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Comparison of the Efficacy of Hyaluronic Acid and Platelet-Rich Plasma Applied Together and Alone with Arthrocentesis in the Treatment of Temporomandibular Joint Internal Irregularities: A Prospective Clinical Study

Temporomandibular Eklem İç Düzensizliklerinin Tedavisinde Artrosentez ile Birlikte ve Tek Başına Uygulanan Hyalüronik Asit ve Trombositten Zengin Plazmanın Etkinliklerinin Karşılaştırılması: Bir Prospektif Klinik Çalışma

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Bu çalışma, Rojdan Ferman Güneş Uysal'ın "Temporomandibular Eklem İç Düzensizliklerinin Tedavisinde Artrosentez ile Birlikte ve Tek Başına Uygulanan Hyaluronik Asit ve Trombositten Zengin Plazmanın Etkinliklerinin Karşılaştırılması" başlıklı doktora tezinden üretilmiştir (Diyarbakır: Dicle Üniversitesi; 2018).

ABSTRACT Objective: This clinical study aims to determine the effectiveness of hyaluronic acid (HA) and platelet-rich plasma (PRP) injections alone and with arthrocentesis on pain, maximum mouth opening (MMO) and lateral and protrusive movements of the mandible in non-reduction disc displacement temporomandibular joint (TMJ) disorders. **Material and Methods:** This research is a randomized, single-blind and prospective study. 60 adult patients diagnosed clinically and radiographically with non-reducing disc displacement were included in the study. Initial and postoperative pain levels of all patients were measured using the 10-unit Visual Analog Scale (VAS). The amount of lateral and protrusive movement of mandible and MMO was also noted before and after the procedure. The patients were randomly divided into four groups: Group 1 (HA), Group 2 (arthrocentesis + HA), Group 3 (PRP), Group 4 (arthrocentesis+PRP). **Results:** According to this study, there was no statistically significant relationship between Group 1 and Group 3 and Group 2 and Group 4 in all time intervals and all symptoms. At the end of the 6th month, a significant relationship was found in VAS and MMO values between Group 4 and Group 1 and Group 3. Although there was no significant relationship between Group 4 and Group 2, the average values were found to be higher in the PRP group. **Conclusion:** It was observed that the results were more successful in the groups in which injections were applied after arthrocentesis than in the groups in which injections were applied without arthrocentesis. PRP injection has shown very successful results in the treatment of TMJ with disc displacement without reduction.

Keywords: Temporomandibular joint; arthrocentesis; platelet-rich plasma; hyaluronic acid

ÖZET Amaç: Bu klinik çalışma, redüksiyonsuz disk deplasmanlı temporomandibular eklem (TME) rahatsızlıklarında hyaluronik asit (HA) ve trombositten zengin plazma [platelet-rich plasma (PRP)] enjeksiyonlarının tek başına ve artrosentez işlemi ile uygulamalarının ağrı, maksimum ağız açıklığı (MAA) ve mandibulanın lateral ve protrüsiv hareketleri üzerinde etkinliğini karşılaştırmayı amaçlamaktadır. **Gereç ve Yöntemler:** Bu araştırma randomize, tek kör ve prospektif bir çalışmadır. Klinik ve radyografik olarak redüksiyonsuz disk deplasmanı teşhisi konulan ve konservatif tedavilerden sonuç alınamayan erişkin 60 hasta araştırmaya dâhil edilmiştir. Bütün hastaların başlangıç ve postoperatif ağrı derecesi 10 birimlik Görsel Analog Skala kullanılarak ölçülmüştür. MAA ve mandibulanın lateral ve protrüziv hareket miktarları da işlem öncesi ve işlem sonrası not edilmiştir. Hastalar rastlantısal olarak Grup 1 (HA enjeksiyonu), Grup 2 (artrosentez + HA enjeksiyonu), Grup 3 (PRP enjeksiyonu), Grup 4 (artrosentez + PRP enjeksiyonu) olmak üzere 4 gruba ayrılmıştır. **Bulgular:** Bu çalışmaya göre tüm zaman aralıklarında ve tüm semptomlarda Grup 1 ve Grup 3 ile Grup 2 ve Grup 4 arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır. 6. ayın sonunda Grup 4 ile Grup 1 ve Grup 3 arasında VAS ve MAA değerlerinde anlamlı bir ilişki bulunmuştur, Grup 4 ile Grup 2 arasında ise anlamlı bir ilişki bulunmamakla birlikte PRP grubunda ortalama değerlerin daha yüksek olduğu görülmüştür. **Sonuç:** Artrosentez sonrası enjeksiyonların uygulandığı grupların, artrosentez yapılmaksızın enjeksiyonların uygulandığı gruplara göre daha başarılı olduğu görülmüştür. Redüksiyonsuz disk deplasmanlı temporomandibular eklem tedavisinde PRP enjeksiyonu oldukça başarılı sonuçlar göstermiştir.

