Original Article

Evaluation of Treatment Outcomes of Injecting Plasma Rich in Growth Factors versus Hyaluronic Acid in Arthroscopically Treated Temporomandibular Joints

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ABSTRACT

Objective: This study aims to compare the treatment outcomes of injecting PRGF versus HA in patients with TMJ disorders following arthroscopic treatment with a focus on biochemical markers and pain relief.

Methods: A prospective, randomized clinical trial was conducted with 12 patients diagnosed with TMJ disorders, all of whom underwent arthroscopic disc release. randomly divided into two groups Gp A: received HA injections & Gp B: received PRGF injections. Synovial fluid samples were collected before surgery and immediately prior to each injection to measure levels of (IL-6) and(TNF-α) in each sample, and statistical analysis was conducted also pain levels were assessed using the Visual Analog Scale (VAS)

Results: In this study, the comparison of TNF-α levels between both groups revealed that TNF-α levels significantly higher in PRGF group compared to the HA group, indicating a more pronounced inflammatory response. While regarding comparison of IL-6 levels between both groups showed a slightly more significant decrease in the PRGF group, although this difference was not statistically significant. Regarding VAS between both groups there were significantly lower VAS scores at 2 weeks and 1 month compared to those receiving HA injections. While the PRGF group exhibited a marginally greater reduction in VAS scores overall, the difference was not statistically significant when compared to the HA group.

Conclusion: Both PRGF and HA injections appear to be effective adjuncts to arthroscopic treatment for TMJ disorders and alleviated pain. PRGF demonstrated superior efficacy in decreasing TNF-α levels and achieved greater pain reduction compared to HA throughout all follow-up periods. These findings highlight the potential of PRGF as a more effective therapeutic option for TMJ disc displacement management.

Key Words: Temporomandibular joint, Plasma Rich in Growth Factors, Hyaluronic Acid, Arthroscopy, Treatment outcomes, Pain management, Joint function.

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INTRODUCTION

Arthroscopic temporomandibular joint surgery (TMJ) showed significant evolutions during the last two decades. After the settlement of the primary technique for gaining arthroscopic access to the TMJ as a safe and valuable modality for diagnosing and managing TMJ disorders at the end of the last century, different supplementary surgical techniques were subjected to clinical trials in order to improve the treatment outcomes [1- 6].

The techniques utilized in this study encompassed a range of interventions, such as injecting various substances like sodium hyaluronate and corticosteroids into the joint, as well as the utilization of a second working cannula to facilitate surgical procedures involving the internal structures of the joint [4, 5, 7, 8]. Recently, plasma rich in growth factors (PRGF) injection in TMJ has garnered the attraction of researchers after its promising results in managing knee osteoarthritis [5, 7].

The findings of the reports demonstrate the effectiveness of PRGF factors compared to sodium hyaluronate in managing knee joints. As a result, maxillofacial surgeons have incorporated PRGF as an additional injectable substance during arthroscopic surgery [9].

In contrast, arthroscopic surgical techniques to modify the position of the displaced disc in internal derangement cases are readily available and gained popularity among maxillofacial surgeons. These techniques utilize laser, coblation technology, pins, and new stabilizing sutures [4, 5]. Currently, there is a growing inclination to evaluate the treatment outcomes of different TMJ surgical interventions using biochemical analysis in correlation to pain as a clinical finding [10]. The main focus is on various cytokines, including interleukins (1, 6, and 10) and the tumor necrosis factor-alpha (TNFα).[11, 12]

Hyaluronic acid (HA), sodium hyaluronate, is a glycosaminoglycan that is synthesized by synoviocytes and chondrocytes present in all joints [7]. In cases of TMJ inflammation, a gradual decrease in HA's molecular weight and concentration might gradually diminish by 35–50%,

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which may result in osteoarthritic changes [7]. The rationale for using HA in the inflammatory conditions impacting TMJ is rooted in the ability of direct intra-articular injection to facilitate viscosupplementation, thereby replenishing depleted HA levels and promoting the synthesis of endogenous HA within the joint [7, 13]In the clinical setting, intraarticular injection of HA has been documented to enhance the clinical manifestations and alleviate symptoms associated with arthritic joints. Consequently, it has gained significant recognition as an effective therapeutic approach for addressing TMJ disorders [14]. The demonstrated advantages of this intervention extend beyond the alleviation of joint pain as well as enhancement of masticatory efficiency and mandibular dynamics, encompassing its impact on inflammatory mediators as well [10].

