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EVALUATION OF VISCOSUPPLEMENTATION USING MEDIUM MOLECULAR WEIGHT HYALURONIC ACID IN TREATMENT OF INTERNAL DERANGEMENT OF THE TEMPOROMANDIBULAR JOINT

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ABSTRACT

Objective: This study is aimed to evaluate the efficacy of series of 4 consecutive injections of medium molecular weight hyaluronic acid (MMW-HA) within the superior joint space (SJS) in patients with internal derangement of temporomandibular joint (TMJ-ID). **Patients and methods:** In this prospective interventional clinical trial (case series), twenty patients with TMJ-ID were treated with four consecutive injections of 1 ml of MMW-HA with one-week intervals. All patients followed one week after each of the four injections and at one, three, and six months after the fourth injection. The postoperative evaluation included maximum unassisted mouth opening (MUMO), modified Helkimo's clinical dysfunction index, and pain intensity on a visual analog scale (VAS). **Results:** All patients showed clinical improvement after MMW-HA injection. The pain, as well as clinical dysfunction index values, showed improvement just after the first injection, while MUMO needed a second injection to start a significant improvement. The fourth injection added a very minute improvement. These improvements continue to the end of the follow-up period. **Conclusion:** Viscosupplementation is an effective simple minimally invasive treatment option for treatment of TMJ-ID in case of failure of conservative treatment that easily performed in outpatient clinic. Two injections showed to be enough for clinical improvement however randomized controlled trials are required to compare between different protocols regarding number and intervals of HA injections.

KEYWORDS: Viscosupplementation, hyaluronic acid injection, TMJ, Internal derangement.

INTRODUCTION

Internal derangement of TMJ is a change in a normal relationship between the disc from one side and mandibular fossa and condyle from another side. The most common clinical findings of ID include clicking, pain in the preauricular region, limitation in jaw movements, headache, and deviation of the mandible during mouth opening. The patients may also suffer from difficulty in eating and swallowing and complain about a significant reduction in quality of life ⁽¹⁾.

Initial treatment should be conservative including lifestyle changing, diet habits modification, pharmacological agents, and physical therapy ⁽²⁾. Surgery is indicated when non-invasive and minimally invasive managements have failed to improve patient symptoms. The surgical interventions may include disc plication, discectomy or eminectomy^(3,4).

Intra-articular injection within the SJS of TMJ usually considered the first line of minimally invasive treatment. Non-steroidal anti-inflammatory

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drugs, opioids, corticosteroids, and hyaluronic acid reported within the literature as injectable materials with variable success rates ^(5,6).

Viscosupplementation is the procedure of repeated hyaluronic acid injection within the SJS to increase the viscosity of the synovial fluid, and so lubricating and cushioning the joint⁽⁷⁾. A very viscous material such HA plays a significant role in joint lubrication and cartilage protection in TMJ-ID⁽⁸⁾. In addition, it alleviates pain by decreasing the level of inflammatory mediators ⁽⁹⁾.

This study is aimed to evaluate the efficacy of series of 4 consecutive medium molecular weight hyaluronic acid injections within the SJS of TMJ in patients with TMJ-ID.

PATIENTS AND METHODS

Study design:

It is a prospective interventional clinical trial (case series).

Study setting and population:

Twenty patients with TMJ-ID were included in this study. The patients were selected among those attending the outpatient clinic of Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Boys, Cairo, Al-Azhar University.

Criteria for patient selection:

Inclusion criteria:

Patients diagnosed with TMJ-ID according to DC/TMD⁽¹⁰⁾ aged between 20 and 40 years old. All patients selected did not respond to conservative treatment including behavior modification, physical therapy, occlusal splints and/or adjustments, and pharmacologic agents as the first line of treatment as the first line of treatment.

Exclusion criteria:

Exclusion criteria included patients with degenerative joint disease, myofascial pain, polyarthritis, previous minimally invasive or invasive treatment of TMJ, and history of mandibular fracture to avoid misleading results regarding pain sensation. In addition, lactating or pregnant women were excluded as HA intra-articular injection is forbidden for them. Patients with known hypersensitivity (by history taking) to HA or clear biocompatible photopolymer resin were also excluded.