Anahtar Kelimeler: Temporomandibular eklem; artrosentez; trombositten zengin plazma; hyaluronik asit

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Temporomandibular joint (TMJ) internal disorders, which are quite common today, are a joint disorder caused by many factors. Among these factors, especially trauma and bruxism, parafunctional jaw activities and occlusal problems cause irregularities and pain in the TMJ. Such situations cause the biochemical structure of the joint to deteriorate and the accumulation of inflammatory cytokines in the joint.[1,2] With arthrocentesis, a minimally invasive method, biochemical mediators and effusions that cause pain in the upper joint space and limitation of mandibular movements are removed by lavage, thus supporting physiological synovial fluid production.[3] Clinical studies have shown that sodium hyaluronate, one of the intra-articular injection agents, not only has anti-inflammatory properties, but also is very effective in wound healing, and that it also transforms the biochemical structure of the inflamed joint to normal.[4]

Platelet-rich plasma (PRP) is defined as an autogenous blood component obtained from the person's own blood and containing a higher number of platelets than whole blood. Since many studies have shown that PRP is very successful in wound healing, this preparation has begun to be used frequently for treatment purposes in medical fields and dentistry.[5]

In our study, we aim to contribute to arthrocentesis application techniques by comparing the effectiveness of intra-articular injection applications of hyaluronic acid (HA) and PRP in our patients with non-reducing disc displacement, where conservative treatment methods could not yield results.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENTS

This study was designed as a single-blind, randomized clinical trial and was conducted in accordance with the Principles of the Declaration of Helsinki. It was conducted at Dicle University Faculty of Dentistry Department of Oral and Maxillofacial Surgery, with the approval of the ethics committee with date September 6, 2017 and protocol number 2017/23.

Sixty TMJs of 60 patients, aged between 18 and 60, who did not get results from previous conservative treatments, who complained of pain and limitation in mouth opening, who were at the 3rd stage of the Wilkes classification or exceeded this stage, and who were clinically and radiographically diagnosed with disc displacement without reduction, were included in the study. The clinical diagnosis of the patients was made as a result of the examination performed by the same physician according to the clinical diagnostic criteria of TMJ (clinical diagnostic criteria/temporomandibular disorders) and was confirmed by magnetic resonance image (MRI).[6] Before starting the treatment, patients were informed about the causes and treatments of TMJ diseases, and the arthrocentesis procedure, intra-articular injection and potential complications of the procedure were explained. Patients whose consent was obtained were included in the study.

INCLUSION CRITERIA

Patients over 18 years of age, who had previously received conservative treatment but had no improvement in their symptoms, and who had disc displacement without reduction were included in this study.

EXCLUSION CRITERIA

Patients for whom arthrocentesis, PRP, sodium hyaluronate injections or MRI are contraindicated, patients who have experienced TMJ trauma or a history of surgical procedures in this area, patients with facial development disorder, systemic inflammatory joint disease, condylar pathology and signs of myalgia, and patients during pregnancy and lactation were not included.

Initial symptoms of all patients were recorded using the 10-unit Visual Analog Scale (VAS), the degree of pain, maximum mouth opening (MMO), and the amount of lateral and protrusive movement of the mandible.

In order not to affect the mechanism of action of platelets in patients who will undergo PRP, the use of non-steroidal anti-inflammatory analgesics is discontinued 7 days before and 7 days after the procedure.