In the musculoskeletal domain, there has been a notable surge in research interest regarding platelet-rich plasma (PRP) products, a product of autologous blood characterized by a significantly elevated platelet concentration than normal blood levels. This increased concentration is achieved through the process of concentrating as well as sequestering the blood using centrifugation of gradient density. The concentrated platelets are comprised of numerous growth factors (GFs) [7]. The autologous platelet preparations have the ability to alter the inherent healing process through various mechanisms. The observed phenomenon is linked to a heightened presence of GFs as well as bioactive proteins that are released by activated platelets. These substances appear to possess the capability to facilitate tissue regeneration. The application of PRP at a local level has been observed to elicit stimulatory impacts on cells involved in the process of tissue repair while also exerting an inhibitory effect on certain proinflammatory cytokines. The simultaneous augmentation of tissue repair and reduction in tissue degradation may enable the expeditious advancement of the tissue healing process, resulting in a more rapid recovery.[15]

In relation to the optimal HA session number required to yield sustained positive outcomes, Manfredini et al. demonstrated that a treatment regimen consisting of five interventions involving joint lavage in combination with low-molecular-weight hyaluronic acid injections should be regarded as the standard protocol [16]. However, Guarda-Nardini et al. postulated that the five-session protocol is not optimal for managing TMJ disorder symptoms from a cost-to-benefit ratio [17]. They suggested conducting a study to determine the effectiveness of a three-session protocol, following its encouraging results in treating knee osteoarthritis, to reduce the total number of sessions required [17].

Concerning the optimal quantity of hypnotherapy sessions required to yield sustained positive outcomes, Manfredini et al. demonstrated that a treatment regimen consisting of five interventions, which involve joint lavage in combination with injections of low-molecular-weight hyaluronic acid, should be regarded as the standard protocol [16]. Nevertheless, Guarda-Nardini et al. postulated that the five-session protocol is not viable for managing TMJ disorder symptoms from a cost-to-benefit ratio [17]. They suggested conducting a study to evaluate the efficacy of a three-session protocol, following its favorable results in knee osteoarthritis, with the aim of reducing the total number of sessions required [17].

One of the PRP products is the PRGF, an autologous PRP distinguished by leukocyte absence as well as the presence of a particular concentration of growth factors as well as platelets [5]. PRGF provides endogenous fibrin scaffolds and platelet-derived growth factors for the purpose of generation. Multiple autologous growth factors and PRGF's fibrin scaffold-released proteins may substantially impact damaged cartilage regeneration or repair. Recently, PRGF and PRP utilization has been extended to TMJ and ID treatment following promising results of their utilization in knee osteoarthritis [7, 9]. Consequently, the comparison of outcomes between the injection of HA and PRGF following TMJ arthroscopic surgery is a topic of interest, particularly in terms of clinical and biochemical measures.

The current prospective study aims to compare HA and PRGF outcomes versus HA injection following TMJ arthroscopic surgery in terms of biochemical analysis and pain records.

MATERIALS AND METHODS:

The current prospective study was carried out on 12 patients selected from patients seen in the TMJ clinic of the Oral and Maxillofacial Surgery Department at Minia University Dental Hospital who were planned to undergo arthroscopic surgery. The study candidates were recruited after subjecting patients who are planned to undergo arthroscopic anterior disc release surgery to definite inclusion and exclusion criteria. The selected study candidates were randomized into two equal groups. Group (A) received both superior and inferior joint space HA injections at the surgery's end and two injections at 2 and 4 postoperative weeks [9].

Group (B) received superior and inferior joint space PRGF injections at the surgery's end and two injections at 2 and 4 postoperative weeks [9]. Synovial fluid samples were collected immediately before the surgery and before each injection. The levels of TNFα and IL-6 assay were measured in every sample and analyzed statistically for changes. The visual analog scale (VAS) records of pain were recorded for preoperative, 2 weeks, 4 weeks, and then every 4 weeks interval till 16 weeks postoperative period. The pain records of both groups were compared and subsequently subjected to statistical analysis. The purpose and characteristics of the study were clearly stated to all eligible participants, and written informed consent was obtained from each patient prior to the study procedures.

Inclusion criteria

- Patients included in either of the following diagnostic groups (axis I; group II.b, II.c, and III) according to the RDC/TMD system.
- MRI signs of disc displacement and/or arthritis.
- Persistent symptoms and signs of anterior disc displacement and/or arthritis are non-responsive or refractory to conservative non-surgical treatment, including medications, physiotherapy, and splints.
- Age ranges from 18-50 years.
- Complete the injection protocol.
- Complete a follow-up period of four months.
- Assign informed consent.

Exclusion criteria

- Joints with prior TMJ surgery.
- History of mandibular fractures.
- Concurrent use of steroids or narcotics.
- Pregnant and lactating females.
- Interrupted injection protocol.
- Incomplete follow-up period.
- Patients who refuse to join the study.

Pain assessment

All the study candidates were assessed clinically following RDC/TMD specifications. Joint pain was measured subjectively using VAS from 1-10 and objectively. These parameters were recorded by a single clinician who was blinded to the surgical procedure.

Synovial fluid sample collection

Before the surgery and the following injections, saline solution (2 ml) was injected into the superior joint space. This was accomplished utilizing a 3 ml syringe, which was inserted through an inferolateral approach following the administration of a subcutaneous local anesthetic. The solution underwent aspiration and subsequent reinjection for a total of five iterations, facilitating the thorough blending of the saline solution with the synovial fluid. Subsequently, the combined solution was aspirated (for the biochemical analysis). The synovial fluid samples were stored at a temperature of -20° C.

