Journal of Craniomaxillofacial Research

Vol. 11, Issue. 4 Autumn 2024

Efficacy of Blood Factors for Treatment of Temporomandibular Disorders: A Review

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ARTICLE INFO

Article Type:
Review Article

Received: 12 July 2024
Revised: 12 August 2024
Accepted: 11 September 2024

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ABSTRACT

Introduction: To date, no consensus has been reached on one single efficient treatment for temporomandibular disorders (TMDs). Considering the existing controversy regarding the efficacy of blood factors for the treatment of TMDs, this study aimed to do a comprehensive review of the efficacy of blood factors for the treatment of TMDs.

Materials and Methods: In this review study PubMed, ISI Web of Science, and Scopus databases were searched for articles published from 2012 to 2023 using platelet-rich plasma (PRP), platelet-rich fibrin (PRF), injection, temporomandibular joint (TMJ) disorders, blood supply, and blood as keywords. Eligible articles were included and reviewed.

Results: Nineteen eligible articles were reviewed, of which, TMJ pain had been evaluated in 10, ankylosis in 9, disc displacement in 5, and disc dislocation in 3 studies. The remaining studies evaluated other TMJ problems such as clicking, dull maxillofacial pains, ear pain, referred pain in teeth, and lockjaw. TMJ pain and ankylosis had the highest frequency among different TMJ problems. The most commonly adopted frequency of injections was 5 times as reported in 8 studies.

Conclusion: PRP and PRF had optimal efficacy for the reduction and resolution of TMD symptoms especially severe TMJ pain, ankylosis, disc displacement, and disc dislocation. PRP and PRF showed comparable efficacy for this purpose, and the efficacy of PRP and PRF injections for treatment of TMDs was considerably higher than other materials/methods such as chitosan, arthrocentesis, hyaluronic acid, isotonic saline, and hydrocortisone. Five injections appear to be efficient in achieving optimal therapeutic results.

Keywords: Blood factors; Temporomandibular disorders; Platelet-rich plasma; Platelet-rich fibrin.

Please cite this Article as:
Ghannadpour A, Honar Sh, Toumaj A, Mousavi Sangsaraki SP, Razmara F. Efficacy of Blood Factors for Treatment of Temporomandibular Disorders: A Review. J Craniomaxillofac Res 2024; 11(4): 195-208. DOI: 10.18502/jcr.v11i4.18707

Introduction

The temporomandibular joint (TMJ) is a complex joint in the human body comprised of the mandibular condyle as the inferior part of the joint and the temporal bone as the superior part of the joint [1,2]. Temporomandibular disorders (TMDs) are a group of conditions affecting the TMJ and the muscles of mastication [3-6]. TMDs are among the most difficult clinical conditions to diagnose and treat in oral and maxillofacial surgery [4]. The prevalence of TMJ disorders ranges from 10% to 70%, and they are twice as common in females (between 20 to 40 years) than males [7]. Several etiologic factors have been proposed for development of TMDs, which have not been clearly elucidated [8]. Malocclusion, parafunctional habits, stress, and trauma are among the main causes of TMDs, as reported in the literature [9-13]; however, the share of each factor in development of TMDs has not been precisely identified [9,10,14]. The reason may be that each factor can lead to development of TMDs alone and can also affect other factors. For instance, given that stress is considered a type of energy (psychophysiological theory), stressful conditions generate energy in the human body, which needs to be released. Theoretically, there are two methods to release energy: external and internal. Internal energy release is associated with complications such as the development of stomach ulcers, hypertension, asthma, cardiovascular disorders, TMDs, parafunctional habits, etc. This method of stress release is often more common than the external method. Thus, stress may not only cause TMDs directly but also can cause TMDs through parafunctional habits [11]. TMDs have symptoms like pain, articular sounds, limited range of jaw movements, impairments in jaw function, and deviation or deflection when opening or closing the mouth [3,15]. TMDs that are associated with pain significantly impair daily activities and psychosocial functions, and decrease the quality of life of patients [3].

