Observational Study

Medicine®

OPEN

Effect of arthrocentesis plus platelet-rich plasma and platelet-rich plasma alone in the treatment of temporomandibular joint osteoarthritis

A retrospective matched cohort study (A STROBE-compliant article)

Shang-Lun Lin, MD[a,b,c], Chiang-Chin Tsai, MD[d,e], Shang-Liang Wu, PhD[f], Shun-Yao Ko, PhD[g], Wei-Fan Chiang, DMD[h,i], Jung Wu Yang, DDS[j,k,l,*]

Abstract

Although the research on using platelet-rich plasma (PRP) for temporomandibular joint osteoarthritis (TMJ-OA) has advanced, no unified standards exist for determining the joint use of arthrocentesis and the injection dose and frequency of PRP. This study aimed to compare the efficacy of 2 TMJ-OA treatment approaches, arthrocentesis plus platelet-rich plasma (A+PRP) and PRP alone, and attempted to provide another potential treatment option with a single injection of 2 mL of high-concentration and high-purity PRP.

This retrospective matched cohort study enrolled 208 patients who were treated for temporomandibular disorders (TMDs) in the Department of Oral and Maxillofacial Surgery of Tainan Sin-Lau Hospital between August of 2013 and January of 2016, from which 90 patients were selected for the final analysis. The predictor variables were treatment outcome indicators, including joint crepitus sounds, TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, temporomandibular joint (TMJ) arthralgia, pain when chewing most foods, and maximum assisted opening (MAO). The data were analyzed using χ^2 tests, *t* tests, and multiple regression analyses.

Among the 90 patients, 30 were assigned into the A+PRP group, and 60 were included in the PRP group. A matching method was used to ensure no statistically significant differences in the categorical and continuous variables between the 2 groups. After treatment, both the A+PRP and PRP groups showed improvements in TMJ-OA. The 2 treatment groups did not show statistically significant differences in the symptom improvement rates of joint crepitus sounds, reparative remodeling, and TMJ arthralgia. However, compared with PRP alone, the A+PRP treatment demonstrated superior performance in improving TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, and pain when chewing most foods.

Both A+PRP and PRP treatments can effectively improve multiple symptoms of TMJ-OA. Based on the results from this study, we recommend a single injection with 2 mL of high-concentration and high-purity PRP for TMJ-OA treatment. For patients with TMJ-OA accompanied by other clinical symptoms, including TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, and pain when chewing most foods, a treatment approach using arthrocentesis prior to a PRP injection can achieve a higher efficacy.

Abbreviations: A+PRP = arthrocentesis plus platelet-rich plasma, CBCT = cone-beam computed tomography, DC/TMD = diagnostic criteria for TMD, DDWR = disc displacement with reduction, EGF = epidermal growth factor, FGF = fibroblast growth factor, FPS = flat plane splint, IAOMS = International Association of Oral and Maxillofacial Surgeons, IGF = insulin-like growth factor, LPCGF = liquid phase concentrated growth factors, MAO = maximum assisted opening, PDGF = platelet-derived growth factor, PPP = platelet poor plasma, PRP = platelet rich plasma, RBC = red blood cell, TGF = transforming growth factor, TMDs = temporomandibular disorders, TMJ = temporomandibular joint, TMJ-OA = temporomandibular joint osteoarthritis, VAS = visual analog scale, VEGF = vascular endothelial growth factor.

Keywords: arthrocentesis, osteoarthritis, platelet-rich plasma, temporomandibular disorders, temporomandibular joint

Editor: Li Wu Zheng.

The authors have no conflicts of interest to disclose.

[a] *Department of Psychiatry, Kaohsiung Armed Forces General Hospital Pingtung Branch, Pingtung,* [b] *Department of Microelectronics Engineering, National Kaohsiung Marine, University, Kaohsiung,* [c] *Graduate Institute of Medical Science, College of Health Science, Chang Jung Christian University, Tainan,* [d] *Department of General Surgery, Tainan Sin Lau Hospital, Tainan, the Presbyterian Church,* [e] *Department of Health Care Administration, Chang Jung Christian University, Tainan, Taiwan.,* [f] *School of Medicine, Griffith University, Gold Coast, Australia,* [g] *Graduate Institute of Medical Science, College of Health Science, Chang Jung Christian University, Tainan, Taiwan,* [h] *Department of Oral and Maxillofacial Surgery, Chi-Mei Medical Center, Liouying,* [i] *School of Dentistry, National Yang-Ming University, Taipei,* [j] *Department of Oral and Maxillofacial Surgery, Tainan Sin Lau Hospital, Tainan, the Presbyterian Church,* [k] *Graduate Institute of Medical Science, College of Health Science, Chang Jung Christian University,* [l] *Chief Executive Officer, Yuan Yuan Dental Federation, Tainan, Taiwan.*

[*] *Correspondence: Jung Wu Yang, 701 No. 57, Sec. 1, East Gate Road, East Dist., Tainan City, Taiwan, R.O.C. (e-mail: jungwuyang1979@gmail.com).*

Medicine (2018) 97:16(e0477)

Received: 30 January 2018 / Received in final form: 28 February 2018 / Accepted: 26 March 2018

http://dx.doi.org/10.1097/MD.0000000000010477

1. Introduction

Temporomandibular joint (TMJ) osteoarthritis (OA) results from wear and degenerative changes in the synovium, cartilage, capsules, tendons, condyles, and/or articular eminences in the TMJ region that are accompanied by remodeling of the underlying subchondral bone.[1–3] The main clinical complaints of affected patients include limitation of the mandible range of motion, chewing function impairment, TMJ arthralgia, clicking or crepitus sounds, and stiffness. In addition, flattening, erosion, generalized sclerosis, osteophytes, and subchondral cysts on the surface of the condylar head are often detected by cone-beam computed tomography (CBCT).[2,3] Various nonsurgical approaches, such as reassurance, physiotherapy, pharmacotherapy, and occlusal splint treatment, have been applied to treat TMJ-OA, as reported in a number of articles. The minimally invasive treatments for TMJ-OA include arthrocentesis and intra-articular injection, among others.[4]