PRGF preparation

In order to obtain the platelet-rich growth factor (PRGF), 36 ml of peripheral venous blood was collected from Group (B) patients within the operating room. This blood was immediately collected into four extraction tubes containing 3.8% sodium citrate as an anticoagulant. The blood that was obtained was subjected to centrifugation at a force of 580 g for a duration of 8 minutes at ambient temperature within the confines of the surgical theater. Following blood tube centrifugation, the plasma fractions were isolated using pipetting techniques under aseptic conditions. Only 2 ml of platelet-rich plasma located above the red blood cell layer was collected to prevent leukocytes. Before injection, the 2-ml fractions were combined in a single tube, resulting in a total volume of 8 ml. The tube was gently inverted in a sterile glass container for activation. Subsequently, 400 ml of calcium chloride was added for injection [5, 9].

Surgical protocol

Both groups underwent arthroscopic surgery under general anesthesia. The surgical procedures for all patients were done by the same surgical team using the same instrumentation. A standard fossa portal of entry was established first to perform a diagnostic sweep. A second working portal was established following the concepts of triangulation [4]. The anterior release of the disc was done utilizing a sickle knife and electrocautery. The synovium at the disc synovium crease was incised using the electrocautery tip. After exposing the pterygoid muscle, all muscle fibers were resected from the disc (under direct visualization of arthroscopy). Posterior mobilization of the disc was carried on with a blunt probe, and then scarification of the posterior disc attachment was performed using the electrocautery tip. At the end of surgery, HA was injected in superior and inferior joint spaces in Group (A), while PRGF was injected in both joint spaces in Group (B). All subjects underwent the exact postoperative instructions and medications consisting of NSAIDs, soft diet, and physiotherapy, including range of motion, isometric exercises, and thermal application.

Statistical analysis

Data analysis was done utilizing the 28th version of the SPSS software (IBM Co-Armonk- NY-USA). Data distribution normality was determined utilizing the Shapiro-Wilks test. Quantitative parametric data were presented as standard deviation (SD) as well as mean and were analyzed utilizing unpaired student t-test. The analysis involved conducting a Repeated Measures ANOVA test (to compare different measurements) within the same group.

The study utilized quantitative non-parametric data, represented using the median and interquartile range (IQR). These data were subjected to analysis utilizing the Mann-Whitney test. The analysis of intragroup comparison between different measurements was conducted using the Friedman test. The qualitative variables were represented in terms of frequency and percentage (%) and were subjected to analysis using either Fisher's exact test or the Chi-square test.

RESULTS

This prospective randomized study assessed 30 patients for eligibility; 11 did not fulfill the criteria, and 7 refused to participate. The remaining 12 patients were randomly allocated into two equal groups (6 patients each). All patients were followed up and analyzed statistically (Fig. 11).

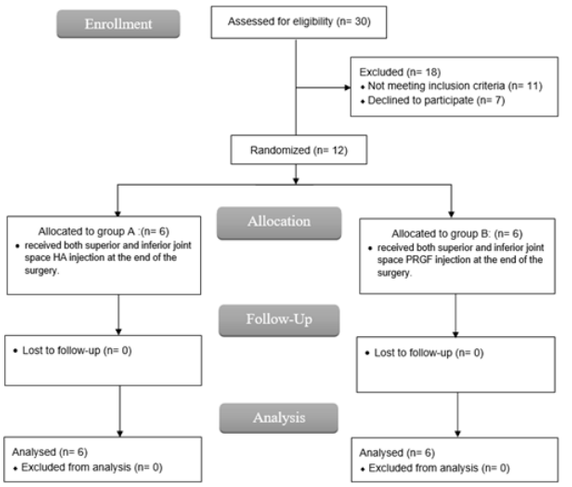

Figure (11): CONSORT flowchart of the progress through the phases of a 2-group parallel randomized trial

As demonstrated in Table 1, each group included (1 male and 5 females), with ages ranging from (22 to 54 years) as well as 38 ± 12.12 mean age in Group A and from (18 to 42 years) with a 30 ± 8.25 mean age in Group B. No substantial differences were noted between both groups regarding sex and age (Fig. 12 and Fig. 13)

		Group A (n=6)	Group B (n=6)	P value
Age (years)	Mean ± SD	38 ± 12.12	30 ± 8.25	0.211
	Range	22 – 54	18 - 42	
Gender	Male	1 (16.67%)	1 (16.67%)	1.00
	Female	5 (83.33%)	5 (83.33%)	

Table 1: THE studied groups' demographic data
Data are presented as frequency (%) unless otherwise mentioned

