Clinical & Biochemical assessment of arthrocentesis for cases of disc displacement without reduction. Is interleukin-6 a valid biomarker?

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Abstract: ***Purpose:*** The aim of this clinical study was to measure the level of interleukin-6 (IL-6) in the synovial fluid of temporomandibular joints (TMJ) suffering from disc displacement without reduction (DDwoR), before and after arthrocentesis, to evaluate the efficacy of the procedure, to evaluate the interleukin-6 validity as a biochemical monitor, and for clinical assessment of visco-supplementation after arthrocentesis. ***Material and methods:*** Twenty eight TMJs in twenty two patients with DDwoR were included in this study. They were complaining of pain and tenderness over the joint region besides severe limitation in mouth opening and jaw function. All patients included in the study were subjected to clinical examination including pain, tenderness, and maximal mouth opening. Radiographic examination and magnetic resonance imaging (MRI) for the affected joint were also performed. Synovial fluid aspirates were obtained prior to arthrocentesis and after infusion of 300 ml into the superior joint compartment. The aspirates were used to measure the levels of interleukin-6 via immunoenzymometric assay. The patients were divided consecutively into two equal groups where group 1 underwent arthrocentesis followed by injection of 1 ml of sodium hyaluronate (SH) and group 2 did not receive any additional injections after arthrocentesis. The clinical criteria, visual analogue scale (VAS) pain scores and maximal mouth opening (MMO), were recorded pretreatment and 1 day post-treatment then at 1, 3, and 6 months post-treatment. The clinical parameters recorded as well as the interleukin-6 levels were analyzed statistically using one-way ANOVA. ***Results:*** The cases presented with 28 affected joints. The cases were 15 females and 7 males and the age ranged from 19- 47 years with a mean of 30.76 years. The pain scores decreased significantly after arthrocentesis in both groups. Group 1 showed significant decrease than group 2. The maximum mouth opening increased significantly also in both groups, however there was no statistical significant difference between the two groups. The interleukin-6 levels showed significant decrease after arthrocentesis. ***Conclusion:*** Arthrocentesis proved efficacy in improving the clinical parameters in cases of DDwoR, however SH injection after arthrocentesis was superior to arthrocentesis alone. The interleukin-6 proved validity as a monitoring biochemical marker.
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Keywords: Disc displacement without reduction, Sodium hyaluronate, Arthrocentesis, Interlukin-6.

Introduction

Internal derangements are the most frequent articular causes of temporomandibular joint dysfunction, which involve progressive slipping or displacement of the articular disc. The disc supports the bones in the joint, preventing them from rubbing together and allows the joint to move smoothly. If the disc slips out of place or is displaced, it can prevent the proper movement of the condyle and cause dysfunction. The disc can degenerate; becoming misshapen or even torn.[1] This proposed phenomenon involves the disk becoming adherent to the glenoid fossa through increased intra-articular friction, with or without the formation of adhesions within the joint. Lysis of adhesions with joint lavage has been reported efficacious in restoring mandibular range of motion and decreasing pain in these clinical scenarios.[2] TMJ arthrocentesis is the lavage of the upper joint space that is done with no direct vision, aiming primarily to remove necrotic tissue, blood and pain mediators from the joint.[3] It is one of the least invasive, simplest, and highly successful surgical techniques in re-establishing a normal range of mouth opening in patients with anteriorly displaced discs without reduction weather the severe, sudden onset, closed lock, or those with disc adhesion or "stuck disk" phenomenon.[4]

Hyaluronic acid (HA) is a linear, hydrophilic, polyanionic high molecular weight polysaccharide exclusively composed of repeated disaccharide units of glucuronic acid and N-acetylglucosamine. It is a major natural component of the synovial fluid largely responsible for its viscosity. HA importance in the lubrication of synovial tissues has been established, but the mechanism by which it affords improvement in joint diseases is not precisely known. Introduction

of HA intra-articular injection in TMJ dysfunction patients after arthrocentesis was suggested in order to improve function and lessen pain. This was suggested based on its ability to reduce the levels of inflammatory mediators, and its joint lubrication function that lessens joint wear and reduces friction within the intraarticular space. It is a good soft tissue lubricant under loads and has been reported to prevent intraarticular adhesions.[5,6] The indications for such technique were expected to extend to other TMJ disorders, and encouraging results were reported in patients with inflammatory degenerative disorders but it is not clear which cases will respond to this procedure.[7] Despite the fact that its half-life is about 13 hours, the intraarticular injection of HA seems to lead to persistent beneficial effects.[5]