At the end of the clinical and radiographic examinations, the patients were randomly divided into four groups to be treated with Group 1 (only HA in-

jection), Group 2 (arthrocentesis and HA injection), Group 3 (only PRP injection), Group 4 (arthrocentesis and PRP injection).

SODIUM HYALURONATE

Orthovisc® 2 mL, 15 mg/mL (Biomeks medicines, Ankara) containing 15 mg/mL sodium hyaluronate (NaHA) dissolved in physiological serum was used.

PREPARATION OF PRP

Approximately 10 mL of venous blood was taken from the patients who would undergo PRP and placed in a tube containing sodium citrate and anticoagulant. According to the manufacturer's instructions, the tube was centrifuged at 3,000 rpm for 10 min. After centrifugation, the buffy coat, which is the middle layer and the upper plasma part, except for the bottom layer where erythrocytes are dense, were aspirated into the syringe.

ARTHROCYNTHESIS AND INTRA-ARTICULAR INJECTION TECHNIQUE

Before arthrocentesis and intra-articular injection, the skin of the ear and preauricular region was wiped with povidone-iodine and the areas outside this region were covered with a sterile drape. The joint area was anesthetized with approximately 1 cc of lidocaine (Jetokain®; Adeka, Türkiye). Entry points of syringe needles; on the tragus and lateral canthus line, 10 mm in front and 2 mm below the tragus was determined as the first entry point, and 20 mm in front and 8 mm below the tragus was determined as the second entry point. For the groups in which arthrocentesis would be performed by entering with 20 Gauge needles from the entry points with the mouth open, irrigation was performed with an average of 150 mL of 5% Ringer's lactate solution, then the needle at the second entrance was removed and 1 mL of adjuvants were injected. In the groups where arthrocentesis would not be performed, 1 mL of PRP or HA was injected only from the first entry point.

POSTOPERATIVE EVALUATION

After the treatment, antibiotics and analgesics were prescribed to the patients and a soft diet was recommended. After the treatment, patients were checked at the 1st week, 1st month, 3rd month and 6th month. At each control, VAS pain values, MMO, and lateral and protrusive movement amounts were recorded.

The success of our treatment was evaluated according to the criteria set by the American Association of Oral and Maxillofacial Surgery. These criteria are no or minimal pain (VAS<2), MMO of more than 35 mm, and lateral movements of more than 6 mm.[7]

STATISTICAL EVALUATION

In this study, mean, minimum and maximum values, standard error and standard deviation are given as descriptive statistics. The homogeneity of the study was determined with the Levene test, and the compliance of continuous variables with the normality distribution assumption was investigated with the Kolmogorov-Smirnow test.

Repeated measurements analysis of variance was used to compare the differences between the means of independent groups, and Tukey HSD tests were used for multiple comparisons.

Statistical evaluation was carried out within the 95% confidence interval; analyzes and descriptive statistics were performed using R version 3.2.3 (2015-12-10), Copyright (C) 2015 The R Foundation for Statistical Computing free software computer package program. Statistical significance level was accepted as $p<0.05$.

RESULTS

Although there was no statistically significant difference between the mean age and gender distribution between the groups ($p>0.05$), it was observed that the number of female patients was high in all groups (Table 1) and (Table 2).

No significant difference was found between the groups in VAS pain score values before treatment ($p>0.05$). At the 6th month after treatment, a statistically significant difference was observed between Group 1, Group 2 and Group 4 ($p=0.000$). Additionally, statistically significant differences were observed between Group 3, Groups 2 and Group 4 ($p=0.000$). At all control times, the highest VAS mean value was in Group 1, while the VAS mean values decreased in Group 3, Group 2 and Group 4, respectively (Table 3).

TABLE 1: Comparison of average ages by groups.

Groups	n	$\bar{X}$	Standard deviation	Standard error of mean	Minimum	Maximum
HA	15	33.67	13.957	3.604	18	59
Arthrocentesis+HA	15	32.33	13.767	3.555	20	59
PRP	15	32.93	12.533	3.236	18	56
Arthrocentesis+PRP	15	31.13	11.892	3.070	18	51

F=0.101; p=0.959 non-significant; HA: Hyaluronic acid; PRP: Platelet-rich plasma.