Treatment of TMDs has been the topic of numerous investigations. Nonetheless, no consensus has been reached on one efficient treatment applicable to all patients. Pharmaceutical therapy, physiotherapy, splint therapy, surgery, and intraarticular injection of commonly used drugs are among the most frequently administered treatments [4,16]. Blood factors are among the modalities that may be effective for treatment of TMDs. Several studies have evaluated the efficacy of injection of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) for treatment of TMDs [6,17-19]. Currently, autologous blood products such as PRP, which are derived from patients' own blood have been the topic of numerous investigations, aiming to benefit from the effects of such growth factors to enhance tissue healing. Such attempts are based on the ability of platelets to release growth factors from the alpha-granules, which play a pivotal role in mediation of tissue healing [20]. PRP can serve as a source of chemical mediators during inflammation, and release growth factors. PRF or the second-generation platelet concentrate was first introduced by Choukroun et al, in France [21]. It is an autogenous fibrin matrix that contains growth factors, platelets, leukocytes, and cytokines [18,22]. Some pulp cells remain viable even in the presence of extensive periapical lesions. PRF can induce the proliferation of these residual cells, which can differentiate to odontoblasts following root canal disinfection and reduction of inflammation [22].

The release profile of growth factors such as transforming growth factor-B (TGF-B), and platelet-derived growth factor (PDGF) is different from PRP and PRF. In the use of PRP, release of TGF-B and PDGF significantly decreases after the first day, whereas, in the use of PRF, significant release of TGF-B and PDGF is recorded by up to 2 weeks [23]. Ehrenfest et al.[24] confirmed some differences in release profile of vascular endothelial growth factor from leukocytes in the use of PRP, compared with PRF [24]. In total, evidence suggests that PRF membranes are probably capable of releasing higher amounts of growth factors for a long period [25]. Also, PRF can be converted to injectable form (I-PRF) by pressing the PRF membranes between metal sheets. I-PRF can become coagulated right before injection to form biomaterials and can be mixed with any selected biomaterial to form covalent bonds [26]. Injection of PRP or PRF for management of TMDs is a novel treatment, and differences in the adopted techniques, compositions, and applications make it difficult to compare their efficacy. Therefore, considering the possibly optimal efficacy of blood factors for treatment of TMDs and the existing controversy in this regard, this study aimed to do a comprehensive review of the efficacy of blood factors for treatment of TMDs.

Materials and Methods

In this review study, PubMed, ISI Web of Science, and Scopus databases were searched for articles published from 2012 to 2023 using the following keywords: PRP, PRF, Injection, TMJ Disorders, Blood Supply, and Blood. Article selection was done according to the eligibility criteria. The title and abstract of the retrieved articles were first assessed by two researchers, and then

DOI: 10.18502/jcr.v11i4.18707

the articles were evaluated in terms of meeting the eligibility criteria. Inclusion criteria: Clinical trials, case reports, and prospective studies regarding the efficacy of blood factors for treatment of TMDs, studies with available full-text in the English language, and articles relevant to the topic published from 2012 to 2023. Exclusion criteria: Unavailability of the full texts or available full texts in languages other than English, systematic reviews, narrative reviews, and animal studies. The following variables were extracted from the articles: Journal name, publication year, title, authors, study characteristics, results, and conclusion.

Results

A total of 19 eligible articles were included after applying the eligibility criteria (Figure 1). Also, of 19 eligible articles that were reviewed, TMJ pain had been evaluated in 10 [11,12,20-22,24,25,27,28], ankylosis in 9 [8,10,20,22,24,25,27,28], disc displacement in 5 [8,13,15,23,27], and disc dislocation in 3 studies [13,15,26]. The remaining studies had evaluated other TMJ problems such as clicking, dull maxillofacial pains, ear pain, referred pain in teeth, and lockjaw. Thus, TMJ pain and ankylosis had the highest frequency among different TMJ problems. It should be noted that in the majority of studies that reported TMJ pain, ankylosis was also present (Table 1). The frequency of injections was 5 times in 7 studies [7,12,14,20,21,23,25], 4 times in 4 studies, [9,11,13,26] 3 times in 5 studies, [8,10,15,27,28] 2 times in 2 studies, [22, 24] and 1 time in 1 study [16]. The majority of studies reported that 5 injections were efficient for the reduction/resolution of TMD symptoms (Table 1).

