



EVALUATION OF EFFECT OF INTRAARTICULAR INJECTION OF CHITOSAN-HYALURONATE GEL MIXTURE VS HYALURONIC ACID IN MANAGEMENT OF TMJ INTERNAL DERANGEMENT

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ABSTRACT

Objective: To evaluate the effect of sodium hyaluronic acid Vs chitosan-hyaluronate hybrid gel injection into the upper cavity of the temporomandibular joint for management of anterior disk displacement without reduction. **Subjects and methods:** This study was conducted on 20 patients with 20 joints had anterior disc displacement without reduction. All patients were selected from those attending the outpatient of Oral Maxillofacial Surgery at Faculty of Dental Medicine, Al - Azhar University, Cairo, boys. The patients were divided into two groups. Group one (control group) included 10 patients receiving Sodium Hyaluronic acid (HA) injected into the upper compartment of the TMJ cavity while Group two involved 10 patients receiving Chitosan-Hyaluronate Hybrid Gel (CH) injected into the upper compartment of the TMJ cavity. T-test was used for comparison before treatment and at 1 and 3 months after treatment. **Results:** Before treatment, there was a statistically non-significant difference in mean MMO in the two groups. At 1 and 3 month there was a statistically a significant difference in mean MMO in the two groups. HA/Chitosan group showed a higher MMO than HA group. Both groups showed a statistically significant increase in mean Pain measurements at 1 and 3 months. **Conclusion:** Chitosan-hyaluronate and HA are safe substances that can be injected into the TMJ cavity without any problems. In individuals with anterior disc displacement without reduction, chitosan-hyaluronate injection with arthrocentesis is more successful and predictable than HA.

KEY WORDS: Temporomandibular; TMJ; Chitosan; Hyaluronic; Dental.

INTRODUCTION

A disturbance in the internal components of the temporomandibular joint (TMJ) in which the disc is moved from its typical functional interaction with the mandibular condyle and the articular section of the temporal bone is known as internal derangement

of the TMJ⁽¹⁾. Temporomandibular joint ID treatment aims to reduce pain, promote mouth opening, and alleviate the inflammatory status of the joint cavity. Physical therapy, arthrocentesis, lavage, and pharmaceutical injections into the joint cavity are the initial line of treatment for ID ⁽²⁾.

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In order to decrease pain by removing inflammatory mediators from the joint or to improve mandibular mobility by removing intra-articular adhesions through hydraulic pressure from irrigation of the upper TMJ compartment, arthrocentesis is commonly defined as the lavage of the TMJ without viewing the joint space. Arthrocentesis involving the injection of specific biotic or abiotic substances into the TMJ's superior cavity to support the healing process⁽³⁾.

As a result, certain intra-articular injectable medications like Ringer's lactate, physiological saline, and sodium hyaluronic acid can speed up tissue repair. A linear polysaccharide is sodium hyaluronic acid. The cartilage cells are shielded from stress waves by this barrier and shock absorber. It possesses anti-inflammatory properties that include inhibiting and phagocytosing of polymorphonuclear leucocytes and macrophages, scavenging for free radicals, and lowering vascular permeability. It also possesses painkilling qualities⁽⁴⁾.

In numerous earlier experiments, animals' intraarticular joints received injections of chitosan-hyaluronate hybrid gel. When chitin is deacetylated, chitosan, a naturally occurring biodegradable polymer, is created. It is non-toxic, biocompatible, and known to have a number of beneficial properties, including the ability to produce a biological barrier, prevent tissue adhesion, promote cartilage repair, induce the differentiation of mesenchymal stem cells, and have excellent lubricating effects. It also has anti-inflammatory, antimicrobial, antioxidant, mucoadhesive, hemostatic, and analgesic effects⁽⁵⁾.

The aim of our study was to evaluate the effect of sodium hyaluronic acid Vs chitosan-hyaluronate hybrid gel injection into the upper cavity of the temporomandibular joint for management of anterior disk displacement without reduction.