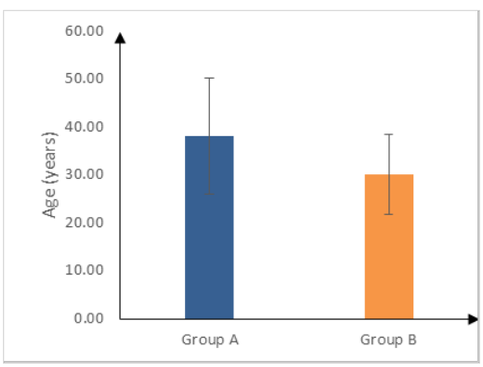

Figure (12): Age of the studied groups

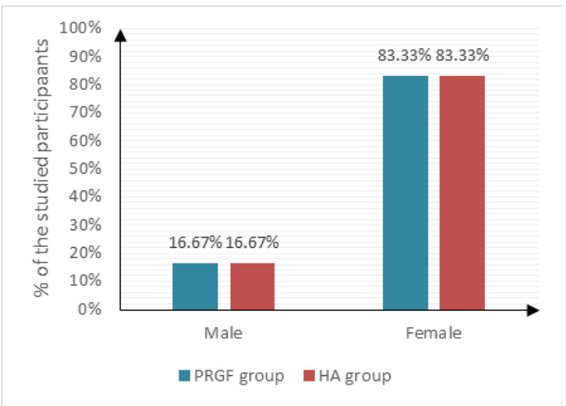

Figure (13): Gender distribution in the studied groups

Regarding group A (received HA injection), the mean TNF-α level preoperatively was 34.77 ± 4.72 (Pg/ml), which significantly decreased 2 weeks after the first injection to be 27.51 ± 3.97 (Pg/ml) and further decreased 4 weeks postoperatively to be 22.88 ± 3.55 (Pg/ml), (P values<0.001).

As regards group B (that received PRGF injection), the mean preoperative TNF-α level was 34.64 ± 6 (Pg/ml), which significantly decreased 2 weeks after the first injection to be 25.87 ± 4.71 (Pg/ml) and continued to decrease significantly 4 weeks postoperatively to be 18.7 ± 3.5 (Pg/ml), (P values<0.001).

By comparing both groups, the TNF-α level was comparable at all time follow-ups. Conversely, the change in TNF-α level was markedly elevated in patients receiving PRGF injection than cases on HA injection (P-value= 0.029) (Table 2 and Fig. 14)

TNF-α (Pg/ml)	Group A (n=6)	Group B (n=6)	P between groups
Preoperative	34.77 ± 4.72 [a]	34.64 ± 6 [a]	0.968
2 week	27.51 ± 3.97 [b]	25.87 ± 4.71 [b]	0.531
4 weeks	22.88 ± 3.55 [c]	18.7 ± 3.5 [c]	0.067
Change	11.89 ± 2.52	15.94 ± 2.99	0.029*
P between measurements	<0.001*	<0.001*	

Table 2: Comparison between the studied groups in terms of TNF-α levels)at different follow-ups)

Data are expressed as mean ± SD.
Different lower-case letters denote substantial differences.
*: Statistically significant as p-value<0.05

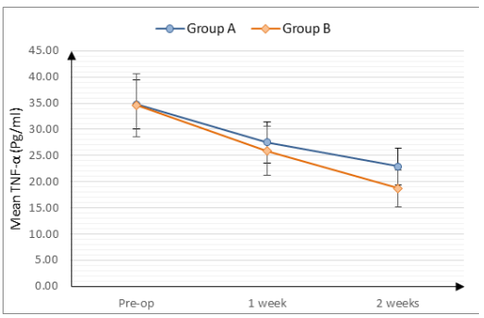

Figure (14): Comparison between the studied groups regarding TNF-α levels at different follow-ups

In terms of IL-6 level, patients who received HA injection had a preoperative mean of 47.41 ± 11.48 (Pg/ml), which significantly decreased 2 weeks after the first injection to 37.55 ± 7.62 (Pg/ml) and continued decreasing significantly 4 weeks postoperatively to be 31.35 ± 7.31 (Pg/ml), (P values<0.001).

As regards patients on PRGF injection, the mean preoperative IL-6 level was 45.23 ± 11.59 (Pg/ml), which significantly decreased 2 weeks after the first injection to 33.57 ± 10.85 (Pg/ml) and further decreased after 4 weeks to 25.01 ± 9.79 (Pg/ml), (P values<0.001).

