cages and fed a standard laboratory diet and water *ad libitum*. They were kept in a room with constant temperature and humidity (approximately 22°C and 60%, respectively) under a 12-h light/dark cycle. The animals were randomly divided into two experimental groups with equal numbers, including PRP (six TMJs) and AB (six TMJs) injection groups. The injections were administered unilaterally by the same surgeon. The contralateral sides of the 12 TMJs were injected with isotonic saline to serve as controls for both groups. Ketamine hydrochloride (35 mg/kg) and xylazine (5 mg/kg) were injected intramuscularly as anesthetics. Before administering the injections, we shaved the preauricular region and used povidone-iodine for disinfecting the injection site. The injection site was determined as specified by Artuzi et al. (19). A 28-gauge needle was used for injections. Blood samples were drawn from the femoral arteries of the rabbits. For AB injection treatment, 1.5 mL of blood was taken, 1 mL of which was injected into the upper space of the TMJ and 0.5 mL into the pericapsular tissue. The PRP was prepared as described by Comert Kilic et al. (20). For the study, 6 mL of blood was drawn into sterile tubes containing an anticoagulant (acid citrate and dextrose; 3.2% sodium citrate). The tubes were centrifuged at 1000 rpm for 10 min. The buffy coat was carefully collected with a pipette. The PRP was injected without activating by $CaCl_2$, as the non-activated PRP could enhance the mesenchymal stem cell proliferation. The study used 1.5 mL of PRP for injection, 1 mL of which was injected into the upper joint cavity and 0.5 mL into the pericapsular tissue. Moreover, 1.5 mL of isotonic saline was injected into the control group, comprising 1 mL

administered to the upper space of the TMJ and 0.5 mL to the pericapsular tissue.

Mandibles were fixed with orthodontic brackets for one day to avoid the elongation of the newly forming fibrous tissue (Figure 1). No medication was used postoperatively. One month after the experimentation, the animals were sacrificed using high-dose anesthetics. Ketamine hydrochloride (45 mg/kg) and xylazine (5 mg/kg) were injected intramuscularly for maintaining deep anesthesia. Under deep anesthesia, 20 mg of xylazine was injected into the pinna vein for scarification. Then, the TMJ region was carefully dissected and remained in buffered formalin 10%.

Samples from the experimental groups were decalcified with a working solution containing hydrochloric acid 8% and formic acid 8%, after being fixed for 72 h in 10% buffered formalin. Routine light microscopy was applied to paraffin blocks sliced using Leica RM 2125RT and cut into a thickness of 6 μm with a microtome. The sections were stained with Mallory-Azan for showing the collagen fibers of bundles. The study aimed to evaluate fibrosis and tissue reactions in the samples.

4. Results

All the animals well tolerated the procedure and healed uneventfully. The histopathological examination was done by two independent observers who were kept unaware of treatment groups. In the histopathological evaluation of the PRP group, high levels of inflammation were observed in the retrodiscal ligament, especially below the ligament in the possible injection site. Inflammatory cells accompanied by increased adipose tissues in the field invaded the area extensively. Fibrin deposition was observed in the upper part of the disk toward the temporal region. The increase of collagen fibers, described as fibrosis, was observed in the retrodiscal ligament beginning from the outer surface. Additionally, the spreading of fine collagen fibers was observed between the inflamed area and the adipocyte cells. When the study evaluated two poles of the collateral (discal) ligament where it was connecting with the articular disk, a thicker connection zone, and more newly formed collagen fibers were observed in the lateral (injection) pole while thinner collagen fibers were observed in the medial (non-injection) pole. Chondrocyte activation, especially on the contralateral temporal bone surface, was remarkable when compared to other groups.

In the AB-injected group, increased adipocytes, inflammation, and fine collagen bundles were observed in the injected side. A zone of collagen bundles and fibrin formation, organized under the disk adhered to it, was noted.

In the isotonic saline group, fascicular thin bundles of collagen fibers were observed in collateral ligaments. Adipocytes and a small amount of fibrin accumulation were observed in this area, as well. No inflammation was detected.