Interlukin-6 (IL-6) is a multifunctional cytokine with a central role in host defense and can be produced by many cell types, such as monocytes macrophages, T cells, fibroblasts and endothelial cells. IL-6 plays an important role in the enhancement of T-lymphocyte proliferation, B-lymphocyte differentiation and complement cascade activation . In addition, this cytokine also acts synergistically with IL-1b inducing bone resorption.[8] Other actions include the up-regulation of IL-2 and its receptor expression, stimulation of platelet production from megakaryocytes, differentiation of macrophage and osteoclast as well as the production of acute phase reactants .[9]

2.Patients & Methods

This study was a multi-center study carried out in the Oral and Maxillofacial Surgery departments in Suez Canal and Cairo Universities as well as private practice between 2010 and 2012. Twenty two patients were randomly chosen from those presenting with complains of pain and tenderness over the joint region with severe limitation in mouth opening and jaw function and diagnosed as having DDwoR. All patients included in the study were subjected to full case history recording, clinical examination including pain, tenderness, and maximal mouth opening registration, as well as radiographic and magnetic resonance imaging (MRI) examination of the affected joint. Patients with history of degenerative joint disease, condylar hypoplasias/hyperplasias/ tumours, patients who had performed previous arthrocentsis or TMJ surgical treatment, and patients with limited mouth opening caused by only muscle pain or spasm, patients with systemic inflammatory joint disease, and patients with contraindica-tions for arthrocentesis and MRI were excluded from the study. The diagnosis was made based on the patient's history, clinical examination, and MRI findings (Figures 1 & 2).

All patients were informed about the materials used, the procedure and its possible complications. Informed consents were obtained from all patients concerning the treatment option and inclusion of the data in the study. All patients were to undergo arthrocentesis for the superior compartment of the affected joints. The affected joints were divided consecutively into two equal groups.

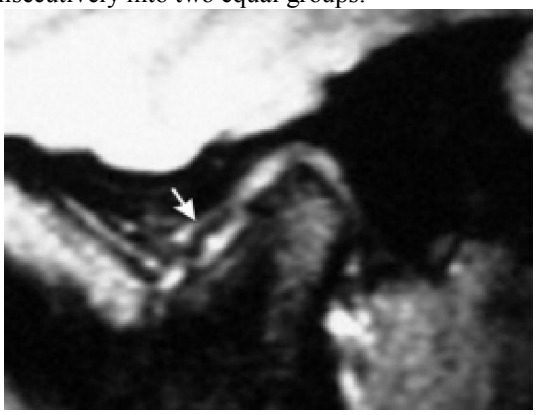

Figure 1: T2 weighted closed mouth MRI showing anteriorly displaced disc (arrow).

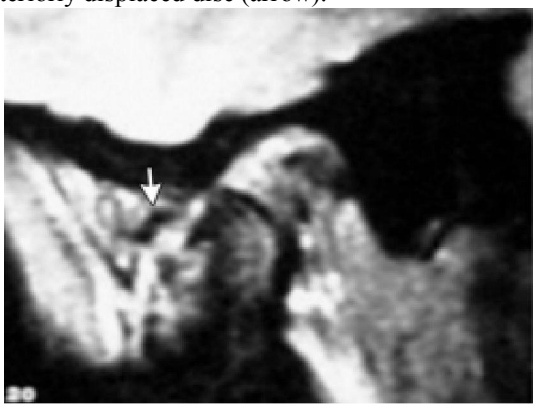

Figure 2: T2 weighted open mouth MRI showing anteriorly displaced disc without reduction (arrow).