The IL6 level was comparable at all-time measurements by comparing both groups. Similarly, the change in IL-6 level was slightly higher in patients receiving PRGF injection yet insignificantly different than those on HA injection, as shown in Table 3 and Fig. 15

IL-6 (Pg/ml)	Group A (n=6)	Group B (n=6)	P between groups
Preoperative	47.41 ± 11.48 [a]	45.23 ± 11.59 [a]	0.75
2 week	37.55 ± 7.62 [b]	33.57 ± 10.85 [b]	0.479
4 weeks	31.35 ± 7.31 [c]	25.01 ± 9.79 [c]	0.233
Change	16.06 ± 6.78	20.22 ± 4.97	0.253
P between measurements	<0.001*	<0.001*	

Table 3: Comparison between the studied groups with respect to IL-6 levels (at different follow-ups)

Data are presented as mean ± SD
Different lower-case letters demote substantial difference
*: Statistically significant as p-value<0.05

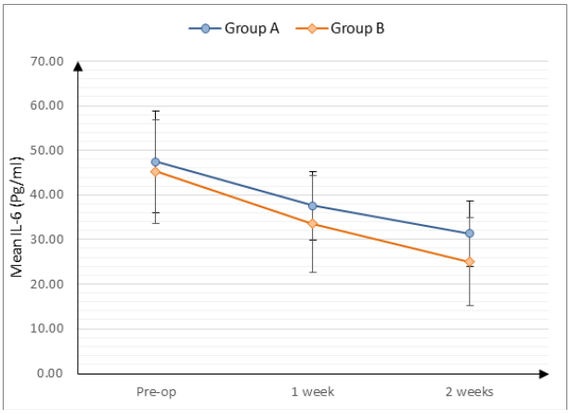

Figure (15): Comparison between the studied groups regarding IL-6 levels at different follow-ups

In relation to the Visual Analog Scale (VAS) score, patients who underwent hyaluronic acid (HA) injection exhibited a preoperative median VAS score of 8.5. This score exhibited an insignificant decrease to 7 and 6 at 2 and 4 weeks postoperatively, respectively. However, the VAS score continued to decrease significantly at 2, 3, and 4 months postoperatively, reaching scores of 4, 2, and 1, respectively (P values<0.05). Significant reductions in postoperative measurements were observed at 3 and 4 months when compared to measurements taken at 2 and 4 weeks (P values<0.05).

The patients who underwent PRGF injection demonstrated a preoperative median VAS score of 8.5. This score showed a non-significant decrease to 7 and 4.5 at 2 and 4 weeks postoperatively, respectively. However, there was a significant decrease in VAS scores at 2, 3, and 4 months postoperatively, with scores of 2.5, 1.5, and 1, respectively (P values<0.05). Significant reductions in postoperative measurements were observed at 2, 3, and 4 months compared to the measurements taken at 2 weeks (P values<0.05). Similarly, there was a notable decrease in VAS scores after a period of 4 months compared to the measurements taken at the 4-week mark (p-values<0.05).

Upon conducting a comparative analysis between both groups, it was observed that the sole notable distinction pertaining to VAS was observed after a duration of 4 weeks and 2 months, wherein patients who received the PRGF injection exhibited lower VAS scores in comparison to those who received HA injection (P value= 0.011, 0.012 respectively). However, it should be noted that the increase in VAS was marginally greater in patients who received PRGF injections, although the difference compared to patients who received Hyaluronic Acid (HA) injections was not statistically significant, as indicated in
Table 4 & Fig. 16.

VAS	Group A (n=6)	Group B (n=6)	P between groups
Preoperative	8.5 (8 - 9) [a]	8.5 (8 - 9) [a]	0.604
2 week	7 (7 - 7.75) [ab]	7 (7 - 7.75) [ab]	0.93
4 weeks	6 (5.25 - 6) [abc]	4.5 (4 - 5) [abc]	0.011*
2 month	4 (3.25 - 4.75) [bcd]	2.5 (2 - 3) [cd]	0.012*
3 months	2 (2 - 2) [de]	1.5 (1 - 2) [cde]	0.241
4 months	1 (1 - 1) [def]	1 (0.25 - 1) [def]	0.336
Change	7.33 ± 1.03	8 ± 0.63	0.207
P between measurements	<0.001*	<0.001*	

Table 4: Comparison between the studied groups regarding VAS at different follow-ups
Data are presented as mean ± SD
Different lower-case letters demote substantial difference
*: Statistically significant as p-value<0.05

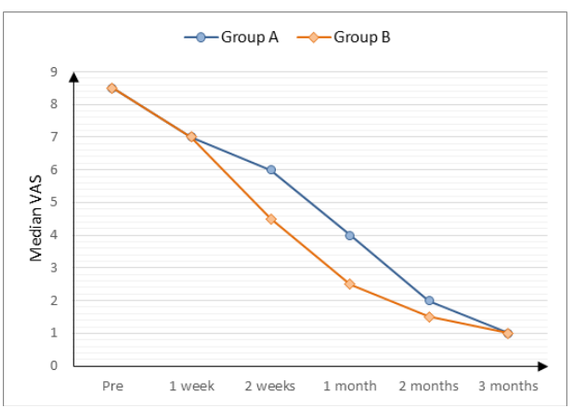

Figure (16): Comparison between the studied groups regarding VAS at different follow-ups