TABLE 2: Comparison of gender distributions of groups.

	Sex		
Groups	Female (%)	Male (%)	Total
HA	13 (86.7)	2 (13.3)	15
	21.7%	3.3%	25.0%
Arthrocentesis+HA	12 (80.0)	3 (20.0)	15
	20.0%	5.0%	25.0%
PRP	14 (93.3)	1 (6.7)	15
	23.3%	1.7%	25.0%
Arthrocentesis+PRP	13 (86.7)	2 (13.3)	15
	21.7%	3.3%	25.0%
Total	52 (86.7)	8 (13.3)	60 (100.0)
Chi-square=1.154; p=0.764			

HA: Hyaluronic acid; PRP: Platelet-rich plasma.

There was no significant difference between the groups in MMO values in the pre-treatment period (p=0.435). At the 6th month after treatment, a statistically significant difference was found between Group 1 and Group 3 values and Group 4 values (p=0.003). At the end of all control periods, the highest average MMO values were observed in Group 4, while the average MMO values were observed to decrease in Group 2, Group 3 and Group 1, respectively (Table 4).

There was no significant difference between the groups in contralateral movement values before treatment (p=0.999). After the treatment, it was observed that there was improvement at all time controls, but there was no statistically significant difference between the groups (p=0.079) (Table 5).

In the intra-group comparison of clinical findings; In Group 1, while a significant difference was observed in pain, MMO and contralateral movements before treatment and at the 1st week, 1st month and 3rd month after treatment (p<0.05), at the end of the 6th month, the improvement continued but there was no statistically significant difference.

In Group 2, a significant difference was observed in pain and MMO values at all time intervals between pre-treatment and post-treatment, while no significant difference was found in contralateral movements (p=0.000).

In Group 3, in addition to a significant difference in pain levels before and after treatment at all times, there was also a significant difference between the 1st and 6th months after treatment (p<0.05). While there was a significant difference in contralateral movements with MMO only between the pre-treatment and the 1st month after treatment, it was observed that there was an improvement in the scores in other periods, but it was not significant.

In Group 4, a significant improvement was observed in MMO and contralateral movements before and after treatment in all control periods (p<0.05).

TABLE 3: Comparison of VAS pain scores by groups.

VAS	Group $\bar{X}$±SD	Group II $\bar{X}$±SD	Group III $\bar{X}$±SD	Group IV $\bar{X}$±SD	F value	p value
Prearthrocentesis	8.60±0.50	8.46±0.74	8.00±1.41	8.06±1.43	1.071	0.369
1st week	5.40±2.77	4.06±2.78	4.40±2.38	2.46±2.55	3.211	0.030
1st month	4.13±3.27	2.33±3.30	3.73±2.34	1.00±1.25	4.253	0.009
3rd month	5.00 ±3.46	2.53±3.35	3.13±0.80	0.60±1.24	7.627	0.000
6th month	6.26±3.45	2.33±3.41	3.45±0.89	0.60±1.24	1.120	0.000

VAS: Visual analog scale; SD: Standard deviation.

TABLE 4: Comparison of groups according to MMO.

MMO	Group I $\bar{X}$±SD	Group II $\bar{X}$±SD	Group III $\bar{X}$±SD	Group IV $\bar{X}$±SD	F value	p value
Prearthrocentesis	31.60±5.53	32.80±3.02	32.86±2.16	33.73±2.31	0.924	0.435
1st week	33.93±6.80	38.02±5.88	35.46±4.65	38.53±3.56	2.545	0.065
1st month	36.26±7.03	38.86±6.88	37.40±5.42	42.86±5.01	3.290	0.027
3rd month	35.53±7.61	39.93±6.23	37.26±5.45	43.00±4.92	4.223	0.009
6th month	34.93±7.66	39.66±6.70	35.86±5.06	43.00±4.92	5.360	0.003

MMO: Maximum mouth opening; SD: Standard deviation.

TABLE 5: Evaluation of groups according to the amount of contralateral movements.