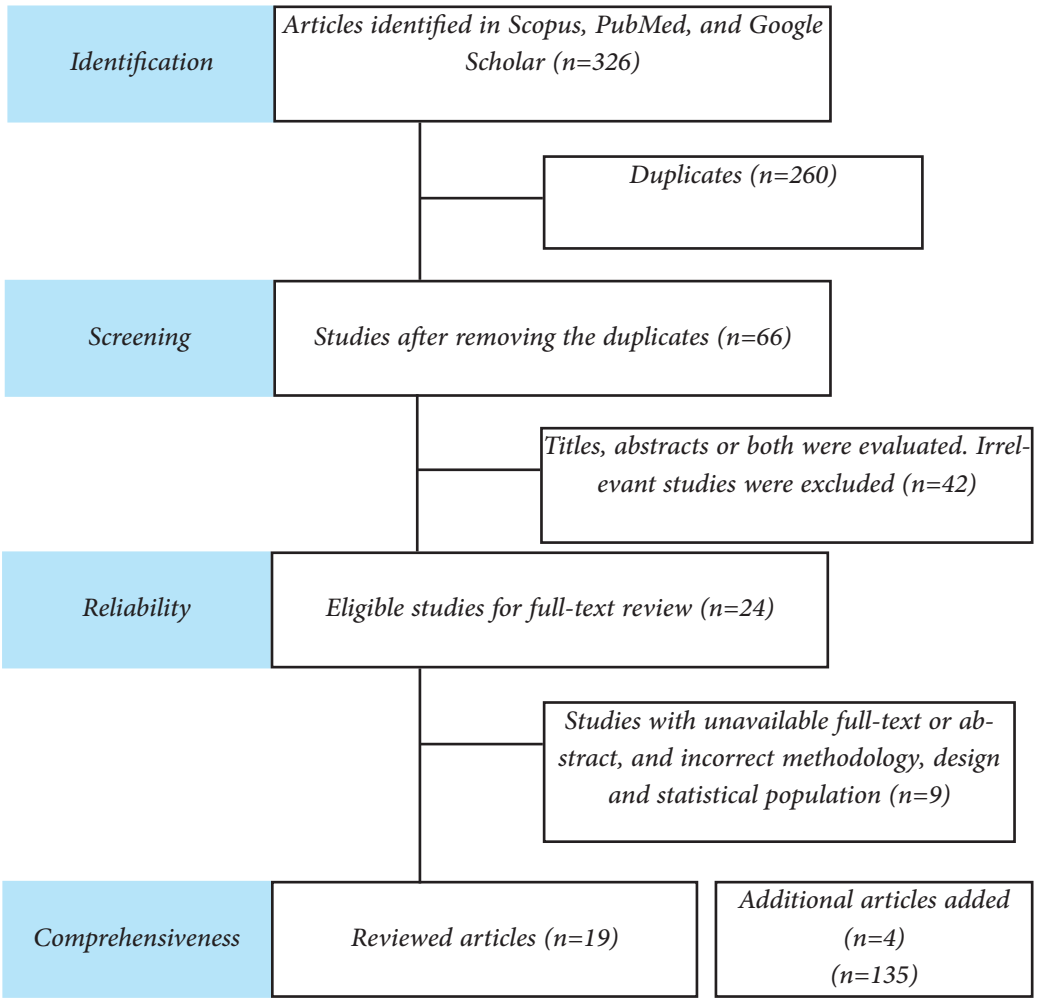

Figure 1. Article selection algorithm.

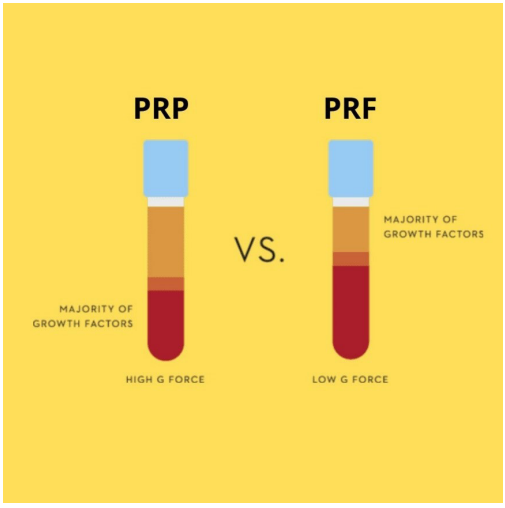

Figure 2. PRF versus PRP.