Because of its advantageous characteristics, such as high safety and the quick removal of inflammatory tissue and tissue degradants, the effectiveness of arthrocentesis in improving TMJ-OA from the "dysfunctional state" to the "functional state" has been proven.[5] Although platelet-rich plasma (PRP) was developed as early as the 1970s, it was not until 1997 that the clinicians used it to accelerate the healing process.[6] After research in the 20th century demonstrated that platelets contain large number of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF),[7] PRP began to be widely used in maxillofacial[8] and cosmetic surgeries.[9] In recent years, several studies have reported the use of PRP in intra-articular injection to treat temporomandibular disorders (TMDs), which achieved satisfactory outcomes.[1,6,10–15] However, the treatment methods used in these studies were inconsistent, with some using PRP alone and some using arthrocentesis plus PRP (A+PRP). In addition, these studies mostly used traditional PRP in varying doses, from 0.5 to 2 mL, and with different frequencies, from a single injection to 4 injections. Therefore, researchers have been calling for establishing a standardized protocol regarding the use of PRP in TMJ-OA treatment.[16]

To the best of our knowledge, there is no existing study comparing the efficacies of A+PRP and PRP alone in treating TMJ-OA. We hypothesized that the A+PRP treatment is superior to the treatment using PRP alone. In addition, the specific aim of this study was to provide another potential TMJ-OA treatment option that uses a single injection of high-concentration and high-purity PRP (also known as liquid phase concentrated growth factor, LPCGF) at a maximal dose of 2 mL according to the maximal volume of the joint space.

2. Materials and methods

2.1. Participants

This retrospective matched cohort study enrolled 208 TMJ-OA patients who were treated in the Department of Oral and Maxillofacial Surgery of Tainan Sin-Lau Hospital between August of 2013 and January of 2016. All subjective and objective findings were obtained from the data modified based on the definitions provided in the "diagnostic criteria for temporomandibular disorders (DC/TMDs)"[17,18] and "the recommended criteria for success of the International Association of Oral and Maxillofacial Surgeons (IAOMS)."[19] The inclusion criteria were the following: patients who were at least 18 years old; who were confirmed to have OA due to at least one symptom of subchondral cysts, erosions, osteophytes, or generalized sclerosis diagnosed by TMJ CBCT; and who had a follow-up duration longer than 1 year after A+PRP or PRP treatment. The exclusion criteria were uncontrolled systemic disease, anticoagulant use, neurologic disorders, head and neck cancer, oral submucosal fibrosis, previous TMJ surgery, and incomplete data. According to the criteria above, 168 patients were selected for matching. The matching procedure was conducted based on propensity scores in terms of 12 variables: gender, bruxism, habitual chewing of hard foods, clenching, occlusion, deep bite, open bite, mandibular fracture history, orthodontic treatment history, third molar extraction history, age, and mean time of being affected by OA. Finally, 90 patients were divided into 2 groups at a ratio of 1:2, with 30 in the A+PRP group and 60 in the PRP group (Fig. 1).

2.2. Treatment protocols

All participants' surgeries were performed by the same doctor (JWY). The landmarks for surgical access were determined according to the method used by Murakami et al[20] (Fig. 2). First, a tragus-lateral canthus line was drawn from the tragus to the lateral canthus, and another line was drawn along the skin crease in the front of the tragus. The landmark Point A was the midpoint between the tragal tip and the intersection point of the crease line and the tragus-lateral canthus line. On the tragus-lateral canthus line, Point B was 1 cm away from the front of Point A, and Point C was 1 cm away from the front of Point B. Subsequently, the point that was 2 mm below Point B on the line perpendicular to the

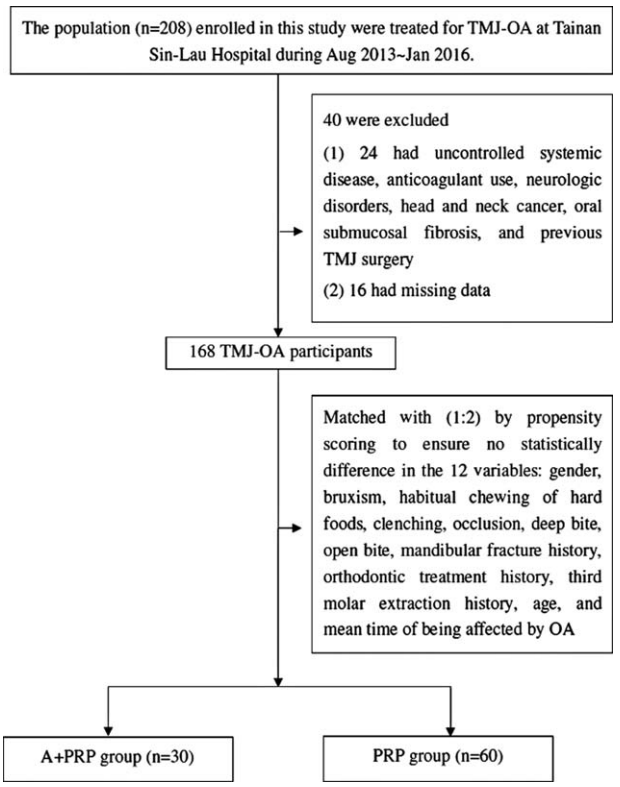

Figure 1. Flowchart of the sample selection. Note: A+PRP = arthrocentesis plus platelet rich plasma; OA = osteoarthritis; PRP = platelet rich plasma; TMJ = temporomandibular joint.