Group 1 included the joints which received hyaluronic acid injection after finishing the joint lavage as visco supplementation measure, whereas Group 2 joints did not receive any additional injections rather than saline lavage only. Synovial fliud sampling was performed in both groups at 2 stages, the first before the start of arthrocentesis procedures and the second after infusion of 300 ml saline solution into the joint superior compartment after arthrocentesis

Technique of Arthrocentesis: The procedure was done under general anesthesia in 10 cases, whereas auriculotemporal nerve block (1-2 carpules) was resorted to in the rest of the cases in the outpatient clinic. The operative site was prepared aseptically using Betadine solution and the area was isolated with sterile drapes. The point of needle insertion was

determined by drawing the canthal-tragus line and a point 10 mm in front of the tragus and 2 mm below the canthal-tragus line was marked. Another point 2 mm anterior to the former one was marked to serve as the point of insertion of the second needle used for collecting the synovial fluid aspirates. The TMJ was palpated and the upper joint space enlarged by downward and forward displacement of the mandible. Hydraulic pressure was created by injecting about 2 mL of saline solution into the space prior to arthrocentesis and the patients were asked to open and close the mouth, or jaw manipulation was done in case of under general anesthesia, to mix the saline solution with the synovial fluid. The mixture of synovial fluid and saline was pumped; that is, it was aspirated and reinjected a total of 10 times, and then 1.69 mL on average (range, 1.2 to 2.1 mL) was collected on sterile tubes (Figure 3).

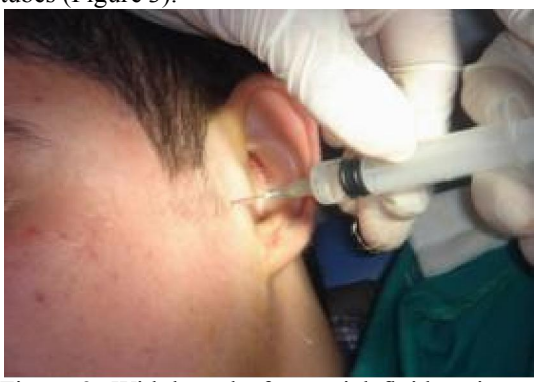

Figure 3: Withdrawal of synovial fluid aspirate prior to arthrocentesis.

A second 20-gauge needle was placed approximately 2 mm anterior to the former needle to establish outflow according to Alpaslan and Alpaslan[5]. The joint was then lavaged with 300-500 mL of saline solution injected into the upper joint compartment. The outflow needle was periodically occluded in order to create hydraulic pressure within the joint space (Figure 4).

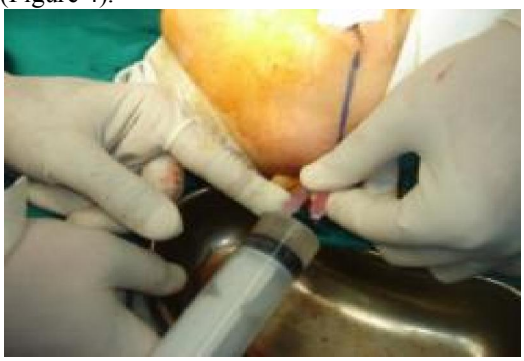

Figure 4: Injection of the saline solution into the upper joint compartment during the process of arthrocentesis and outflow through the second needle.

The second sample was collected after infusion of 300 ml in the superior joint compartment during arthrocentesis by collection of the outflow of the mixture of synovial fluid and saline solution (Figure 5). All of the samples were immediately centrifuged at 3,000 rpm for 20 minutes to remove cells before storing the supernatant at -70°C until assay. On termination of the procedure, one ml of commercially available sodium hyaluronate (Curavisc 20mg/2ml syringe, IDT Biologika GmbH Company, Germany) was injected into the upper joint space in patients of Group I (Figure 6).