Amount of contralateral movements	Group I $\bar{X}$±SD	Group II $\bar{X}$±SD	Group III $\bar{X}$±SD	Group IV $\bar{X}$±SD	F value	p value
Prearthrocentesis	2.00±0.69	1.98±0.83	2.02±0.28	2.00±0.46	3.218	0.029
1st week	2.32±0.81	4.52±8.17	2.27±0.25	2.50±0.54	7.301	0.000
1st month	2.57±0.75	2.50±0.71	2.40±0.29	2.83±0.51	6.579	0.001
3rd month	2.52±0.75	2.60±0.75	2.20±0.35	2.76±0.55	7.978	0.000
6th month	2.32±0.75	2.58±0.78	2.20±0.35	2.76±0.55	14.452	0.000

SD: Standard deviation.

DISCUSSION

This study aims to see how HA and PRP injections, with or without arthrocentesis, affect clinical symptoms in TMJs with disc displacement without reduction. Our study has shown that direct applications of HA and PRP injections are quite successful, but arthrocentesis further increases the success of these adjuvants. It has also been shown that intra-articular PRP injection provides better clinical results than HA in terms of increasing MMO values and reducing VAS scores, and HA has a positive short-term effect in the treatment of disc displacement without reduction.

Conservative treatments such as physical therapy, behavioral therapy and pharmacological therapy can be applied in the treatment of TMJ disc displacement without reduction.[8] Frost and Kendell suggested that the symptoms should be improved by first applying conservative treatment to patients with disc displacement without reduction, and that it is better to perform interventional procedures in cases where no results are obtained.[9] Because they thought that the joint needed time to heal itself before invasive procedures. However, some authors have suggested that arthrocentesis as the first treatment for patients with disc displacement without reduction increases success, since the main purpose of arthrocentesis, which is a minimally invasive procedure, is to remove pain mediators, blood and tissue debris from the environment.[10,11] As in a study conducted by Diraçoğlu et al., they followed up the patients in whom they applied occlusal splint with conservative treatment and the patients in whom they underwent arthrocentesis for 1, 3 and 6 months. As a result of the study, they found that arthrocentesis was more successful than conservative treatment in reducing the level of pain and increasing lower jaw movements.[12] In our study, we planned to perform an interventional procedure as the next treatment step in patients who did not respond to conservative treatment.

Literature has shown that PRP, HA, dextrose, corticosteroids and various analgesic injections can be applied to support the weak healing capacity of the joint. For example; Dasukil et al. observed that there was an improvement in symptoms in the follow-up of patients with TMJ dysfunction after prolotherapy.[13,14] In a study conducted by Giraddi et al., they stated that the corticosteroid they applied into the joint reduced pain and effusion, had an anti-inflammatory effect on the synovial fluid, and thus increased the amount of joint movement.[15] In another study, only arthrocentesis was applied to a group of patients with TMJ osteoarthritis, and HA injection

was administered to another group of patients after 5 sessions of arthrocentesis, and the pain level and mobility of the mandible were examined. According to the results obtained, it was determined that HA injection applied after arthrocentesis was more successful than the groups that received only arthrocentesis.[16] In other studies conducted by various authors, they observed that the increase in the MMO of the patients and the improvement in other symptoms were superior in the follow-up period after PRP or HA injection.[5,17-20] However, a study by Haigler et al. showed that HA or PRP injections after arthrocentesis did not make a significant difference in improving clinical symptoms.[21] Alpaslan et al., in their study in which they applied arthrocentesis and sodium hyaluronate together and separately to patients with early-stage TMJ disease and followed them up for 3 months, stated that both techniques were successful, but the results were not significant.[22] Similar to these studies, Bouloux et al. study showed that HA or corticosteroid injection had no additional benefit in reducing pain and increasing mouth opening. They attributed this situation to two reasons. The first is the formation of cytokines and fragmented glycosaminoglycans that cause inflammation in the joint, and the second is that joint pain occurs as a result of the constant stimulation of mechanoreceptors in the joint capsule due to the pressure increased by inflammation. They observed that since these harmful products are removed and normal synovial fluid production is supported by the arthrocentesis process, there is no need for an additional injection.[23] Our study partially agrees with the results of this study. In our study, the fact that PRP and HA injections after arthrocentesis were more effective than the groups without arthrocentesis supports the effectiveness of arthrocentesis, as stated by previous studies, while the clinical improvement in the groups without arthrocentesis showed that HA and PRP injection alone is also beneficial. This aspect of our study is also incompatible with the studies of Bouloux and Haig.[23]