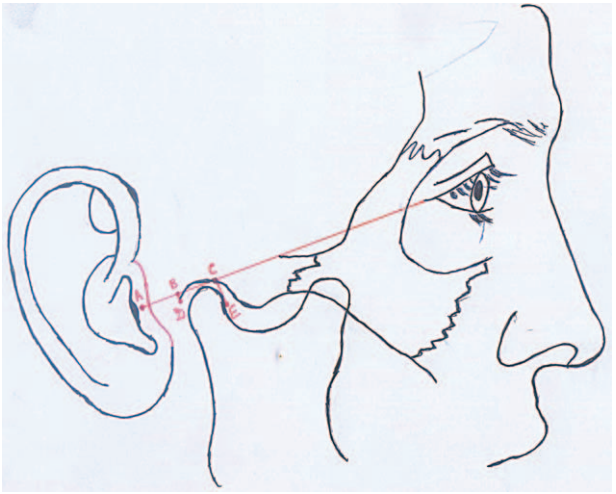

Figure 2. Landmarks in surgical intervention approaches.

tragus-lateral canthus line was marked as Point D, and similarly, the point that is 1 cm below Point C on the line perpendicular to the tragus-lateral canthus line was marked as Point E. After local disinfection, 1.8 mL of local anesthetic solution containing 1:100,000 epinephrine was subcutaneously injected into Points D and E. PRP was prepared according to Sacco's protocol.[21] The detailed process was as follows: First, 10 mL of venous blood was collected from the patient (20 mL for patients who were to receive injections on both sides) and was transferred into plastic white-capped tubes (Greiner Bio-One, GmbH, Kremsmunster, Austria) without anticoagulants and reagents. These tubes were then immediately centrifuged at 2400 to 3000 rpm in a special machine (Medifuge; Silfradent srl, Sofia, Italy) using the following program: 30 seconds of acceleration, 2 minutes at 2700 rpm, 4 minutes at 2400 rpm, 4 minutes at 2700 rpm, 3 minutes at 3000 rpm, 36 seconds of deceleration, and then stop. At the end of the process, there were 3 blood fractions: the upper layer, consisting of platelet-poor plasma (PPP); the middle layer, consisting of a very large and dense liquid-phase PRP; and the lower layer, consisting of red blood cells (RBCs). The PRP was then separated using a spinal needle. During the time when the PRP was in the preparation process, 2 G21 syringe needles were inserted into the superior joint space from Points D to E, through which a rinsing with 50 mL of normal saline was conducted in patients in the A+PRP group; an injection of 1 mL of normal saline was performed to ensure that the needle tips had reached the superior joint space in the patients in the PRP group. When the PRP was ready to use, the G21 needle at Point E was withdrawn, and 2 mL of extracted PRP was injected through the G21 needle at Point D. All patients were orally administered 500 mg paracetamol once every 8 hours for 3 days and were asked to eat only soft foods for one week after their surgery. All patients were required to continuously wear a 5-mm-thick flat plane splint (FPS) for at least 6 to 8 hours at night after the injection.

2.3. Variables and assessments

The outcome variables used for assessment included joint crepitus sounds, TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, TMJ arthralgia, pain when chewing most foods, and maximum assisted opening (MAO). Three approaches were jointly used to determine whether joint crepitus sounds were induced by the maximum unassisted opening, MAO, lateral excursive movements, and protrusive movements: TMJ palpation performed by a doctor, patient's self-reporting of the sounds, and stethoscopic examination of the TMJ area by a doctor. The absence of joint crepitus sounds was determined only if all 3 approaches yielded negative results; in other words, the presence of joint crepitus sounds was considered even when only 1 of the 3 approaches derived positive results. TMD-associated headache was determined by the patient's positive answer to the question of whether the TMD-associated pain referred to the temple area during pain episodes. The variable of jaw range of motion <6 mm was evaluated by measuring the jaw range using a caliper during lateral excursive movements and protrusive movements of the patient. The myofascial pain with referral was determined by the patient's positive answer to when asked whether the pain exceeded the range of the palpated and pressed muscle during the palpation of the masticatory muscle regions by the doctor. TMJ arthralgia was determined through palpation of the TMJ region by the doctor during maximum unassisted opening, MAO, lateral excursive movements, and protrusive movements of the patient. Pain when chewing most foods was evaluated based on the patient's answer regarding the intensity of pain while chewing most foods. To assess TMJ arthralgia and pain when chewing most foods, a visual analog scale (VAS) was used for the questionnaire, in which a score of 0 indicated no pain and a score of 10 indicated unbearable pain. MAO refers to a patient's maximum assisted mouth opening (in millimeter) and was measured using a hard caliper. All of the above assessments were conducted by the same doctor and recorded by the same physician assistant.

2.4. Data analysis

The sample size (*t* tests, means: differences between the 2 independent means of groups) was determined by a priori power analysis using G-power 3.1.2. When type I error was set at 0.05 (5%), power was 0.9 (90%), and the mean ±standard deviation of the VAS scores of the 2 groups for the outcome variable "pain when chewing most foods" at baseline were 2.97 ± 2.56 and 1.17 ± 2.00, and the minimal sample sizes required for the A+PRP and the PRP groups were 21 and 41, respectively. All data were input into Excel worksheets and analyzed using SPSS Statistical Software (version 20 for windows; IBM; New York). χ^2 tests were used to analyze categorical variables, and *t* tests were used to analyze continuous variables. The 2 groups were matched in terms of basic characteristics to avoid the interference of confounding factors. The 2 groups were compared by multiple regression analysis of treatment indicators, and the results are presented in bar graphs.

This study complied with the Declaration of Helsinki[22] and received review and approval from the Medical Ethics Committee of Tainan Sin Lau Hospital (Approval Certificate no. SLH919-106-011).

3. Results

This study included 90 TMJ-OA patients for final analysis, with 30 in the A+PRP group and 60 in the PRP group. The 2 groups were matched (1:2) by propensity scoring to ensure that the intergroup differences in categorical (Table 1) and continuous variables (Table 2) were not statistically significant.

Table 1

Comparisons of the categorical variables of 2 groups.

Variables		Groups A+PRP n (%)	Groups PRP n (%)	χ^2	*P*
Gender				1.23	.267
	Female	25(83.3)	42(70)		
	Male	5(16.7)	18(30)		
Bruxism				0.51	.477
	No	18(60)	42(70)		
	Yes	12(40)	18(30)		
Habit of chewing hard foods				0.00	1.000
	No	17(56.7)	35(58.3)		
	Yes	13(43.3)	25(41.7)		
Clenching				0.05	.821
	No	14(46.7)	25(41.7)		
	Yes	16(53.3)	35(58.3)		
Occlusion				0.01	.931
	No	22(73.3)	46(76.7)		
	Yes	8(26.7)	14(23.3)		
Deep_bite				※	.714
	No	28(93.3)	54(90)		
	Yes	2(6.7)	6(10)		
Open_bite				※	1.000
	No	28(93.3)	56(93.3)		
	Yes	2(6.7)	4(6.7)		
Mandibular fracture history				※	.598
	No	28(93.3)	58(96.7)		
	Yes	2(6.7)	2(3.3)		
Orthodontic treatment history				※	.659
	No	29(96.7)	55(91.7)		
	Yes	1(3.3)	5(8.3)		
Third molar extraction history				※	.598
	No	28(93.3)	58(96.7)		
	Yes	2(6.7)	2(3.3)		

A+PRP = arthrocentesis plus platelet rich plasma; PRP = platelet rich plasma; ※= Fisher's exact test.