SUBJECTS AND METHODS

Our study was a prospective randomized controlled clinical study. The patients were selected from the Department of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Boys, Cairo, Al-Azhar University. Every patient was signing an informed consent agreement before the treatment. The study was carried out on 20 patients after approval of the ethical committee with code 563/3200, Faculty of Dental Medicine, Boys, Cairo, Al Azhar University. The patients were divided into two groups. Group one (control group) included 10 patients receiving Sodium Hyaluronic acid (HA) injected into the upper compartment of the TMJ cavity while Group two involved 10 patients receiving Chitosan-Hyaluronate Hybrid Gel (CH) injected into the upper compartment of the TMJ cavity. T-test was used for comparison before treatment and at 1 and 3 months after treatment. We included patients diagnosed with TMJ internal derangement (anterior disk displacement without reduction Stage III, Stage IV Wilkes classification) based on clinical symptoms and MRI evaluations, aged 25 - 50 years old with sufficient clinical and magnetic resonance imaging (MRI) data that could be obtained before and after the treatment. On the other hand, we excluded patients with hematological or neurological diseases, inflammation or connective tissue diseases, head and neck malignancies, history of treatment of TMJ disease or history of craniofacial surgery not related to ID treatment or patients with insufficient clinical and MRI data.

The selected patients were informed about the nature of the study and signed an informed consents about details of the procedure before starting the study. All details were recorded in a questionnaire by the examiner including personal data, chief complaint, medical history and past dental history. After that, we performed a thorough clinical examination. One or more of the following clinical signs and symptoms could usually be noticed

by inspection and palpation; limitation of mouth opening, pain during mouth opening or tenderness to palpation over the affected TMJ and muscles of mastication, presence of TMJ sounds (Clicking) or deviation of mandibular midline during mouth opening and closure. Magnetic resonance imaging (MRI) was taken to evaluate the disc displacement. Then, all patients were subjected to arthrocentesis with Ringer lactate. Hyaluronic acid was injected into the patients after arthrocentesis in group (A), and a Chitosan-hyaluronic acid hybrid gel was injected into group (B). After the operator hand felt the condyle while the mandible moved in the lateral, open, and closed orientations, an arthrocentesis injection was performed. A second 20-gauge needle was placed 20 mm away and 10 mm below the first one, which was positioned 10 mm anterior to the tragus on the tragus-canthus line. The joint was then continuously flushed with 200–300 cc of ringer solution. Mouth opening (the target was 35 to 40 mm interincisal opening), absence of TMJ sounds, normal movement of the jaw, MRI imaging, and a pain scale were all part of the monitoring phase. The criteria proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS), in which treatment is considered to be successful in the presence of mild or no pain (VAS score ≤ 3)⁽⁶⁾.

Statistics/data analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Shapiro-Wilk test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Data will be compared using t test (paired t test within the same group and independent t test between groups) or (Wilcoxon signed Rank test within the same group and Mann Whitney U test between groups) according to normality.