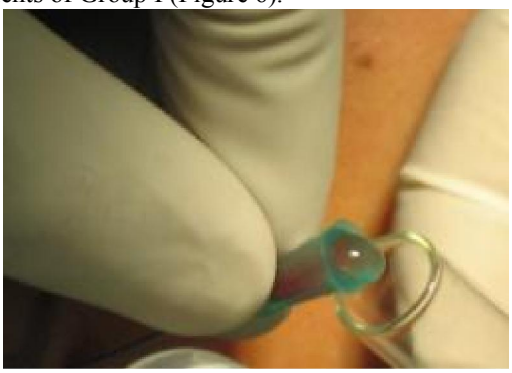

Figure 5: Collection of the outflow of the mixture of synovial fluid and saline solution during the process of arthrocentesis after 300 ml infusion.

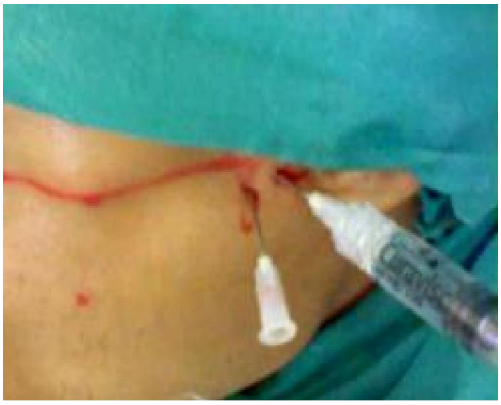

Figure 6: Injection of Sodium Hyaluronate (Curavisc) in upper compartment of the joint.

After removal of both needles the mandible was gently manipulated in order to evaluate joint movement. Postoperative antibiotic, Augmentin (Amoxicillin/ Clavulanate potassium) 625mg was prescribed to the patients 3 times daily for 3 days.

The following clinical parameters were assessed preoperatively, after one day postoperatively, then at one, three, and six months postoperatively. Intensity of the joint pain was assessed using a visual analog scale (VAS; 0–10) with endpoints marked score 0 (no pain) and score 10 (worst pain ever experienced), maximum mouth opening (MMO) was measured with a ruler and rounded to the nearest

millimeter at each follow-up visit. The rates of IL-6 were measured in the preoperative samples and the samples collected after 300ml infusion to detect the relation between IL-6 concentration and the presence of internal derangement and inflammation of the joints. The concentrations of soluble IL-6 were quantified in these samples by immunoenzymometric assay human IL-6 kit (Orgenium Labs, AniBiotech, Finland) and measured as (pg (pictogram)/ ml (milliliter)) (Figure 7).

Statistical analysis: Data were tabulated and presented as mean and standard deviation (SD) values. The clinical parameters recorded as well as the IL-6 levels were analyzed statistically using one-way ANOVA. The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM® (®IBM Corporation, NY, USA) SPSS® Statistics Version 20 for Windows (® SPSS, Inc., an IBM Company).

Figure 7: Orgenium AviBion Human Interleukin-6 ELISA, the enzyme-linked immunosorbent assay kit used for the quantitative detection of human IL-6 (Orgenium Labs, AniBiotech, Finland).

3. Results

Twenty two patients were included in this study. They presented with 28 affected joints. The age of group 1 patients ranged from 22 to 47 years with a mean of 28.69 years, whereas that of group 2 ranged from 19 to 37 years with a mean of 32.07 years. The gender distribution of group 1 was 7 females and 4 males, whereas that of group 2 was 8 females and 3 males. The mean VAS pain scores decreased significantly during the 3rd session mean ± SD (15.3± 14.88 and 26.20± 12.47) for groups (1, 2) respectively and also during the 4th sessions mean ± SD (4±8.4 and 10±9.7) for groups 1,2 respectively, of postoperative follow up period compared to the preoperative scores, mean ± SD (87.90±8.81) where $P \leq 0.001$. Group 1 showed a statistically significant lower mean in the pain scores, mean ± SD (15.3±14.88), than group 2, mean ± SD (26.2±12.47) in the 3rd session which was 3 months after treatment. The pain scores of group 1 remained lower (4±8.4) than group 2 (10±9.7) in the 4th postoperative session which was 6 months after treatment, where $P < 0.05$ (Figure 8).