3.1. Outcome of joint crepitus sound

Before treatment (Pre-Tx), all patients in the 2 groups (100%) had joint crepitus sounds; the difference was not statistically significant between the groups ($P > .999$). At 1 week post-treatment (Post-Tx), the proportion of the patients in the A+PRP group who had joint crepitus sounds decreased from 100% to 83%, but the decrease was not statistically significant ($P = .115$). However, only 55% and 47% of the patients in the A+PRP group had joint crepitus sounds at 1 month and 12 months post-treatment, respectively, showing statistically significant decreases compared with the pretreatment level of 100% ($P < .001$ for both). There were no statistically significant differences in the percentages of patients having joint crepitus sounds between the 2 groups before treatment and after treatment (until 12 months post-treatment). In other words, similar to the A+PRP group, the PRP group demonstrated a remarkable improvement of joint crepitus sounds starting from one month post-treatment (Fig. 3A).

3.2. Outcome of TMD-associated headache

Before treatment, the proportion of patients who had TMD-associated headache was statistically significantly different between the A+PRP group (33%) and the PRP group (8%) ($P < .001$). At 12 months post-treatment, the A+PRP group showed a statistically significant improvement, as evidenced by the data that none of the patients suffered from TMD-associated headache (0%, $P < .001$). In the PRP group, despite the improvement in the proportion of the patients having TMD-associated headache from a pretreatment level of 8% to 0% at 12 months post-treatment, the difference was not statistically significant ($P = .136$). A comparison between the 2 groups indicated that the A+PRP group showed a more prominent improvement of TMD-associated headache than that of the PRP group at 12 months post-treatment; the intergroup difference was statistically significant ($P = .019$) (Fig. 3A).

Table 2

Comparisons of the continuous variables of 2 groups.

Variables	Groups A+PRP Mean ± SD	Groups PRP Mean ± SD	*t*	*P*
Age, y/o	42.73 ± 10.87	38.73 ± 14.88	1.31	.195
MTA, days	1188.6 ± 1622.38	969.75 ± 1734.33	0.58	.566

MTA = mean time of being affected by osteoarthritis, PRP = platelet rich plasma.

3.3. Outcome of jaw range of motion <6 mm

Before treatment, 47% of the patients in the A+PRP group and 20% of the patients in the PRP group had a jaw range of motion <6 mm, with a statistically significant difference between the 2 groups ($P < .001$). At 1 week post-treatment, only 30% of the patients in the A+PRP group had a jaw range of motion <6 mm, with a statistically significant declination ($P = .034$). At 1 month and 12 months post-treatment, the rates of jaw range of motion <6 mm declined to 14% and 0% in the A+PRP group, respectively, both showing statistically significant differences compared with the pretreatment level of 47% ($P < .001$ for both). In the PRP group, compared with the pretreatment level of 20%, the rate of jaw range of motion < 6 mm began to significantly decrease and reached 7% at one month post-treatment ($P = .020$). At this time point, the A+PRP group demonstrated a statistically significant improvement compared with the PRP group in terms of this outcome indicator ($P = .042$). At 12 months post-treatment, only 2% of the patients in the PRP group had a jaw range of motion <6 mm, showing a statistically significant improvement compared with the pretreatment level of 20% ($P = .003$). At this time point, the A+PRP group still demonstrated a statistically significant improvement compared with that of the PRP group ($P = .011$) (Fig. 3A).

3.4. Outcome of myofascial pain with referral

Before treatment, 67% of the patients in the A+PRP group and 22% of the patients in the PRP group suffered myofascial pain with referral, and the difference between the 2 group was significant ($P < .001$). At 1 week, 1 month, and 12 months after treatment, the rates of myofascial pain with referral in the A+PRP decreased from the pretreatment level of 67% to 60%, 55%, and 40%, respectively, but all the decreases were not statistically significant ($P = .576$, $P = .340$, and $P = .068$, respectively). In the PRP group, 1 month after treatment, the rate of myofascial pain with referral even increased from the pretreatment level of 22% to 41%, showing a statistically significant deterioration ($P = .021$). Although the A+PRP treatment did not result in any statistically significant improvements at 1 month and 12 months post-treatment compared with the pretreatment level, it was remarkably superior to the treatment using PRP alone ($P = .035$