RESULTS

Table (1) summarizes comparison between the two studied groups according to demographic data: ten patients ranged in age between 25.0 – 49.0 years with a mean age of 33.60 ± 7.07 years for study group and ten patients ranged in age between 25.0 – 50.0 years with a mean age 36.30 ± 7.96 years for control group. There was statistically non-significant difference between the two groups regarding to the mean of age. Study group had 3 males and 7 females, and control group had 3 males and 7 females. There was statistically non-significant difference between gender distributions in the two groups. Table (2) shows a comparison between the two studied groups according to MMO. Before: there was a statistically non-significant difference in mean MMO in the two groups ($p=0.306$). At 1 and 3 month there was a statistically a significant difference in mean MMO in the two groups ($p=0.003^*$, $<0.001^*$ respectively). HA/Chitosan group showed a higher MMO than HA group. Table (3) demonstrates a comparison between the different time periods in each group according to Pain. Both groups showed a statistically significant increase in mean Pain measurements at 1 and 3 months ($p=0.001^*$). A comparison between the two studied groups according to pain is shown in table (4). Before and at 1 month, there was a statistically non-significant difference in mean pain in the two groups ($p=0.063, 0.393$ respectively). At 3 month there was a statistically a significant difference in mean pain in the two groups ($p=0.043^*$). HA/Chitosan group showed a lower pain than HA group. Table (5) shows a comparison between the two studied groups according to clicking. Before and at 1 and 3 months: there was a statistically non-significant difference in mean clicking in the two groups ($p=1.000, 0.628, 0.0628$ respectively). Table (6) clears a comparison between the different time periods in each group according to Lateral Movement. Regarding right: HA groups showed a statistically non-significant difference in mean Lateral Movement measurements at 1 and 3 months ($p=0.134$). Regarding right: HA/

Chitosan groups showed a statistically a significant increase in mean Lateral Movement measurements at 1 and 3 months ($p=0.007^*$). Regarding Left: HA groups showed a statistically a significant increase in mean Lateral Movement measurements at 1 and 3 months ($p=0.005^*$). Regarding Left: HA/Chitosan groups showed a statistically a significant increase in mean Lateral Movement measurements at 1 and 3 months ($p=0.005^*$). Table (7) shows a comparison

between the two studied groups according to pain. Right (before, 1 and 3 months): there was a statistically non-significant difference in mean Lateral Movement in the two groups ($p=0.915, 0.667, 0.667$ respectively). Left (before, 1 and 3 months): there was a statistically non-significant difference in mean Lateral Movement in the two groups ($p=0.196, 0.491, 1.000$ respectively).

TABLE (1) Comparison between the two studied groups according to demographic data.

	HA (n = 10)	HA/Chitosan (n = 10)	Test of Sig.	p
Sex				
• Male	3 (30.0%)	3 (30.0%)	$\chi^2=$	$^{FE}p=$
• Female	7 (70.0%)	7 (70.0%)	0.000	1.000
Age (years)				
• Min. – Max.	25.0 – 49.0	25.0 – 50.0		
• Mean \pm SD.	33.60 \pm 7.07	36.30 \pm 7.96	t=	0.433
• Median	31.50	39.0	0.802	
<i>SD: Standard deviation t: Student t-test χ^2: Chi square test FE: Fisher Exact</i>				
<i>p: p value for comparing between the studied groups</i>				

TABLE (2) Comparison between the two studied groups according to MMO.

	HA (n = 10)	HA/Chitosan (n = 10)	Test of Sig.	p
MMO (mm)				
• Before	29.80 \pm 4.80	32.50 \pm 6.54	t=1.053	0.306
• 1 month	33.60 \pm 4.35	42.30 \pm 6.58	t=3.486	0.003*
• 3 months	37.10 \pm 3.87	44.90 \pm 3.0	t=5.037	<0.001*
% of increase from Before				
• 1 month	13.75 \pm 11.89	31.91 \pm 15.96	U=20.0*	0.023*
• 3 months	26.91 \pm 21.68	42.31 \pm 23.47	U=32.0	0.190
<i>Data was expressed using Mean \pm SD. SD: Standard deviation t: Student t-test</i>				
<i>U: Mann Whitney test p: p value for comparing between the studied groups</i>				
<i>*: Statistically significant at $p \leq 0.05$</i>				

TABLE (3) Comparison between the different time periods in each group according to pain.

	Pain			Fr	p
	Before	1 month	3 months		
HA (n = 10)	6.40 ± 1.17	4.60 ± 0.97	3.50 ± 0.85	18.667	<0.001*
P₀		0.007*	<0.001*		
HA/Chitosan (n=10)	7.40 ± 1.43	3.90 ± 1.37	2.60 ± 0.84	18.865	<0.001*
P₀		0.010*	<0.001*		

Data was expressed using Mean ± SD. SD: Standard deviation
 Fr: Friedman test, Sig. bet. periods were done using Post Hoc Test (Dunn's)
 p: p value for comparing between the studied periods
 p0: p value for comparing between Before and each other period in each group
 *: Statistically significant at p ≤ 0.05

TABLE (4) Comparison between the two studied groups according to pain.