The maximum mouth opening, measured as maximum interincisal distance in mm, showed improvement and increased in the follow up sessions. The MMO was mean ± SD (23.1 mm ±4.012) before treatment and it became (35.9 ±4.48) after 3 months and (40.6±5.19) after 6 months of treatment in Group 1 which were significantly different than the preoperative value in both follow up sessions. The MMO in group 2 was (23.7 mm ±2.58) before treatment and it became (39.9 ±3.57) after 3 months and (39.±3.59) after 6 months of treatment which were also significantly different than the preoperative value in both follow up sessions. Regarding the comparison between the 2 study groups, there was no significant difference at any time point during the study period in the MMO measures (Figure 9).

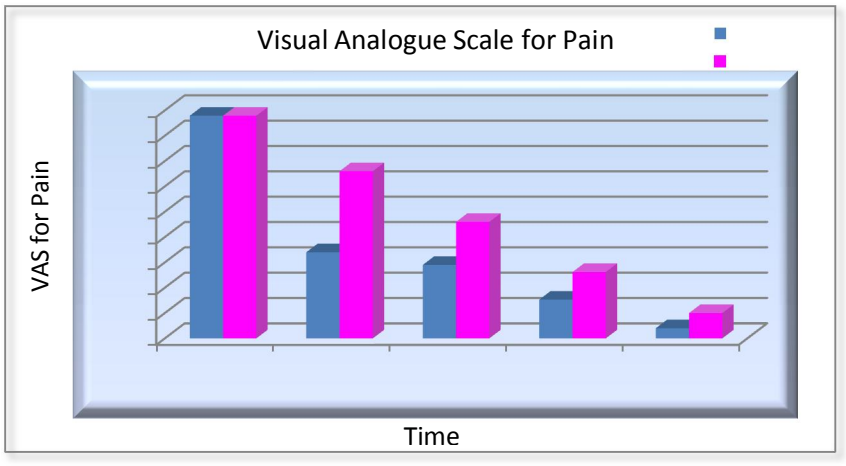

Figure 8: Histogram representing the VAS Pain scores for both groups, preoperative and throughout the 6 months follow up period.

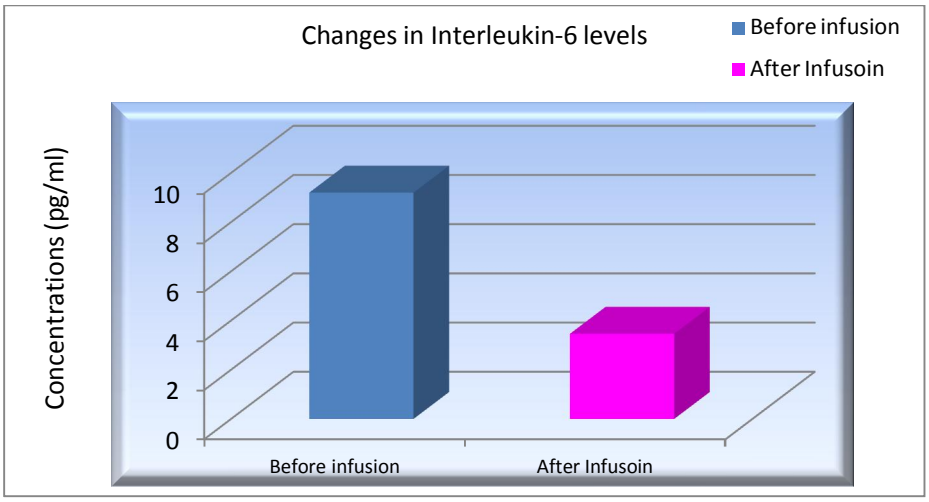

Figure 9: Histogram representing the maximum mouth opening measurement values, preoperative and throughout the 6 months follow up period