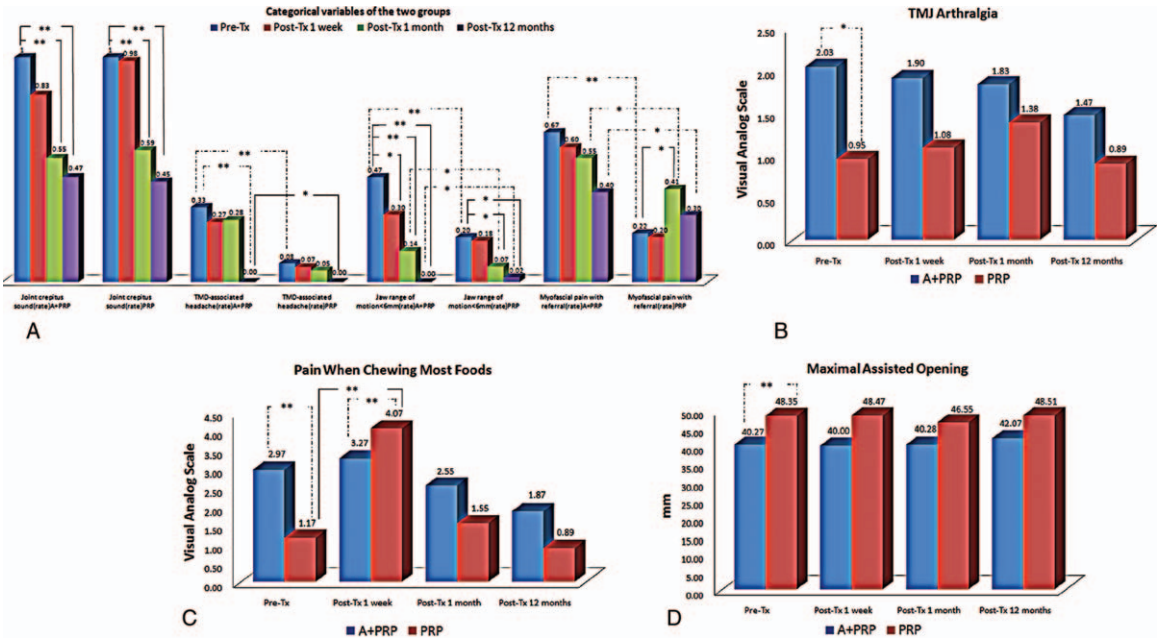

Figure 3. Trends in the variables between the 2 groups. (A) Trends in categorical variables between the 2 groups. (B) Trends in TMJ arthralgia between the 2 groups. (C) Trends in pain when chewing most foods between the 2 groups. (D) Trends in maximum assisted opening between the 2 groups. Note: $^{**} = P < ,001$; $^{*} = P < .05$. A+PRP = arthrocentesis plus platelet-rich plasma; post-Tx = post-treatment; pre-Tx = pretreatment; PRP = platelet-rich plasma, TMJ = temporomandibular joint.

and $P = .043$ at 1 month and 12 months post-treatment, respectively) because myofascial pain with referral deteriorated in the patients receiving the latter treatment (Fig. 3A).

3.5. Outcome of TMJ arthralgia

Before treatment, the average VAS scores of TMJ arthralgia were 2.03 and 0.95 for the A+PRP and PRP groups, respectively, with a statistically significant difference between the 2 groups ($P = .005$). Both groups showed no significant improvements at 1 week, 1 month, and 12 months post-treatment, and there were no statistically significant differences between the 2 groups (Fig. 3B).

3.6. Outcome of pain when chewing most food

Before treatment, the average VAS scores for pain when chewing most foods were 2.97 and 1.17 for the A+PRP and PRP groups, respectively, with a significant difference between the 2 groups ($P < .001$). Although the average VAS score decreased from 2.97 to 1.87 at 12 months post-treatment, the A+PRP group still did not show statistically significant improvement in terms of the pain when chewing most foods ($P = .072$). Similarly, the treatment with PRP alone failed to improve the pain when chewing most foods; even worse, the average VAS score increased markedly from the pretreatment level of 1.17 to 4.07 at 1 week post-treatment ($P < .001$). Therefore, the patients in the A+PRP group suffered less pain than those in the PRP group at 1 week post-treatment, with a statistically significant difference ($P < .001$) (Fig. 3C).

3.7. Outcome of MAO

Before treatment, the average MAOs were 40.27 mm and 48.35 mm in the A+PRP and PRP groups, respectively, with a significant difference between the 2 groups ($P < .001$). Both groups showed no significant improvements at 1 week, 1 month, and 12 months post-treatment, and there were no statistically significant differences between the 2 groups (Fig. 3D).

3.8. Outcome of CBCT

Before treatment, CBCT identified 47 joints with OA in the A+PRP group (including 13 OA joints of 13 patients with only one side affected and 34 joints of 17 patients with both sides affected) and 79 OA joints in the PRP group (including 41 OA joints of 41 patients with only one side affected and 38 joints of 19 patients with both sides affected). At 12 months post-treatment, 30 joints (64%) in the A+PRP group and 53 joints (67%) in the PRP group showed evidence of reparative remodeling, indicating statistically significant improvements in both groups; however, the intergroup difference was not statistically significant (Table 3).

4. Discussion

This study aimed to compare the efficacies of treatments using arthrocentesis plus PRP and PRP alone for TMJ-OA. Although

Table 3

Comparisons of the outcomes of CBCT in the 2 groups at 12 months post-treatment.

Variables	Groups		*P*-value
	A+PRP n (%)	PRP n (%)	
Reparative remodeling	30(64) **	53(67) **	>.05
Progressive degeneration	1(2)	0(0)	>.05
No change	16(34)	26(33)	>.05
Total	47(100)	79(100)	>.05

A+PRP = arthrocentesis plus platelet rich plasma, CBCT = cone-beam computed tomography, PRP = platelet rich plasma.
** *P* value < .001, indicating a statistically significant improvement in the group

both approaches effectively treated TMJ-OA and did not show statistically significant differences in improving the joint crepitus sounds, reparative remodeling, and TMJ arthralgia, the A+PRP treatment was superior to PRP alone in terms of the performance in improving symptoms such as TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, and pain when chewing most foods.