	HA (n = 10)	HA/Chitosan (n = 10)	U	p
Pain				
• Before	6.40 ± 1.17	7.40 ± 1.43	25.00	0.063
• 1 month	4.60 ± 0.97	3.90 ± 1.37	38.50	0.393
• 3 months	3.50 ± 0.85	2.60 ± 0.84	23.0*	0.043*

Data was expressed using Mean ± SD. SD: Standard deviation U: Mann Whitney test
 p: p value for comparing between the studied groups *: Statistically significant at p ≤ 0.05

TABLE (5) Comparison between the two studied groups according to clicking.

Clicking	HA (n = 10)	HA/Chitosan (n = 10)	χ ²	p
Before				
• No clicking	5 (50.0%)	6 (60.0%)	0.493	MCp= 1.000
• Crepitation	3 (30.0%)	2 (20.0%)		
• Painless clicking	0 (0.0%)	0 (0.0%)		
• Painful clicking	2 (20.0%)	2 (20.0%)		
1 month				
• No clicking	6 (60.0%)	8 (80.0%)	0.952	FEp= 0.628
• Crepitation	0 (0.0%)	0 (0.0%)		
• Painless clicking	4 (40.0%)	2 (20.0%)		
• Painful clicking	0 (0.0%)	0 (0.0%)		
3 months				
• No clicking	6 (60.0%)	8 (80.0%)	0.952	FEp= 0.628
• Crepitation	0 (0.0%)	0 (0.0%)		
• Painless clicking	4 (40.0%)	2 (20.0%)		
• Painful clicking	0 (0.0%)	0 (0.0%)		

χ²: Chi square test MC: Monte Carlo FE: Fisher Exact
 p: p value for comparing between the studied groups

TABLE (6) Comparison between the different time periods in each group according to Lateral Movement.

		Lateral Movement			F	p
		Before	1 month	3 months		
Right	HA (n = 10)	9.30 ± 1.77	9.50 ± 1.65	9.50 ± 1.65	2.250	0.134
	HA/Chitosan (n=10)	9.40 ± 2.32	9.85 ± 1.92	9.85 ± 1.92	6.688*	0.007*
	P ₀		0.029*	0.029*		
Left	HA (n = 10)	7.80 ± 1.14	8.70 ± 1.49	9.10 ± 1.66	11.187*	0.005*
	HA/Chitosan (n=10)	8.40 ± 0.84	9.10 ± 0.99	9.10 ± 0.99	7.230*	0.005*
	P ₀		0.025*	0.025*		

Data was expressed using Mean ± SD.

SD: Standard deviation

F: F test (ANOVA) with repeated measures, Sig. bet. periods were done using Post Hoc Test (adjusted Bonferroni)

p: p value for comparing between the studied periods

p₀: p value for comparing between Before and each other period in each group

*: Statistically significant at p ≤ 0.05

TABLE (7) Comparison between the two studied groups according to lateral movement.

Lateral Movement	HA (n = 10)	HA/Chitosan (n = 10)	Test of Sig	p
Right				
• Before	9.30 ± 1.77	9.40 ± 2.32	t=0.108	0.915
• 1 month	9.50 ± 1.65	9.85 ± 1.92	t=0.438	0.667
• 3 months	9.50 ± 1.65	9.85 ± 1.92	t=0.438	0.667
% of increase from Before				
• 1 month	2.54 ± 5.41	6.15 ± 7.86	U=35.0	0.280
• 3 months	2.54 ± 5.41	6.15 ± 7.86	U=35.0	0.280
Left				
• Before	7.80 ± 1.14	8.40 ± 0.84	t=1.342	0.196
• 1 month	8.70 ± 1.49	9.10 ± 0.99	t=0.705	0.491
• 3 months	9.10 ± 1.66	9.10 ± 0.99	t=0.000	1.000
% of increase from Before				
• 1 month	11.53 ± 11.07	8.69 ± 10.83	U=42.0	0.579
• 3 months	16.71 ± 14.44	8.69 ± 10.83	U=33.0	0.218

Data was expressed using Mean ± SD.