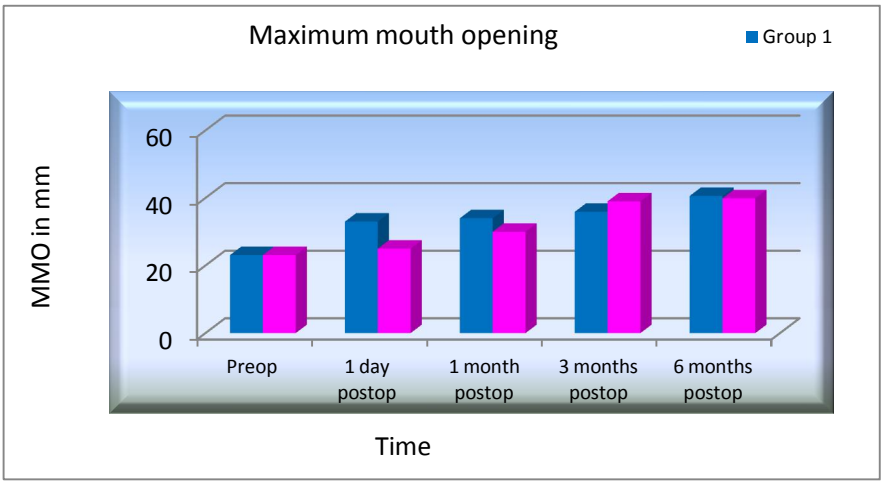

Figure 10: Histogram representing the comparison of interleukin levels quantification in synovial aspirates collected preoperatively and after 300 ml. infusion ($P< 0.001$).

Regarding the quantitative assay of IL-6 in the synovial fluid aspirate, it ranged between 3.46 and 13.05 pg/ml with the mean ± SD was 9.20±3.105 before the arthrocentesis. It then ranged between 1.05 and 16.05pg/ml after 300 ml saline infusion, and the mean ± SD was 4.36±2.376. The IL-6 showed statistically significant decrease in the joints' aspirates after treatment where $P \leq 0.001$ (Figure 10).

4. Discussion

The current study was carried out on 22 cases presented with 28 diseased joints (6 cases had bilateral complaints). We evaluated the pain scores and maximal mouth opening as clinical criteria for the outcome of the treatment and we had significant improvement in both parameters. Most of publications depended on the visual analogue scale, maximal interincisal mouth opening and jaw function as evaluation criteria of arthrocentesis. Sixteen clinical articles regarding arthrocentesis were reviewed by **Monje *et al.***, where a series of clinical and procedure variables were analyzed.[10] Success was considered to be "changing the impaired mandibular function in sufficient measure" as the result of restored movement and reducing pain in the TMJ. The overall success rate was 83.5%, consequently, they concluded that arthrocentesis is a simple, non-invasive, inexpensive and highly effective procedure. It was suggested that it should be considered as an alternative to other more invasive TMJ surgical procedures, provided that it is applied to selected groups of patients. In this study, the overall success rate was 85.71% which is considered satisfactory and in accordance with the reported literature. There were 4 joints of the second group that reported reappearance of the original symptoms though mild and less than the pretreatment values. One case of theses reported the reappearance

of symptoms at the 3rd session (after 3 months) and 3 cases at the 4th session (after 6 months).

Hyaluronic acid is a natural component of joint synovial fluid and is also found in the extracellular matrix of connective tissue. The excellent mechanical and metabolic properties of its molecules define it as an ideal treatment for inflammatory problems of the temporomandibular joint. Hyaluronic acid has been proposed as a therapeutic agent that improve and restore normal lubrication in joints, provides nutrition to the a vascular articulating disc and stabilizes the joint.[11,12] In the current study, all patients in group 1 were subjected to arthrocentesis followed by injection of sodium hyaluronate. Patients were followed up for 6 months. There was a significant reduction in pain with increase in the range of maximal mouth opening. However this increase in mouth opening was not significantly superior to group 2. These results were in accordance with **Manfredini *et al.,***[13] who stated that, all studies in their systematic review about HA intraarticular injection reported a decrease in pain levels and that positive outcomes were maintained over the follow-up period, which was varied among studies, ranging between 15 days and 24 months. The first attempts on TMJ arthrocentesis focused on its application to increase jaw function and achieve relief from pain in patients with restricted mouth opening. Then, with the increase in knowledge on the role of joint lubrication impairment as a risk factor for TMJ internal derangements, visco-supplementation with HA became an option for the management of symptoms in the clinical setting. This led to the progressive expansion of potential clinical indications for the use of arthrocentesis plus hyaluronic acid injection, with particular regard to joints with inflammatory-degenerative disorders.