The severity of fibrosis in retrodiscal ligaments and lateral capsular ligament was evaluated according to the criteria presented by Sairyo et al. (21). Grade 0 indicated normal tissue with no fibrotic region, grade 1 indicated fibrosis in < 25% of the entire area, grade 2 indicated fibrosis in 25% to 50% of the entire area, grade 3 indicated fibrosis between 50% and 75%, and grade 4 indicated > 75% fibrosis (Table 1).

According to fibrosis scoring, a grade 1 fibrotic site was observed in 3 (50%) AB-injected joints whereas grade 3 (33.3%) and grade 4 (16.7%) fibrosis severities were observed in the PRP-injected joints (Figure 2). PRP may be

Figure 1. Bracelet fixation on rabbit jaws

Table 1. Fibrosis Grade in the Injection Areas of TMJs (Grade 0 = -, Grade 1 = +, Grade 2 = ++, Grade 3 = +++, Grade 4 = ++++)

Saline-Injected (N = 6)	AB-Injected (N = 6)	PEP-Injected (N = 6)
-	++	+
-	+	++
-	+++	+
-	+	++
-	+	+++
-	++	++++

used alternatively in clinical use since it makes similar or greater fibrosis than AB does. However, in both AB and PRP-injected tissue samples, similar fibrotic changes were observed when compared to the control group.

5. Discussion

Surgical therapy that involves the manipulation of bony structures is part of the treatment of recurrent condylar dislocation. It displays some complications, such as facial nerve injury (12). Due to the invasive nature of surgical therapy, nonsurgical techniques, such as intracapsular injections of sclerosing agents, physiotherapy, and intramuscular injections of botulinum toxin, are the methods of choice for the less invasive treatment of condylar dislocation (22). Intramuscular injection of botulinum toxin is a noninvasive technique that exhibits fewer complications, but the necessity of electromyography guidance for the identification of the pterygoid muscle before injection limits the applicability of this technique (23, 24).

The AB injection is an easy, cost-effective, and minimally invasive technique compared to other nonsurgical techniques described above. Surgical treatment-related complications such as facial nerve injuries, facial scars, pain, and infections are eliminated with this method. Long-term successful outcomes can be observed in the first injection (25).

The AB injection is used to restrain the mandibular movements. In terms of pathophysiology, blood injection to the TMJ is similar to bleeding in the knee or elbow joint (26). The injection of blood into the TMJ acts as an artificially created wound, initiating inflammatory reactions that may cause fibrosis induction, adhesion formation, and periarticular soft tissue scarring, with the restriction of mandibular movement to avoid early stretching of newly formed fibrous tissue (9, 27). Fibrotic changes in the capsule and retrodiscal ligament were observed in the experimental study on pigs by Gulses et al. (17). In this study, although fibrotic changes were detected in the AB injection group, more effective fibrosis was seen in the PRP injection group owing to increased collagen bundles.

On the contrary, some researchers stated that the exposure of articular cartilage to blood might cause permanent joint destruction such as degenerative joint damage, chondrocyte apoptosis, and cartilage degeneration (28-30). According to an experimental study on rabbits by Candrl et al., AB injection to the TMJ does not cause degenerative changes in the articular cartilage (31). This study also showed that the injection of autologous blood and PRP did not cause degenerative articular changes.

The PRP injection into the TMJ has been recently applied for treating TMJ osteoarthritis and disk displacement. Although an extensive publication is available about the injection of PRP to other joints, especially the knee, a few studies have been done on the injection of PRP to the TMJ (32). In a literature review, no publication was found discussing the treatment of chronic recurrent TMJ dislocation with PRP injection.

In plastic and reconstructive surgery, the PRP injection induces adipocyte stem cell proliferation and adipogenic differentiation in soft tissue (33, 34). It is possible that the increase of adipose tissue in the PRP group was caused by the activation of possible adipocyte stem cells, leading to proliferation.