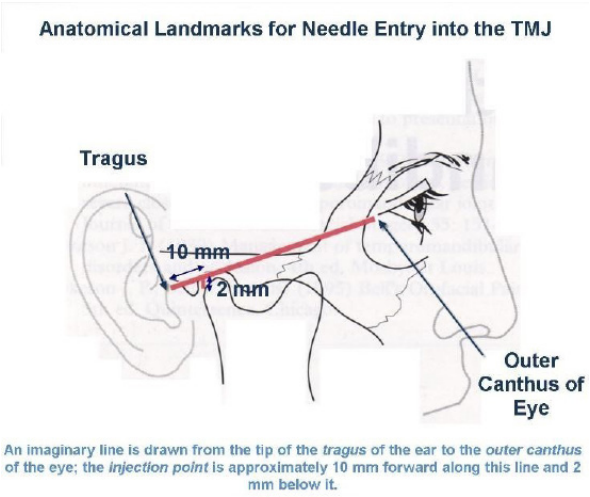

Figure 3. Injection site.

Table 1. Effect of PRF on TMDs.

Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effect	Conclusion
1	Işık et al [7], 2022	36	PRF	10 cc, venous blood	1	Intraarticular injection	5 times	TMJ pain, ankylosis, and disc displacement	Positive	A significant difference was found between the groups regarding pain score, MMO, lateral movements, and protrusion at the 12-month follow-up, and PRF significantly decreased pain and increased jaw movements.

DOI: 10.18502/jcr.v11i4.18707

Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effect	Conclusion
2	Sikora et al [8], 2022	40	PRP	8 cc, peripheral venous blood	0.4	upper portion of TMJ	3 times	Ankylosis and disc displacement	Positive	TMJ pain relief was reported in 71% of treated joints. Improvement of mastication efficiency was reported in 63% of patients after completion of injections.
3	Prakash et al [12], 2022	40	PRP	10 cc, NR	0.6	TMJ's superior joint region	5 times	Severe TMJ pain and lockjaw	Nosignificant differences	No significant difference was found between PRF and hydrocortisone injection with local anesthetic injection in TMD outcome. Nonetheless, the results were slightly superior in those who received PRF injection.
4	Manafikhi et al [11], 2022	20	PRP	20 cc, peripheral blood	1	NR	4 times	Clicking, severe TMJ pain	Positive	Clicking sound was totally resolved in 14 out of 20 patients at 1 week after the first injection, and in all patients at 1 week after the second injection. At 6 months after the first injection, clicking recurred in 2 patients. They concluded that PRF injection can efficiently manage clicking in patients with TMDs.

Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injectio	Type of disorder	Treatment effect	Conclusion
5	Rajput et al [13], 2022	24	Arthrocentesis and PRP	10 cc, NR	1	upper joint space	4 times	Disc displacement and dislocation	Positive	Both groups experienced significant improvement in painless MMO, lateral movements towards the intact side, and pain. The arthrocentesis group also showed significant improvement in MMO. Both modalities were effective but arthrocentesis was more effective for pain relief and PRP was more effective for resolution of articular sounds and jaw deviation.
6	Harba et al [9], 2021	24	PRP	10 cc, peripheral blood	0.5	intra-articular injection	4 times	Referred pain in teeth	Positive	Injection of HA and PRP caused greater improvement in TMD symptoms than HA injection alone, which may be due to the properties of both HA and PRP.

DOI: 10.18502/jcr.v11i4.18707

Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effect	Conclusion
7	Li et al [10], 2021	27	PRP and chitosan	NR, Peripheral blood	1	-	3 times	Ankylosis and severe pain	Positive	PRP group showed superior inter-incisal MMO and lower pain than chitosan group. However, the two groups were the same regarding resolution of articular sounds.
8	Karadayi et al [14], 2021	36	Arthrocentesis and PRF	20 cc, NR	2 cc per joint	Temporomandibular joint area	5 times	Ear sounds, backache, and ear pain	Positive	Combination of PRF and arthrocentesis yielded a much better result than arthrocentesis alone but further studies with longer follow-ups are required to better perceive the effects of PRF.
9	Torul et al [15], 2021	54	Arthrocentesis combined with HA or I-PRF	9 cc, NR	1 cc per point		3 times	Disc displacement and dislocation	Positive	Application of I-PRF after arthrocentesis was more effective than arthrocentesis alone or with HA in the short-term. Also, HA alone had no extra advantage over arthrocentesis.

Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effect	Conclusion
10	Singh et al [16], 2021	24	Arthrocentesis and I-PRF	6 cc, antecubital vein	1 cc	The first point was marked 10 mm anterior to the tragus and 2 mm below the CTL; the second point was marked 20 mm anterior and 10 mm below the CTL.	1 time	Dull pain in the maxillofacial region	Positive	Both groups showed improvement in pain score, MMO, and TMJ sounds at all time points. However, arthrocentesis alone had no significant difference with arthrocentesis combined with PRP.
11	De Sousa et al [20], 2020	80	Bite splint, betamethasone, hyaluronate sodium, and PRF	Not reported	2 cc	TMJ	5 times	Severe TMJ pain and ankylosis	Positive	All treatments decreased pain and increased painless MMO. Splinting plus PRP injection resulted in long-term success.
12	Yuce et al [28], 2020	47	Arthrocentesis alone, and in combination with HA injection or PRF injection	10 cc, venous blood per joint	2 cc	Superior joint space	3 times	Severe pain and ankylosis	Positive	All conventional treatments can decrease pain and improve MMO. Nonetheless, intraarticular injection of I-PRF combined with arthrocentesis was superior for gradual pain relief and improvement of MMO.

DOI: 10.18502/jcr.v11i4.18707

Number	Authors, Year	Sample siz	Study grou	Collected blood volume (cc) and type	njected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effec	Conclusion
13	Nitecka-Buchta et al [21], 2019	58	PRP and isotonic saline	40 cc, venous blood	0.5 cc	Bilaterally into the right and left masseter muscles at 3 painful points at each site	5 times	Severe TMJ pain	Positive	Intramuscular injection of PRP is a successful method for reduction of myofascial pain in masseter muscle in TMD patients. Nonetheless, the efficacy of PRP for myofascial pain reduction in masticatory muscles should be assessed in further clinical trials.
14	Elgazzaz et al [22], 2019	12	PRP	20 cc, NR	4 cc	2.5 cc was injected in the superior join space through the first needle, then, the needle was withdrawn outward around 1cm to inject 1.5 cc into the pericapsular tissues.	2 times	Severe pain and ankylosis	Positive	PRF injection is an effective minimally invasive procedure which can be used for treatment of hyperactivity of TMJ. Moreover, all signs and symptoms improved within 6 months after TMJ injection. It is recommended to be repeated annually.
15	Gupta et al [23], 2018	20	PRP and hydrocortisone	5 cc, NR	0.6 cc for each TMJ	10 mm forward from the tragus and 2 mm below the tragus–lateral canthus line	5 times	Disc displacement	Positive	PRP injection significantly decreased pain compared with hydrocortisone and local anesthetic agent. MMO increased equally in both groups, and TMJ sounds were less commonly experienced by patients who received PRP.

Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effect	Conclusion
16	Jonathan Albilia et al [24], 2018	37	PRP and PRF	NR, Antecubital vein	1.5–2 cc for each TMJ	Superior joint space, the retrodiscal tissue and pericapsular	2 times	TMJ Ankylosis, clicking, and pain at the TMJ	Positive	Liquid PRF showed long-term analgesic effects on the majority of patients with painful TMJ ID.
17	Lin et al [25], 2018	90	30 patients in A+PRP and 60 patients in PRP	10 cc, venous blood	2 cc	Point D*	5 times	Severe pain and ankylosis	Positive	Both A+PRP and PRP groups showed some improvements in TMJ-OA. But the two groups had no significant difference in improvement of crepitus, healing and pain. Nonetheless, A+PRP had superior performance in resolution of TMD-related headache, range of jaw movements < 6 mm, myofascial pain, and mastication pain compared with PRP alone.
18	Hancı et al [26], 2015	20	PRP and arthrocentesis	8 cc, NR	0.6 cc for each TMJ	The injection point was marked 10 mm forward from the tragus and 2 mm below the tragus lateral canthus line; the second point was marked 20 mm forward from the tragus and 6 mm below the tragus lateral canthus line	4 times	Dislocation	Positive	Intraarticular injection of PRP for treatment of TMJ disc displacement was more effective than arthrocentesis.