DISCUSSION

TMJ ID condition management remains a prominent area of interest in current maxillofacial literature, which may be attributed to the widespread prevalence of these conditions and their adverse effect on the quality of life of the affected patients [18]. However, the traditional approach to managing TMJ ID using conservative and non-invasive modalities still predominates and is widely accepted by maxillofacial surgeons. This classic principle still holds validity due to its ability to achieve the primary goals of managing such conditions to alleviate pain and improve jaw function. Among those modalities, TMJ arthroscopy and arthrocentesis have gained constantly increasing popularity and acknowledgment throughout the maxillofacial community. Arthroscopy offers surgeons unique advantages in the same procedure. In addition to the procedures of lysis and lavage, which serve to release adhesions and facilitate movement of the adhered disc, arthroscopy provides an opportunity for intraarticular diagnosis of various conditions such as synovitis, chondromalacia, disc perforation, and adhesions. Furthermore, during arthroscopic lysis and lavage, you can inject several therapeutic drugs in both joint spaces to improve the therapeutic outcomes of the procedure. Among those injectable therapeutic substances, hyaluronic acid and PRGF have received much attention in the past few years.

This study was conducted on twelve patients randomized into two equal groups (six patients each). A comprehensive follow-up was conducted on all patients, and their data was subjected to statistical analysis. Group A (who received HA) and Group B (who received PRGF); each group included five females and one male. No substantial differences were detected between both groups regarding sex and age. In the current study, we found a significant reduction of levels of synovial fluid TNF -α in both groups at 1-week follow-up and a further significant decrease in 2 weeks follow-up postoperatively.

By comparing both groups, TNF-α level was comparable at all time follow-ups while the change in TNF-α level was substantially upregulated in patients who received PRGF injection than those on HA injection (P value= 0.029). The findings presented in this study align with prior research conducted by Khalifah et al. [19] supports arthrocentesis utilization as a minimally invasive therapeutic approach, regardless of whether it is followed by intra-articular injections. Arthrocentesis is a procedure that results in the release of adhesions, reduction of intra-articular negative pressure, and removal of inflammatory mediators (e.g., cytokines and TNF-α) levels. Consequently, this procedure alleviates pain and enhances joint function. HA exhibits a lubricating effect, facilitating smoother and less frictional disc movement to the eminence. This effect is particularly pronounced after the removal of adhesions, leading to a decrease in abrupt disc movements and a subsequent reduction in clicking sounds, as well as a decrease in pain. The observed outcomes were a result of the combined effects of arthrocentesis and PRGF. Arthrocentesis, in isolation, demonstrated pain reduction by eliminating inflammatory cytokines like IL-1β and TNFα. Additionally, PRGF exhibited both anti-inflammatory properties, leading to a decrease in TNFα levels, and regenerative capabilities, facilitating the healing of damaged joint tissues, including the synovial tissue. Regeneration has been shown to enhance joint function, resulting in improved mobility, decreased pain, and the provision of a sustained endogenous supply of HA. This finding aligns with the research conducted by Damlar et al., suggesting that PRGF may yield superior outcomes compared to HA [20].

Consistent with this study, Campo et al. [21] and Altman et al. [22] observed that the administration of HA resulted in a significant reduction in the levels of TNF-α, as interleukin-1β (IL-1β) and interleukin-17 (IL-17). In contrast, Sezgin et al. [23] reported no significant alteration in the levels of IL-8 and TNF-α among patients who were administered both hyaluronan and placebo in a randomized controlled trial aimed at treating knee osteoarthritis. Aligning with our findings, Tohidnezhad et al . [24] and Chemel et al. [25] revealed a potential anti-inflammatory effect when PRGF was introduced into the culture medium of synoviocytes stimulated with TNF-α. These studies observed a modulation in the release of cytokines, supporting our findings. The TNF-α, IL-6, and IL-1β levels exhibited a significant decrease compared to the cell cultures that were not stimulated. Conversely, there was an increase in IL-10 and VEGF release. PRGF is characterized by a heightened diversity of cytokines and growth factors, including TGF-β and BMPs, which effectively suppress the expression of proinflammatory cytokines in individuals with rheumatoid arthritis.

Furthermore, the present study findings are consistent with the research conducted by Sundman et al. [26] in terms of the reduction in TNF-α concentration observed in both PRP and HA treatment groups when compared to the control group within synovial culture media. However, there is a discrepancy between the two studies as the TNF-α concentrations in the PRP and HA treatment groups were not found to be significantly different.

In line with this current study, previous animal studies have demonstrated that the administration of PRP effectively mitigated arthritis symptoms, diminished both humoral and cellular immune responses, and yielded positive outcomes in terms of histological parameters, as evidenced by joint tissue histological staining. The administration of PRP to mice with collagen-induced arthritis, rheumatoid arthritis, and arthritis diminished the expression of proinflammatory cytokines, including IL-6, IL-8, IL-17, IL-1β, and TNF-α within inflammatory tissues [27].