SD: Standard deviation

t: Student t-test

U: Mann Whitney test

p: p value for comparing between the studied groups

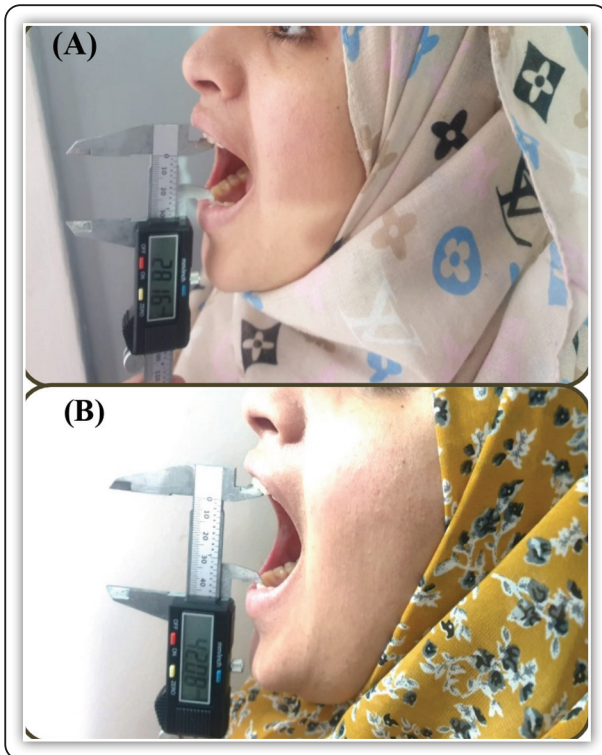


FIG (1) Photograph showing MMO in (HA) group 28.16 pre-operative (A) and 42,08 post-operative (B).

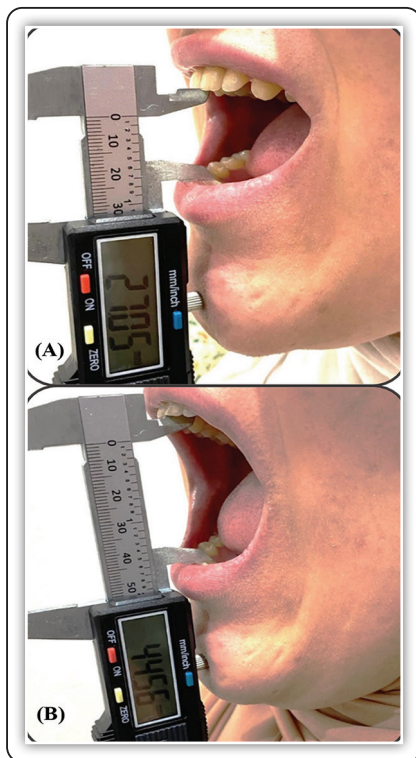


FIG (2) Photograph showing MMO in (Chitosan- Hyaluronic) group 27.05 pre-operative (A) and 44.56 post-operative (B) .



FIG (3) Photograph showing preoperative MRI shows anterior disc displacement without reduction open and closed mouth in HA group.