In a study conducted by Hegab et al., they performed arthrocentesis and administered PRP and HA injection three times, one week apart, to patients with TMJ osteoarthritis. After treatment, there was a continuous increase in MMO values in the HA group in the 1st, 3rd and 6th months, while a decrease in mouth opening was observed in the 12th month. In the PRP group, a continuous increase in values was observed. In terms of pain values, a good decrease was observed in the HA group in the 1st and 3rd months, while there was no significant change between the 3rd and 6th months, and there was an increase in the pain values in the 12th month compared to other control times, but it was still significantly lower than the 1st month. In the PRP group, they found that there was a continuous decrease in pain values at all control times.[18] In a study by Dasukil et al., in which they performed PRP injection after arthrocentesis and HA injection after arthrocentesis, there was a significant decrease in pain scores and a significant increase in MMO in both groups compared to the control group; at the end of the 6th month, they found that the increase in MMO in the PRP group was also significant compared to the HA group, but although the improvement in pain scores was better in the PRP group, the results were not significant.[24] In our study, similar to these two studies, HA and PRP injections showed improvement in all control times within themselves, but there was a better decrease in pain scores in the PRP group, and although there were better scores in the PRP group at MMO, there was no significant difference between these two groups. We saw that there was no difference.

HA is found naturally in synovial fluid and provides nutrition and lubrication to joint tissues. It has been reported that the concentration of HA decreases and its structure deteriorates as a result of inflammatory changes within the joint. Many researchers think that the synovial fluid, whose structure has changed in the joint, regains its viscoelastic properties with HA injection.[25] PRP is frequently used to heal tissues in different areas, such as TMJ dysfunction. The improvement in the movements of the mandible and the reduction of pain are due to the anti-inflammatory, regenerative and natural biogenic activity of PRP.[26]

According to the information we have as a result of our study, we can say that all four different treatment methods significantly improve the symptoms of TMJ disorders with disc displacement without re-

duction, but PRP and HA injection applied after arthrocentesis shows more effective results in the short and long term compared to PRP and HA injection applied alone. In addition, both applications of PRP injection were found to be more successful in increasing MMO and reducing pain.

CONCLUSION

We think that PRP injection after arthrocentesis applied to TMJ patients with disc displacement without reduction significantly increases the quality of life. The fact that it is easy to obtain, does not require extra cost, and does not pose any risk of complications due to its autogenous nature make this situation more advantageous. However, other studies need to be conducted to see how applying this interventional procedure before conservative treatments affects success in the short and long term. We also think that regardless of the agent we will use in temporomandibular intra-articular treatments, arthrocentesis should be included in the treatment protocol. However, we can say that intra-articular injections are successful even without arthrocentesis, as there is no second needle for patients who are afraid of invasive procedures and the short duration of the treatment process.

Source of Finance

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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: *Rezzan Güner, Rojdan Ferman Güneş Uysal;* ***Design:*** *Rezzan Güner, Rojdan Ferman Güneş Uysal;* ***Control/Supervision:*** *Rezzan Güner, Beyza Kaya, Rojdan Ferman Güneş Uysal;* ***Data Collection and/or Processing:*** *Rojdan Ferman Güneş Uysal;* ***Analysis and/or Interpretation:*** *Rezzan Güner, Rojdan Ferman Güneş Uysal, Ersin Uysal;* ***Literature Review:*** *Rojdan Ferman Güneş Uysal;* ***Writing the Article:*** *Rojdan Ferman Güneş Uysal;* ***Critical Review:*** *Rezzan Güner, Rojdan Ferman Güneş Uysal, Beyza Kaya;* ***References and Fundings:*** *Rezzan Güner;* ***Materials:*** *Rojdan Ferman Güneş Uysal.*

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