In this current study, we found a significant reduction of levels of IL-6 in synovial fluid in both groups at two-week follow-up and a further significant decrease in 4 weeks follow-up postoperatively. The IL6 level was found to be comparable at all time measurements when comparing both groups. Likewise, the observed alteration in IL-6 concentration exhibited a slightly more significant elevation among patients who received PRGF injection, although the difference in comparison to those who received HA injection was not statistically significant. The findings of our study are consistent with those of Tong et al. [27] and Chemel et al. [25] who found that levels of IL-6 significantly decreased in synovial fluid previously injected by HA and PRGF. Similarly, Sezgin et al., [23] reported substantially elevated IL-6 levels in the group injected by HA.

Furthermore, the results of our study agreed with a study done by El-Sharkawy et al. [28] in which PRP led to significantly increased levels of growth factors and significantly suppressed inflammation reported, a significant decrease of inflammatory markers such as IL-6 and TNF-α. Another study by Hur et al. [29] indicated that PRP significantly reduced multiple inflammatory protein expressions such as IL-6. PRP diminished inflammatory IL-1β-mediated effects on human osteoarthritic fibroblast-like synoviocytes.

Conversely, Textor et al. [30] observed a notable decrease in TNFα and IL-6 levels in synovial fluid following thrombin-activated PRP intra-articular injection administration in horses. Moreover, Maria et al. [31] illustrated that PRP also releases pro-inflammatory cytokines including IL-1α, IL-1β, TNFα, IL-6, IL-8, IL-17, and IL-18. However, it should be noted that the concentrations of these proinflammatory cytokines are significantly lower than those of anti-inflammatory cytokines.

This study examines the VAS scores of patients who underwent HA injections. Prior to the procedure, the median VAS score was 8.5. Following the operation, there was a slight decrease in VAS scores at 1 and 2 weeks postoperatively, with scores of 7 and 6, respectively. However, these reductions were not statistically significant. Subsequently, there was a significant decrease in VAS scores at 1, 2, and 3 months postoperatively, with scores of 4, 2, and 1, respectively (P values<0.05). A significant decrease in postoperative measurements was observed at 2 and 3 months compared to measurements taken at 1 and 2 weeks (P-values<0.05).

Patients receiving PRGF injection had a preoperative median VAS of 8.5, which insignificantly decreased 1 and 2 weeks postoperatively to 7 and 4.5, respectively, and continued decreasing significantly 1, 2, and 3 months postoperatively to 2.5, 1.5, and 1, respectively (P-values<0.05). By comparing postoperative measurements, the decrease was significant after 1, 2, and 3 months as compared to 1-week measurement (P-values<0.05). Likewise, VAS decreased significantly after three months compared to the 2-week measurement (P values<0.05). When comparing both groups, it was observed that patients who received PRGF injection had significantly lower VAS scores after two weeks and one month compared to those who received HA injection (P-value= 0.011, 0.012 respectively). On the contrary, there was a marginal increase in the change observed in the VAS among patients who received PRGF injections. However, this difference was not statistically significant when compared to patients who received HA injections.

These findings align with a study by Fernández-Ferro et al. [32] who reported that the infiltration of PRGF after the arthroscopy procedure shows better results in clinical variables of the study for both pain (VAS) and maximum mouth opening (MMO) concerning HA. The observed improvement demonstrated greater significance and maintained stability over an extended period,

although statistical significance was only observed in relation to the pain variable. The statistical analysis of the study findings indicated that the administration of PRGF injection subsequent to arthroscopy resulted in a notable enhancement of 1.4 in the average pain score compared to the application of HA injection following arthroscopy. Nevertheless, it is noteworthy that based on our observations, the disparity between the two approaches is negligible in a clinical setting. However, this disparity does provide a measure of the procedure's efficacy and indicates that PRGF may have potential therapeutic benefits for TMDs. Additionally, a study conducted by Harba & Harfoush, [33] found that both groups experienced a significant reduction in pain throughout the follow-up period compared to their pre-treatment scores. Furthermore, statistically significant differences were observed between the periods before treatment and after 2 weeks, as well as between 2 weeks and 1 month ($p < 0.05$). Within the HA group, there was a notable resurgence of pain, which exhibited a statistically significant disparity between the time periods of 6 months and 3 months. In contrast, the HA+PRP group experienced a continued decline in pain levels throughout the duration of the follow-up period.

In line with the current study, studies by Pihut et al. [34] and Arboud et al. [35] demonstrated the beneficial effects of PRP in intra-articular injections as a supplement to the primary prosthetic treatment of TMD. The reduction in pain and gradual restoration of functional capabilities of the stomatognathic system as the result of the treatment of interest raises hopes that future studies can lead to the establishment of appropriate management algorithms.

The study by Fernandez et al. [5] demonstrated that PRGF utilization following surgical arthroscopic disc repositioning leads to improved clinical outcomes in comparison to the injection of saline solution. Improved outcomes in terms of pain reduction (measured using the VAS) and maximum mouth opening (MMO) were observed during all subsequent examinations. Nevertheless, the findings exhibited statistical significance solely in relation to pain levels during the 6 and 12-month post-intervention assessments. The aforementioned clinical findings were not observed during the 18 or 24-month postoperative period.