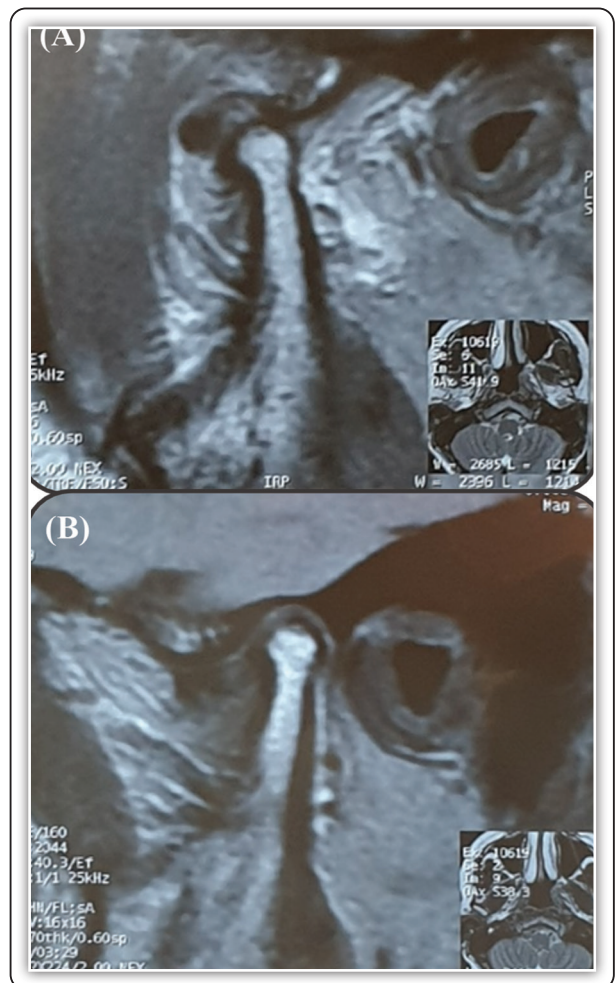


FIG (4) Photograph showing post operative MRI shows anterior disc displacement without reduction open (A) closed (B) in HA group.

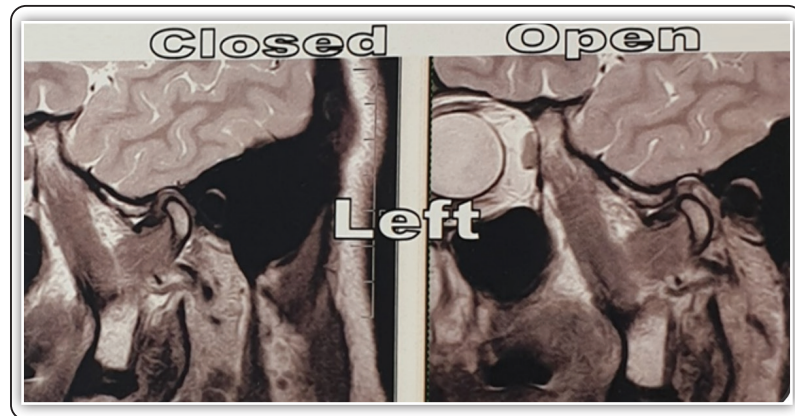


FIG (5) Photograph showing preoperative MRI shows anterior disc displacement without reduction open and closed mouth in chitosan-hyaluronic group.