PRP has a supra-physiologic level of autologous concentrated human platelets. Platelet synthesis growth factors include platelet-derived growth factor, epidermal growth factor, transforming growth factor-beta 1 (TGF-β1), vascular endothelial growth factor, basic fibroblast growth factor, hepatocyte growth factor, and insulin-like growth factor (IGF-I) (35, 36). These growth factors are released from the alpha granules of activated platelets that have a key role in mitogenesis, chemotaxis, differentiation, and metabolism (37). The PRP can strengthen healed tendons and ligaments by increasing fibroblast proliferation and collagen production (36, 38). The PRP stimulates the expression of matrix molecules collagen type I (COL1A1), collagen type III (COL3A1), and cartilage oligomeric matrix protein without increasing the amounts of catabolic cytokines, such as matrix metalloproteinase 3 and matrix metalloproteinase 13 on the equine tendons culture (39). The injection of PRP into the Achilles tendons of rat improved the tensile strength of tendons and the production of collagen in tendons (40). This study showed that the injection of PRP into the TMJ and periarticular tissue induced more collagen tissue than the AB injection did.

This animal study had limitations. The animal model will not make the closest mimics of the human condition, and animal models are inefficient for replicating the exact biomechanics of the human TMJ movements. During chewing, these species show less loading of the TMJ than do the human (41). The restriction period of mouth movements is between one and four weeks after AB injection in clinical trials (42, 43). In animal studies, the restriction of jaw movements is not possible for the long-term. We applied only one-day jaw movement restriction in this study.

Renapurkar and Laskin (44) stated that an injectable agent is the initial treatment of choice for dislocations. In conclusion, the PRP injection for treating chronic mandibular dislocation may be an alternative to AB injection, which increases the success rate of treatment. Further studies are needed to evaluate the efficacy of this technique.

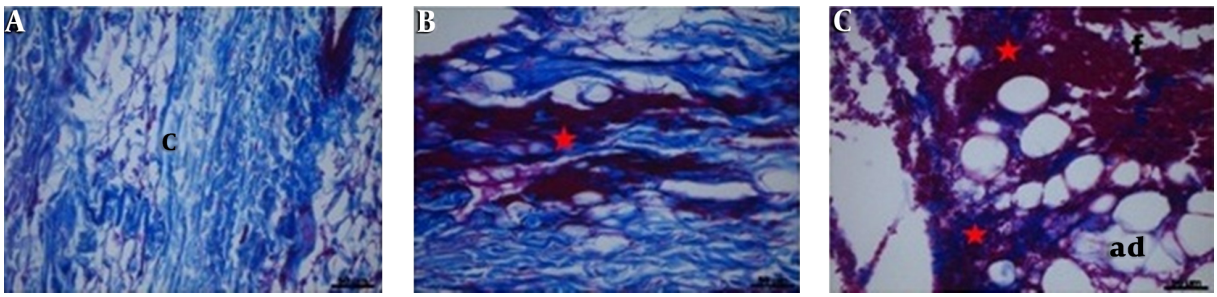

Figure 2. Histological aspects of groups; A, saline group; B, AB group; C, PRP group; ad, adipose tissue; f, fibrin; red star, the area of inflammation; c, connective tissue; (Mallory-Azan staining, A-B-C; original magnification 40X)

Footnotes

Authors' Contribution: Uğur Gülşen and Mehmet Fatih Şentürk designed the study and wrote the manuscript. Elif Aslı Gülşen collected the references and cited them. Uğur Gülşen, Mehmet Emre Yurttutan, and Mehmet Fatih Şentürk performed the animal surgeries. Mehmet Emre Yurttutan was a language supervisor. Derya Özdemir, Pınar Bayram, and Esra Erdemli made the histological analyses and contributed to the manuscript writing.

Conflict of Interests: The authors declare that they have no conflict of interest.

Ethical Approval: This study was approved by the Animal Experimentation Committee, Gazi University, Ankara, Turkey (approval date/number: 04.02.2016/G.Ü.ET-16.004).

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