In recent years, research has clearly revealed that TMDs can cause metabolic overreactions of extracellular matrix, collagen, macromolecules, and proteoglycans and can change the surrounding microenvironment of the temporomandibular joint, leading to cartilage degradation and subchondral bone damage.[23] In addition to the disc displacement, pain and TMJ dysfunction are also associated with intra-articular pressure and cytokine levels in the synovial fluid.[24] Intra-articular injection of PRP can adjust the intra-articular pressure by expanding the space in the articular cavity; most importantly, it can increase growth factor synthesis through degranulation of the alpha granules in platelets.[7] Growth factors promote the repair of the disc, capsule, and retrodiscal pad,[25] and, via interleukin-1 inhibition, can suppress pro-inflammatory cytokines that are released from activated macrophages.[26] The PRP used in this study, which is a new generation of PRP (i.e., LPCGF), was developed by Sacco in 2006.[21] The most distinct difference between LPCGF and the traditional PRP is that the preparation of the former does not require any anticoagulants or other reagents. Using this approach, growth factors at higher concentrations and purity levels than those in traditional PRP can be extracted from the blood simply using a special centrifugal device at specific centrifugation speeds, and the sustained slow-release of the obtained growth factors can continue for at least 7 to 10 days.[21] In animal experiments using rabbits, Kutuk et al[27] found that PRP can promote the regeneration of new bone, fibrocartilage, and hyaline cartilage and can improve the ultrastructural architecture of the collagen fibrils. Among 126 joints of 90 patients included in this study, the condylar head demonstrated reparative remodeling in 30 joints in the A+PRP group (Fig. 4A) and 53 joints in the PRP group (Fig. 4B) at 12 months after the injection of 2 mL of PRP. Both groups showed statistically significant improvements, but the intergroup difference was not significant. In a study using goats, Wang et al[28] found that the TMJ-OA animals treated with PRF, also known as solid-phase concentrated growth factors (SPCGF), showed the significantly enhanced generation of new bone and cartilage compared with the control TMJ-OA animals without PRF treatment. The results from the study by Wang et al using solid-phase PRF were consistent with the results from the present study using liquid-phase PRP. In a study conducted by Kilic et al using 30 TMJ-OA patients whose symptoms could not be improved with treatments following the traditional protocols of TMJ-OA, 32 joints of 18 patients in the study group received initial arthrocentesis (using 100 mL of Ringer's lactate solution) plus a 1-mL PRP injection and then 4 consecutive courses at 1-month time intervals. At 1 year post-treatment, the VAS score of pain complaints decreased from the preinjection level of 5.70 ± 1.35 to 1.02 ± 1.88 ($P < .001$), the maximum interincisal opening (MIO) decreased from the preinjection level of 38.72 ± 7.84 mm to 38.39 ± 8.02 mm ($P > .05$), and the joint sound VAS score decreased from the preinjection level of 5.48 ± 3.46 to 0.70 ± 0.85 ($P < .001$).[10,14] In addition, based on the CBCT findings, Kilic et al[10] found that 87.5% of the joints treated with arthrocentesis plus PRP injections showed osseous reparative remodeling, while 46.6% of the joints treated with arthrocentesis alone in the control group showed osseous reparative remodeling. In this study, neither the A+PRP group nor the PRP group showed statistically significant improvements in the MAO at 1 year post-treatment because the patients included did not have noticeable mouth open limitation even before treatment. In addition, the joints showing osseous reparative remodeling after treatment accounted for 64% and 67% in the A+PRP and PRP groups, respectively, and the improvements were statistically remarkable in both groups, consistent with the study of Kilic et al. Although this study used a different experimental design from the study of Kilic et al, it confirmed more convincingly that the osseous reparative remodeling of TMJ-OA was caused by PRP injection rather than arthrocentesis.

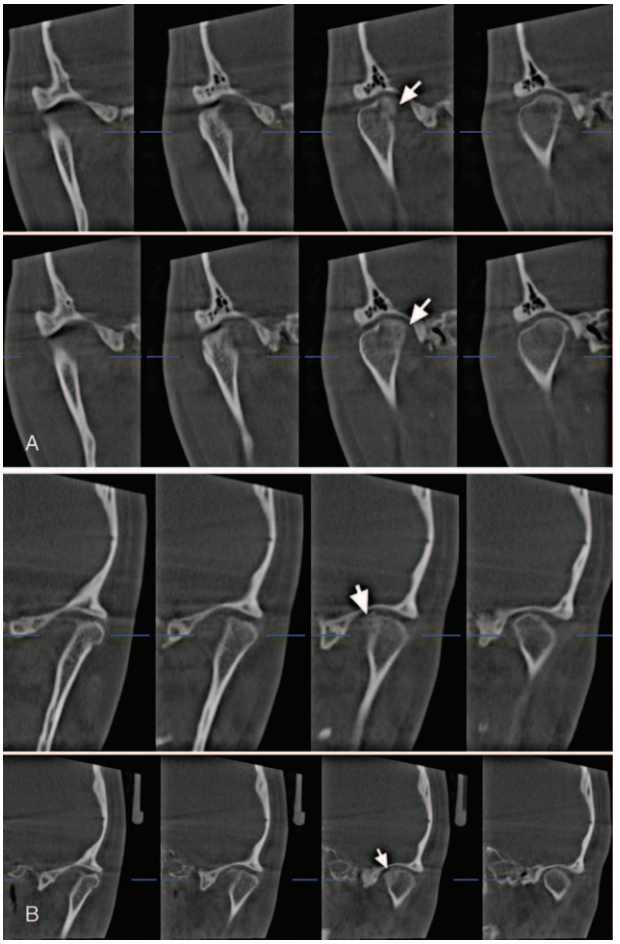

Figure 4. (A) Case 1. Cone-beam computed tomograms of right temporomandibular joint osteoarthritis (upper graph = preoperative coronal view; lower graph = 1 year postoperative coronal view showing reparative remodeling). (B) Case 2. Cone-beam computed tomograms of left temporomandibular joint osteoarthritis (upper graph = preoperative coronal view; lower graph = 1 year postoperative coronal view showed reparative remodeling).

Machon et al[13] conducted a study using 10 TMJ-OA (Wilkes stage IV) joints of 10 patients whose disease was not improved by occlusal splint, arthrocentesis, hyaluronic acid injection, and arthroscopic lavage treatments, in which all 10 patients received 2 injections of 1 mL of PRP over a 2-week time interval. At 3 months post-treatment, the average VAS pain score decreased by 3.2 ± 0.81 from 7.3 ± 0.55 to 4.1 ± 0.77 ($P = .005$), and the MIO was improved by 1.6 ± 1.0 mm at 3 months post-treatment. In the