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Number	Authors, Year	Sample size	Study groups	Collected blood volume (cc) and types	Injected volume (cc)	Injection site	Frequency of injections	Type of disorder	Treatment effect	Conclusion
19	Hegab et al [27], 2015	52	Hyaluronic acid and PRP	Ulnar vein	1 cc, NR	Intra-articular injections	3 times	Severe pain and ankylosis	Positive	In the long-term, PRP was superior to HA acid in treatment of TMJ-OA regarding pain reduction and increased inter-incisal space.

*: 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 1cm away from the front of Point A, and Point C was 1cm away from the front of Point B. Subsequently, the point that was 2mm below Point B on the line perpendicular to the tragus-lateral canthus line was marked as Point D. NR: not Reported.

Discussion

This review study evaluated the efficacy of blood factors for treatment of TMDs. Use of autologous blood, PRP, and PRF are among the novel suggested therapeutic approaches for treatment of TMDs. Schulz was the first to suggest blood injection around the joint for treatment of recurrent joint dislocation in 1973. He reported that of 16 patients, 10 were asymptomatic at the one-year follow-up, 7 were asymptomatic at the 2-year follow-up, and 5 were asymptomatic at the 5-year follow-up [29]. Over time, and following the introduction of PRP and PRF, studies focused on their effects on TMDs. Hermens et al. [30] injected autologous blood into the pericapsular space in 19 patients. At the 18-month follow-up, 17 patients had completely recovered. Hasson et al. [31] injected autologous blood into the pericapsular space and the upper compartment of the TMJ for treatment of recurrent TMJ dislocation. At the 1-year follow-up, of 3 patients, only one still had subluxation. Hjortdal et al. [32] reported treatment of a case of recurrent joint dislocation with a combination of intermaxillary fixation and intraarticular blood injection. Kato et al. [33] injected autologous blood around and into the TMJ capsule in an 84-year-old female patient, and immobilized the mandible with a bandage for 24 hours and obtained acceptable results. By injection of autologous blood, they tried to induce fibrosis in the articular space limit the articular movements, and subsequently prevent disc dislocation. It appears that injection of autologous blood is a more conservative and acceptable method than other materials.

With respect to the injection of autologous blood, it is hypothesized that trauma to the condyle or surgery of the TMJ would induce bleeding at the joint area and subsequent immobility of the jaw, and may cause unwanted consequences such as jaw asymmetry and fibrotic or skeletal ankylosis of the jaw such that after the recovery period, such patients have to undergo jaw physiotherapy. It is believed that blood injection into the joint creates a similar situation. However, clot formation and its maturity can be controlled only by jaw movements and physiotherapy. PRF is composed of a fibrin matrix rich in autologous leukocytes. It has a quaternary molecular structure and contains cytokines, platelets, and stem cells. It serves as a biodegradable scaffold that aids in micro-vascularization and can guide the migration of epithelial cells. Also, PRF can serve as a scaffold for delivery of other cells involved in tissue regeneration. It releases growth factors within 1 to 4 weeks. The PRF preparation protocol only requires blood centrifugation with no anticoagulant or bovine thrombin [34]. PRP recently attracted attention as an orthobiological adjunct treatment. It regenerates the intraarticular hyaluronic acid, increases the synthesis of glycosaminoglycans by chondrocytes, regulates angiogenesis, and provides a scaffold for stem cell migration. Preliminary studies revealed that PRP can induce cell proliferation and production of cartilage matrix by chondrocytes and bone marrow-derived mesenchymal stromal cells, and increases the production of hyaluronic acid by synoviocytes [15]. PRP is obtained by centrifugation of autologous whole blood with thrombin and calcium chloride [35] (Figure 2). In the present study, 19 articles were reviewed, and