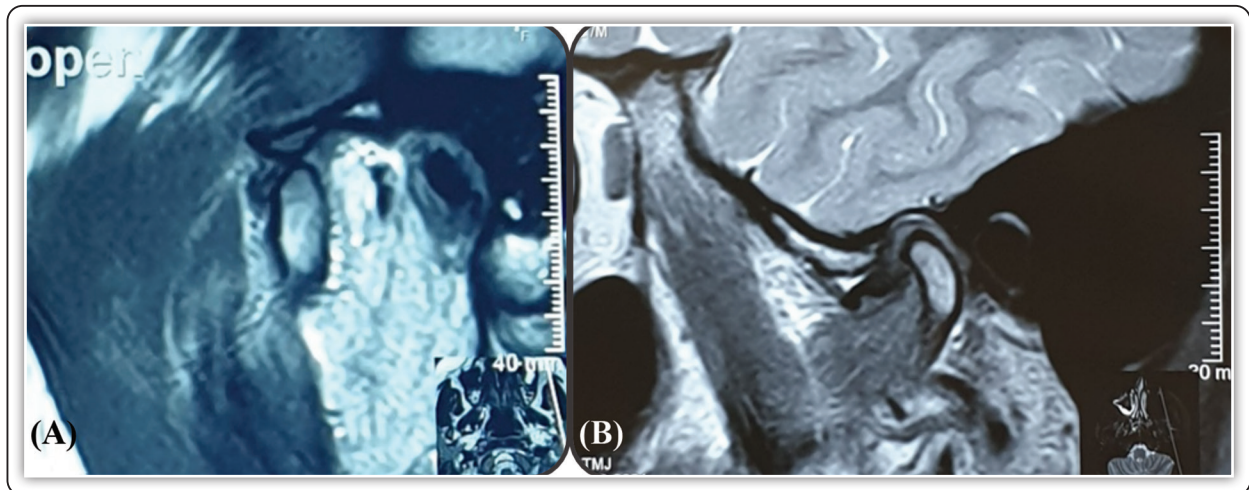


FIG (6) Photograph showing post operative MRI shows anterior disc displacement without reduction open (A) closed (B) in chitosan-hyaluronic group.

DISCUSSION

The first and best option for treatment of internal derangement is the conservative treatment, which includes hot fomentation, medication, physical therapy, splints, and corrected dental issues. Internal derangement is often managed with minimally invasive techniques, particularly in the early and intermediate stages ⁽⁷⁾. The use of arthrocentesis, a minimally invasive procedure, can be used to relieve pain and lessen the consequences of TMD when other treatments are ineffective, particularly when it comes to joint clicking, pain relief, and difficulty opening the mouth ⁽⁸⁾.

Arthrocentesis is a minimally invasive surgical procedure used to treat TMD. It can be used alone or in conjunction with intra-articular injections of regenerative materials such as PRP, PRF, and other injectable materials. Some authors have used anti-inflammatory and lubricant substances like corticosteroids, hyaluronic acid (HA), and chitosan-hyaluronic acid ⁽⁹⁾.

In this study, Arthrocentesis was done with HA or with Chitosan-hyaluronate delivered correctly into the joint space showing better results comparing to the previous studies as Hegab et al. ⁽¹⁰⁾. In present study no significant effects of sex, age and affected

Joints (unilateral or bilateral) on the results in all groups, arthrocentesis was done and affected TMJ injected with Chitosan-hyaluronic acid or HA alone to evaluate outcome response such as, pain intensity, ability to open the mouth and group, clicking of TMJ.

In the present study, HA was the first line of treatment in the study design as evidence-based treatment option based on the previous studies of Bjornland et al. who found that HA patients had significantly better pain relief more than corticosteroids in 40 patients⁽⁸⁾. Also, Manfredini et al. compared arthrocentesis with different injection options and obtained better results with HA compared to corticosteroids. Noticeable improvement was achieved with repeated arthrocentesis combined with HA application⁽¹¹⁾. The principle of these previous studies was that the intra-articular administration of anti-inflammatory drugs into joints can improve lubrication and injectable material, reabsorbed within minutes⁽¹²⁾.

In a prior rat experiment, chitosan and hyaluronic acid were combined to increase the viscosupplementation effect of the hyaluronic acid. Because of its structural resemblance to synovial glycosaminoglycans, anti-inflammatory properties, and capacity to stimulate cartilage development, chitosan was chosen. The synoviocytes accepted this mixture effectively, and there was no edema, pain during probing, or discomfort during movement. Macroscopic examinations revealed no abnormalities of the meniscus or femoral cartilage, no synovial membrane fibrosis, inflammation, or growth of osteophytes⁽¹³⁾.