study of Giacomello et al using 13 TMJ-OA patients who constantly suffered articular pain even after treatment with a mandibular repositioning splint, all 13 patients received 2 injections of 1.5–2 mL of PRP over one month interval. At 6 months post-treatment, the VAS pain score decreased from 7.69 ± 1.9 to 0.23 ± 0.65 ($P < .0001$), and the MIO improved by 9.38 ± 2.21 mm from the pretreatment level of 30.15 ± 4.44 mm to 39.54 ± 4.55 mm ($P < .0001$).[11] The study conducted by Hegab et al enrolled 50 TMJ-OA patients who never received any treatment for TMDs, in which 25 patients in the study group received 3 injections of 1 mL of PRP following arthrocentesis with 50 mL of Ringer's lactate solution over 1-week intervals. At 12 months post-treatment, the VAS pain score decreased from 7.36 ± 1.11 to 0.4 ± 0.76 (power = 97%), and the MIO improved from 33.88 ± 3.09 mm to 41.56 ± 2.31 mm. The joint sounds showed a marked improvement in the first 3 months after the injection treatment and no noticeable changes from 3 to 6 months post-treatment; at 12 months post-treatment, the occurrence of the joint sounds had significantly reduced compared with that at 3 months post-treatment and did not significantly differ from that at 6 months post-treatment.[1] The patients included in the study of Machon et al described above responded to only PRP treatment but not any other treatments, including occlusal splint, arthrocentesis, hyaluronic acid injection, and arthroscopic lavage. Based on our experience, such a population is rarely seen in clinical practice. Compared with the studies conducted by Machon et al and Giacomello et al, the study by Hegab et al revealed the effectiveness of PRP treatment in improving the VAS scores and MIO more accurately because it included patients who did not receive any other treatments before PRP injection. Nevertheless, the study by Hegab et al could not completely rule out the possibility that the improvements in symptoms might be caused by arthrocentesis performed prior to PRP injection. In addition, none of the 3 studies mentioned above evaluated bone regeneration, which is the most desired outcome of TMJ-OA treatment. In this study, the 2 outcome variables, the VAS score for TMJ arthralgia and the MAO, did not show significant changes in either the A+PRP or the PRP group and were not significantly different between the 2 groups, which might be explained by the fact that the patients included in this study had been treated with a 5-mm-thick flat plane splint (FPS), which has been demonstrated to be extremely effective in improving clinical symptoms such as TMJ arthralgia and MAO.[29] Moreover, this study confirmed the improvements in the joint crepitus sounds, jaw range of motion <6 mm, and osseous reparative remodeling in both treatment groups. In addition, the A+PRP treatment resulted in more significant improvements in TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, and pain when chewing most foods compared with the treatment with PRP alone. The above variables assessed in this study were not mentioned in the studies by Machon et al, Giacomello et al, and Hegab et al

Another 2 studies, 1 by Pihut et al and 1 by Hanci et al, on the application of PRP for TMD treatment are also worth mentioning, although they did not use PRP to treat TMJ-OA. In the study conducted by Pihut et al, a single injection of 0.5 mL of PRP was given to 10 patients with Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMDs) stage IIa (i.e., disc displacement with reduction (DDWR)) who had received the occlusal splint treatment for >3 months but did not have satisfactory outcomes. At 6 weeks after injection, the intensity of pain had significantly decreased in all patients, as evidenced by a marked decrease in the mean VAS score from 6.5 to 0.6 ($P = .00005$).[6] In the study conducted by Hanci et al, a single injection of 0.6 mL of PRP was given to 17 joints of 10 patients with DDWR that could not be improved by conservative treatments. The clinical symptoms of all treated patients showed statistically significant improvements at 6 months after injection, as indicated by the decrease in the VAS pain score from 6.69 ± 2.21 to 0.07 ± 0.27 ($P < .05$), the increase in the MIO from 32 ± 8.53 mm to 39.7 ± 10.39 mm ($P = .01$), and the decrease in the number of patients having joint sounds from 12 to 2 (decreased by 83.33%) ($P < .05$).[12] Another interesting study, conducted by Ince et al,[19] a single injection of 1 mL of concentrated growth factor (CGF) was given to 10 patients with joint degeneration and disc displacement with/without reduction that could not be improved by conservative treatments. The clinical symptoms showed improvements after injection, as indicated by decrease of VAS pain score and clicking sound and increase of mouth openness. This study included patients with TMJ-OA, which is more severe than DDWR, and a one-year follow-up confirmed that the improvement of joint crepitus sounds become noticeable at one month post-treatment and became increasingly prominent over time.

In the studies mentioned above, the PRP treatment was inconsistent and varied greatly in the injection dose and times, including 0.5 mL once;[6] 0.6 mL once;[12] 1 mL once every 2 weeks, twice;[13] 1.5 – 2 mL once a month, twice;[11] 1 mL once every week, 3 times;[1] or 1 mL once a month, 4 times,[10] but none of them provided explanations regarding their selection of injection dose and frequency. The injection volume of 2 mL that was used in this study due to a deduction that 2 mL might be the most efficient volume because it is the maximal volume of the joint space. Kim et al[30] revealed that the average volume of the joint space is 1490.5 ± 512.2 mm^3 (between 1–2 mL). Due to the high expectations of the efficacy of high-concentration and high-purity PRP (i.e., LPCGF), we chose a single injection in this study under the consideration that it is very important to minimize the injection-caused pain that patients suffer by reducing the number of injections. Our deduction has been verified in a single-arm study by our research group.[15] In that study, PRP treatment for TMDs showed satisfactory performance in improving joint sounds, as evidenced by the data that an injection of 2 mL of PRP improved the joint sounds of 23 joints (63.9%) at 12.06 ± 8.54 days after treatment and 26 joints (72.2%) at 48.5 ± 64.1 days after treatment, with no significant relapse of symptoms observed during a follow-up period of 258 days.

The strengths of this study include the following. First, a matching process was conducted to eliminate the differences in all characteristics between the 2 groups, ensuring satisfactory internal validity in this study. Second, unlike the previous studies, this study evaluated a relatively complete set of variables associated with TMJ-OA. However, this study also has certain limitations. First, as a retrospective matched cohort study, this study could not avoid the possible bias caused by the study design. Second, the matching process between the 2 groups caused sample loss and reduced the sample size. Third, because this study included only TMJ-OA patients, further research is needed to confirm whether the conclusions drawn from this study can be expanded into other types of TMDs. Finally, the operation requires physicians to be highly skillful. Because the test tubes contain no anticoagulant, the injection must be completed within 5 minutes; otherwise, the blood will become coagulated and PRP cannot be been extracted.

5. Conclusions

Both the A+PRP and PRP alone treatment approaches can effectively improve multiple symptoms of TMJ-OA. Based on the findings from this study, it is recommended to use a single injection of 2 mL of high-concentration, high-purity PRP. In patients with TMJ-OA accompanied by clinical symptoms, such as TMD-associated headache, jaw range of motion <6 mm, myofascial pain with referral, and pain when chewing most foods, an arthrocentesis treatment prior to PRP injection can achieve a more satisfactory outcome.

Acknowledgments

The authors would like to thank Professor Wei-Fan Chiang, a long-term advisor and instructor who provided training in surgical skills. This study had no source of funding.