Prior research has documented that the intra-articular administration of HA was the sole method employed for the treatment of internal derangement, disc displacement with reduction, and degenerative disorders. The utilization of HA in conjunction with arthrocentesis was employed in all of the aforementioned indications, as well as in the management of osteoarthritis, disc displacement without reduction, and unspecified joint pain [36-38]. According to a recent systematic review, the effectiveness of intra-articular hyaluronic acid in alleviating reduced mobility and pain in the TMJ appears to diminish with subsequent administrations of the drug after the initial treatment [39].

In line with our current study, Machoň et al. [40] compared the intraarticular injection of PRP and hyaluronic acid. The study observed reduced pain intensity among patients who administered PRP and HA. A significant proportion (70%) of patients who received PRP injections reported a decrease in pain during their 3-month follow-up evaluation [40]. In contrast, only a minority of patients (20%) who received sodium hyaluronate injections reported a decrease in pain during their 3-month follow-up assessment. Following the intervention, a notable increase in pain relief was observed in the group that received PRP treatment. There was a substantial difference in the VAS scores between the two groups at the 3-month follow-up ($p=0.047$). Subsequently, within-group variations are assessed utilizing the paired Student's T-test. In the PRP group, the mean VAS decreased by approximately 44% compared to its original value. The observed difference exhibited statistical significance ($p=0.005$). Within the hyaluronate group, the average VAS score exhibited a reduction of approximately 6% relative to its initial value, with no statistical significance ($p=0.66$) [40].

Several prior studies have assessed the effects of intra-articular injection of HA and PRP on two outcomes: maximum subjective pain at rest as well as non-assisted mouth opening. These studies have consistently reported significant improvements in both parameters sustained throughout the follow-up period. All patients in the study exhibited a decrease in pain levels during periods of rest and an improvement in mouth opening range following the administration of two injections. However, when considering the enhancement of mouth opening, it is observed that the subsequent iterations yielded diminishing returns, indicating a stabilization of the achieved improvements [9, 41].

A meta-analysis study done by Al-Moraissi et al. [42] (2020) demonstrated that the efficacy of both arthroscopy and arthrocentesis could be boosted by pharmacological installations (PRP, HA), with PRP may offer particular advantages over HA in terms of effectiveness. In a recent systematic review conducted by Derwich et al. [43], various injectable treatments for TMJ disorders were examined. The findings of the study indicated that arthrocentesis as a standalone intervention demonstrated efficacy in alleviating pain and enhancing jaw function among individuals diagnosed with TMJ osteoarthritis. The administration of additional HA, whether low molecular weight HA (LMWHA), high molecular weight HA (HMWHA), or corticosteroids subsequent to arthrocentesis, does not yield enhanced final clinical outcomes. In cases where arthrocentesis is not conducted, the administration of intraarticular HA injections has demonstrated greater efficacy in alleviating pain compared to corticosteroids or injections of physiologic saline solution. Furthermore, it is evident that multiple repetitions of intraarticular injections are necessary in order to attain favorable clinical results. Consequently,

there is a need for further assessment of the optimal quantity of intraarticular injections. The findings pertaining to the administration of supplementary PRP injections exhibit a lack of consistency and raise doubts regarding their efficacy. The findings suggest that PRP injections do not substantially improve maximum mouth opening; however, they exhibit potential efficacy in alleviating pain. Increased assessment is necessary for the research conducted on the efficacy of PRP. The administration dosage and frequency of intraarticular injections of PRP seem to impact the overall clinical outcomes.

In relation to the optimal number of HA sessions required to elicit sustained positive outcomes, the study conducted by Manfredini et al. demonstrated that a treatment regimen consisting of five interventions involving joint lavage in combination with injections of low-molecular-weight hyaluronic acid should be regarded as the standard protocol [16]. However, Guarda-Nardini et al. hypothesized that the five-session protocol may not be the most effective strategy in terms of cost-to-benefit ratio for managing symptoms associated with TMJ [17]. They recommended testing the effectiveness of the session protocol after its promising outcomes in knee OA to reduce the number of sessions [17].

CONCLUSION:

The results of the current study highlighted the efficacy of hyaluronic acid and PRGF intraarticular injection in managing TMJ disc displacement conditions. This efficacy was in terms of alleviating pain and decreasing the levels of IL-6 and TNF in TMJ synovial fluid. However, regarding the comparison between both materials, the PRGF was superior to hyaluronic acid in reducing the levels of TNF in synovial fluid. Moreover, the PRGF showed better pain score alleviation during all follow-up periods, with statistically significant differences at two and four postoperative weeks.

CONFLICT OF INTEREST

This clinical study was self-funded by the authors, with no conflict of interest.

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