Donggang Mou, et al. in 2020 evaluated the efficiency of an injectable and self-healing hydrogel that was synthesized by in situ crosslinking of N-carboxyethyl chitosan (N-chitosan), adipic acid dihydrazide (ADH), and hyaluronic acid-aldehyde (HA-ALD) in treating of osteoarthritis. The supramolecular hydrogel maintains a high level of chondrocyte biocompatibility. By suppressing

inflammatory cytokines in the synovial fluid and cartilage at 2- and even 12-weeks post-injection, the intra-articular injection of this new hydrogel can drastically reduce the local inflammation microenvironment in knee joints⁽¹⁴⁾.

In comparison to HA injection, histological and behavioral tests showed that hydrogel injection prevented cartilage damage and reduced discomfort in OA rats. This new type of hydrogel has greater potential for treating OA than the conventional HA injection since it is more effective. Hepguler et al. managed the patients with a conservative therapy treatment hot - cold fomentation, medication, physical therapy, splints, corrective dental problems for more than two months. His study was done in patients aged more than 1 years, divided into two groups, and followed for 6 months. The first group received 0.5 ml of HA (15 mg / ml) and the other receive same volume of saline solution (SS), injected into superior TMJ compartment 2 times. Clicking and pain intensity improved in the patients using HA as compared to patients using saline solution⁽¹⁵⁾.

Orkun et al in 2000 evaluated the efficiency of sodium hyaluronate in treating certain TMD. Twenty patients have anterior disk displacement with reduction. HA (1ml) injected into superior space. Improvement in mouth opening was detected with decreasing of pain and noisy sounds during movement of lower jaw⁽¹⁶⁾. The result of this research was in -agreement with the present study, which showed improvement of HA injection in treatment of TMD. Aforementioned research was in contrast, Kopp et al in 1991⁽¹⁷⁾. They didn't find any statistical significance in MMO after two HA injections, but tenderness of the muscle was decreased in both HA and saline solution. This may be attributed to the fact that Kopp has studied patients with rheumatoid arthritis of TMJ not only with internal derangement.

In the present study the patients were injected with HA in 1 group, Chitosan-hyaluronic hybrid gel in the 2nd group to evaluate its effect on patient with

anterior disc displacement without reduction. The effect of intra-articular administration of Chitosan-hyaluronic acid was better than HA injection was obtained in this study. This observed in reducing pain intensity, noisy TMJ clicking and increasing in MMO, but no change occurs before or after in MRI for all cases.

In previous study by Fu-long Li, et al. in 2020 to compare between the effect of PRP and Chitosan gel alone. The effect of PRP on the improvement of the maximal interincisal opening and pain intensity of patients with TMJ OA was better than that of chitosan, while the incidence of complications associated with the injection of PRP may be higher than that with injection of chitosan⁽¹⁸⁾.

In the present study, the results were detected represented in pain reduction as well as pain free mouth opening and increase masticatory efficiency, improve, and sometimes eliminate TMJ clicking. This may be due to the anti-inflammatory effect of Chitosan-hyaluronic acid hybrid gel. In the present study, no changes in MRI occurs before and after treatment.

In the present study, all patients complained of severe pain, difficulty in chewing, limited mouth opening with significantly altered emotional states before treatment. After arthrocentesis and Chitosan-hyaluronic acid hybrid gel injection, a significant improvement observed. The survey of patient satisfaction (questionnaire) ratified the treatment success, which was demonstrated after 3 months.

CONCLUSION

Chitosan-hyaluronate and HA are safe substances that can be injected into the TMJ cavity without any problems. In individuals with anterior disc displacement without reduction, chitosan-hyaluronate injection with arthrocentesis is more successful and predictable than HA and is thought of as an alternate option in patients who do not respond to conservative treatment. In the treatment

of anterior disc dislocation without reduction, chitosan-hyaluronic acid infusion exhibits a significantly greater benefit in terms of lowering pain, increasing MMO, and reducing clicking more than HA without rejection or problems.

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