the majority of them confirmed the optimal efficacy of injection of blood factors for treatment of TMDs [8-11,13-16,20-24,27,28]. Also, 9 studies evaluated the effect of PRP injection, and 9 studies assessed the effect of PRF injection. One study [24] compared the efficacy of different treatments for TMDs. Prakash et al. [12] evaluated 40 patients and found no significant difference between the injection of PRF, and hydrocortisone plus local anesthetic agent with respect to TMD outcomes. Nonetheless, the results were slightly better in those who received PRF injections; however, other studies [12] reported resolution of at least one of the TMD symptoms. In the reviewed studies, the amount of collected blood varied from 5mL to 40mL (Table 1). Also, the volume of injected PRF or PRP varied from 0.4mL [8] to 0.5mL, [9,21] 0.6mL, [12,23,26] 1 mL, [10,11,13,15,16,27] 2mL, [14, 20,24,25,28] and 4 mL[22]. The injection site was intraarticular and around the tragus-canthus line (Figure 3). Pain is a common problem in TMD patients, and the positive analgesic efficacy of blood factor injections has been previously confirmed. Işık et al. [27] stated that PRF significantly decreased pain and increased jaw movements. Sikora et al. [8] reported the optimal efficacy of PRP for the reduction of articular pain in 71% of the treated joints. Li et al. [10] confirmed the optimal efficacy of PRP injection. Many other studies reported pain relief in over 70% of patients after the injection of PRP and PRF [13,16,20,21,24-28]. Thus, it may be concluded that injection of blood factors can successfully decrease TMD pain.

Some studies evaluated articular sounds and maximum mouth opening (MMO) and reported controversial results. Singh et al. [16] treated 24 patients in two groups of arthrocentesis and I-PRF and reported improvement of pain, MMO, and TMJ sounds at all-time points in both groups with no significant difference between arthrocentesis alone and in combination with PRP. Rajput et al. [13] evaluated 24 patients in arthrocentesis and PRP groups and reported that PRP was more effective for the resolution of articular sounds and jaw deviation. Li et al. [10] evaluated patients in two groups of PRP and chitosan and concluded that PRP yielded superior results regarding maximum inter-incisal opening and pain severity compared with the chitosan group. However, the two groups were comparable regarding the resolution of articular sounds. De Sousa et al. [20] reported that intraarticular injection of I-PRF in combination with arthrocentesis was superior regarding gradual pain relief and improvement of MMO. Gupta et al. [23] showed comparable efficacy of PRP and hydrocortisone in improvement of MMO and resolution of articular sounds. All reviewed studies compared the efficacy of PRP and PRF with other non-invasive modalities, for treatment of TMDs. Comparison of PRP and PRF with splint therapy and surgery was only performed in one study. De Sousa et al. [20] evaluated the effects of bite splint alone and in combination with betamethasone, sodium hyaluronate, and PRF, and showed that all modalities decreased pain and increased painless MMO. Splint therapy along with PRP showed long-term successful results. However, other studies only compared PRP and PRF with non-invasive and pharmaceutical modalities. The majority of studies compared chitosan, [10] arthrocentesis, [13-16,28] hyaluronic acid, [15,27,28] isotonic saline, [21] and hydrocortisone [23] with PRP and PRF injection, and the majority of them reported the superior efficacy of PRP and PRF [7-11,13-16,20-28].

However, it should be noted that genetic, geographical, nutritional, and psychological differences in different individuals can affect their TMD signs and symptoms. Thus, the therapeutic effects of PRP and PRF injections may be variable in different individuals. Therefore, more definite treatment modalities such as splint therapy should be preferably used in combination with PRP or PRF injection for resolution of TMD signs and symptoms. Although the literature suggests that PRP and PRF have similar efficacy in resolving TMD symptoms, either treatment can be used effectively. Since previous studies reported the effect of psychological factors such as stress, anxiety, depression, and quality of life on the severity of TMDs, future studies are recommended to address these parameters in patients and their effects on the efficacy of PRP and PRF injection. Furthermore, future studies are recommended to use a combination of splint therapy and PRP and PRF to obtain more accurate results. Considering the gap of information in this respect, future clinical trials are required nationwide.

Conclusion

PRP and PRF showed optimal therapeutic efficacy in reduction and resolution of TMD symptoms particularly severe TMJ pain, ankylosis, disc displacement, and disc dislocation. PRP and PRF showed comparable efficacy. Also, PRP and PRF injections for treatment of TMD symptoms were superior to other materials/modalities such as chitosan, arthrocentesis, hyaluronic acid, isotonic saline, and hydrocortisone, and five injections were found to be efficient in achieving favorable treatment results.

DOI: 10.18502/jcr.v11i4.18707

Conflict of Interest

There is no conflict of interest to declare.

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 DOI: 10.18502/jcr.v11i4.18707