A literature search covering the period from 1966 until 2008 in 18 relevant studies on the application of HA in the temporomandibular joint was reviewed by **Escoda *et al.,***[11] Their characteristics of the reviewed studies included three types of comparisons: HA versus placebo, HA versus glucocorticoids, and arthroscopy or arthrocentesis combined with HA versus arthroscopy or arthrocentesis with placebo. Based on these publications there was a high recommendation in favor of the use of HA in the treatment TMJD: reducible disc displacement, non-reducible disc displacement, and other degenerative joint diseases. In this study we evaluated the efficacy of sodium hyalurinate with arthrocentesis compared to plain arthrocentesis. Our results were in accordance to the study which was introduced by **Bjornland *et al.,***[14] as they compared the efficacy and complications of intraarticular TMJ injections with either sodium hyaluronate or corticosteroids. They reported that, injections with a high molecular weight hyaluronic acid were significantly more effective in decreasing pain intensity than injections of corticosteroids in osteoarthritic joints. However, the superiority of HA injections was shown in other studies to be only against placebo saline injections, but outcomes are comparable with those achieved with corticosteroid injections or oral appliances.[13]

In this study, the 1st session (1 day postoperatively) values did not show much improvement in both groups. The reason for that was attributed to the usual operative manipulation sequelae as pain and edema. Interestingly the MMO of group 1 was less than group 2 in the 3 months postoperative follow up session, but that was without statistical significance. Moreover, three cases in group 1 reported masticatory muscles pain and increasing in bruxism, although not reported as frequent finding in patients' history. We presumed that the regain in their normal mandibular function might have played a role for this parafunction and that this spasm and consequent reduction in mouth opening did not match with the reported literature concerning the smoothness of condylar movement and increase in mouth opening. The patients were advised to perform muscle exercise which rendered the condition less remarkable after 6 months.

Our operative protocol and results were similar to those obtained by **Alpaslan and Alpaslan**[5] who investigated the efficacy of arthrocentesis with and without injection of sodium hyaluronate into the upper joint space in the treatment of internal derangements. They found that pain decreased markedly both in the anterior disc displacement with reduction patients and the closed lock patients in the sodium hyaluronate group.

Our results were in agreement with the results of the study published by **Kaneyama *et al.,*** in 2005. [15] They evaluated the levels of various cytokines, cytokine receptors, and cytokine antagonists in the synovial fluid of patients with TMJ disorders and determined the correlations among these expression levels. In their study synovial fluid was obtained from 55 patients with TMJ disorders and from 5 asymptomatic healthy volunteers as controls. The concentrations of tumor necrosis factor (TNF)- α, interleukin (IL)-6, IL-1b, soluble tumor necrosis factor receptors I and II (sTNFR-I and sTNFR-II), IL-6 soluble receptor (IL-6sR), IL-1 soluble receptor type II, and IL-1 receptor antagonist were determined by ELISA. The concentrations of TNF-a, IL-6, IL-1b, sTNFR-I, and sTNFR-II were significantly higher in the synovial fluid of patients than in controls but there were no correlations of pain with any of the cytokines, cytokine antagonists, and protein.

Generally the results of the current study

regarding the elevation of the IL-6 levels in the joints suffering from joint pain and limitation of mouth opening were in accordance with the study carried out by **Keun *et al.,***[16] In that study, they analyzed proinflammatory cytokines, TNF- α and IL-6, in the synovial fluid of TMJ disorder patients with symptoms of pain, mouth opening limitation, and clicking where TNF-α and IL-6 levels were seen elevated in the experimental group compared with the healthy control group and it was also more elevated in the acute pain group compared with the chronic pain group.

In conclusion, arthrocentesis proved efficacy in improving the clinical parameters (pain and MMO) in cases of DDwoR but SH injection after arthrocentesis was superior to arthrocentesis alone. Proinflammatory cytokines in the diseased joints can be efficiently decreased by arthrocentesis using 300 ml infusion in the superior joint compartment. The IL-6 could be considered as a valid biomarker for internal derangement as well as biochemical monitor for the outcome of arthrocentesis.

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