Author contributions

Data curation: Shun-Yao Ko.
Formal analysis: Shun-Yao Ko.
Investigation: Shang-Lun Lin, Wei-Fan Chiang.
Methodology: Chiang-Chin Tsai, Shang-Liang Wu, Wei-Fan Chiang, Jung Wu Yang.
Project administration: Wei-Fan Chiang.
Visualization: Chiang-Chin Tsai.
Writing – original draft: Shang-Lun Lin.
Writing – review & editing: Shang-Liang Wu, Jung Wu Yang.

References

[1] Hegab AF, Ali HE, Elmasry M, et al. Platelet-rich plasma injection as an effective treatment for temporomandibular joint osteoarthritis. J Oral Maxillofac Surg 2015;73:1706–13.
[2] Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache 2014;28:6.
[3] Seo YJ, Park SB, Kim YI, et al. Effects of condylar head surface changes on mandibular position in patients with temporomandibular joint osteoarthritis. J Craniomaxillofac Surg 2015;43:1380–3.
[4] de Souza RF, Lovato da Silva CH, Nasser M, et al. Interventions for the management of temporomandibular joint osteoarthritis. Cochrane Database Syst Rev 2012;4:CD007261.
[5] Nitzan DW, Price A. The use of arthrocentesis for the treatment of osteoarthritic temporomandibular joints. J Oral Maxillofac Surg 2001;59:1154–9. discussion 60.
[6] Pihut M, Szuta M, Ferendiuk E, et al. Evaluation of pain regression in patients with temporomandibular dysfunction treated by intra-articular platelet-rich plasma injections: a preliminary report. BioMed Res Int 2014;2014:132369.
[7] Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg 2004;62:489–96.
[8] Simonpieri A, Del Corso M, Vervelle A, et al. Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: bone graft, implant and reconstructive surgery. Curr Pharm Biotechnol 2012;13:1231–56.
[9] Man D, Plosker H, Winland-Brown JE. The use of autologous platelet-rich plasma (platelet gel) and autologous platelet-poor plasma (fibrin glue) in cosmetic surgery. Plast Reconstr Surg 2001;107:229–37. discussion 38-9.
[10] Kiliç SC, Güngörmüş M, Sümbüllü MA. Is arthrocentesis plus platelet-rich plasma superior to arthrocentesis alone in the treatment of temporomandibular joint osteoarthritis? a randomized clinical trial. J Oral Maxillofac Surg 2015;73:1473–83.
[11] Giacomello M, Giacomello A, Mortellaro C, et al. Temporomandibular joint disorders treated with articular injection: the effectiveness of plasma rich in growth factors-Endoret. J Craniofac Surg 2015;26:709–13.
[12] Hanci M, Karamese M, Tosun Z, et al. Intra-articular platelet-rich plasma injection for the treatment of temporomandibular disorders and a comparison with arthrocentesis. J Craniomaxillofac Surg 2014;43:162–6.
[13] Machon V, Rehorová M, Šedý J, et al. Platelet-rich plasma in temporomandibular joint osteoarthritis therapy: a 3-month follow-up pilot study. Arthritis 2013;2(2).
[14] Comert Kilic S, Gungormus M. Is arthrocentesis plus platelet-rich plasma superior to arthrocentesis plus hyaluronic acid for the treatment of temporomandibular joint osteoarthritis: a randomized clinical trial. Int J Oral Maxillofac Surg 2016;45:1538–44.
[15] Yang J-W, Huang Y-C, Wu S-L, et al. Clinical efficacy of a centric relation occlusal splint and intra-articular liquid phase concentrated growth factor injection for the treatment of temporomandibular disorders. Medicine 2017;96:e6302.
[16] Kim SG. Necessity of standardized protocol for platelet-rich plasma therapy in temporomandibular joint osteoarthritis. J Korean Assoc Oral Maxillofac Surg 2016;42:65–6.
[17] Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network and Orofacial Pain Special Interest Group. J Orofac Pain 2014;28:6–27.
[18] Lin S-L, Wu S-L, Yang J-W. Lucid flowchart of the diagnostic criteria for temporomandibular joint disorders. Oral Health Dent Manag 2017;16:2.
[19] Ince B UI, Yıldırım MEC, Dadacı M, et al. The efficacy of concentrated growth factor (CGF) on temporomandibular joint dysfunction. Selcuk Med J 2017;33:67–70.
[20] Murakami K, Hosaka H, Moriya Y, et al. Short-term treatment outcome study for the management of temporomandibular joint closed lock: a comparison of arthrocentesis to nonsurgical therapy and arthroscopic lysis and lavage. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:253–7.
[21] Rodella LF, Favero G, Boninsegna R, et al. Growth factors, CD34 positive cells, and fibrin network analysis in concentrated growth factors fraction. Microsc Res Tech 2011;74:772–7.
[22] Association W.M.World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191.
[23] De Leeuw R, Klasser GD. Orofacial pain: guidelines for assessment, diagnosis, and management. Am J Orthod Dentofacial Orthop 2008;134:171.
[24] Nishimura M, Segami N, Kaneyama K, et al. Comparison of cytokine level in synovial fluid between successful and unsuccessful cases in arthrocentesis of the temporomandibular joint. J Oral Maxillofac Surg 2004;62:284–7.
[25] Woodell-May JE, Pietrzak WS. Platelet-rich plasma in orthopedics. Musculoskeletal Tissue Regeneration: 2008;Springer, 547–568.
[26] Woodall JJr, Tucci M, Mishra A, et al. Cellular effects of platelet rich plasmainterleukin1 release from prp treated macrophages. Biomed Sci Instrum 2007;44:489–94.
[27] Kutuk N, Bas B, Soylu E, et al. Effect of platelet-rich plasma on fibrocartilage, cartilage, and bone repair in temporomandibular joint. J Oral Maxillofac Surg 2014;72:277–84.
[28] Wang F, Sun Y, He D, et al. Effect of concentrated growth factors on the repair of the goat temporomandibular joint. J Oral Maxillofac Surg 2016;75:498–507.
[29] Lin S-L, Wu S-L, Ko S-Y, et al. Effect of flat plane splint vertical thickness on disc displacement without reduction—a retrospective matched cohort study. J Oral Maxillofac Surg 2017;75:1627–36.
[30] Kim JY, Kim BJ, Park KH, et al. Comparison of volume and position of the temporomandibular joint structures in patients with mandibular asymmetry. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:772–80.