Ethical consideration:

The research protocol is approved by the ethical committee, Faculty of Dental Medicine, Al-Azhar University (364/441/06/11/19). Each patient signed an informed written consent having all details about the procedure.

Preoperative assessment:

» Clinical evaluation:

- A thorough clinical examination performed according to DC/TMD.
- A modified version of Helkimo's clinical dysfunction index (Di) ⁽¹¹⁾ calculated to assess the TMJ dysfunction as the following:
- * Maximum unassisted mouth opening range: Opening range determined by asking the patient to gently open mouth and measure the distance between upper and lower central incisor using vernier digital electronic caliper^{*}. Vertical movement of the mandible corrected by adding the vertical overlap, score 0 – if >40 mm, score 1 – if 30–39 mm, and score 5 – if <30 mm.</p>
- * Mandibular deviation during the opening: Patient asked to open mouth gently and deviation noted between maxillary and mandibular midline, score 0 – if <2 mm, score 1 – if 2–5 mm, and score 5 – if >5 mm
- * TMJ dysfunction: TMJ examined for clicking, locking, and luxation without using a stethoscope, score 0 – no impairment, score 1 – palpable clicking, and score 5 – evident clicking, locking, or luxation.
- * TMJ pain: TMJ palpated for the presence of pain in TMJ, score 0 – no pain, score 1 – palpable pain, and score 5 – palpebral reflex.

- Muscle pain: Bilateral examination was carried out for muscles of mastication, score 0

 no pain, score 1 palpable pain, and score 5 palpebral reflex.
- * Di0 no dysfunction; DiI mild dysfunction (1–4 points); DiII – moderate dysfunction (5–9 points); DiIII – severe dysfunction (9–25 points).
- Visual analog scale (VAS) for assessment of pain experience:

Patients were asked to mark their TMJ-related pain level on a scale from 0 to 10, where 0 is "no pain" and 10 is "severe pain".

- » Radiographic evaluation:
- Panoramic radiography obtained for screening to rule out any significant osseous or dental disease in the mandible or maxilla or severe condylar changes.
- MRI was obtained to confirm the initial diagnosis of internal derangement disorder of TMJ. It was chosen not to follow up by MRI as most of the authors suggested that it is not necessary to reflect the improvement in the clinical status of the patient.

Injection technique:

- Patient was learned to self-apply topical anesthesia (lidocaine 2.5%, prilocaine 2.5%) one hour before injection.
- Topical antiseptic (povidone-iodine) was applied at the site of injection.
- A line was drawn from lateral canthus to the tragus (canthal-tragus line) and point of needle insertion placed 10 mm anterior to tragus and 2 mm below canthal-tragus line ⁽¹²⁾ (figure 1).
- The patient was asked to open the mouth so the condyle and fossa could be palpated.

- A 27 G needle was inserted through the skin into the determined point and advancing in superior, medial, and anterior direction until contact bone of posterior slope of the articular eminence at a depth of about 20–25 mm. one ml of normal saline was injected and aspirated again to ensure the correct position of the needle inside SJS, then 1 ml of MMW (1200 – 1400 kDa) HA (Curavisc, Curasan, Kleinostheim, Germany) was injected (figure 1).
- The procedure was performed four times once a week.



FIG (1) Drawing of canthal-tragus line and MMW-HA injection.

Post-injection instructions:

- Opening the mouth to full range as much as possible exercises started immediately after the injection.
- Postoperative pain and discomfort controlled using Ibuprofen 600mg every 8 hours the day and the day after the injection.
- The patient was instructed to remain the diet strictly non-chewing on the first day, progressing to soft food as tolerated.

Postoperative assessment:

All patients followed one week after each of the four injections and at one, three, and six months after the fourth injection for assessment of the following outcome measures:

- The primary outcome variable was the modified Helkimo's clinical dysfunction index.
- The secondary outcome variables were maximum unassisted mouth opening range (MUMO) and pain intensity on a visual analog scale (VAS).

Data management and analysis:

Descriptive statistics are presented in the form of mean and standard deviation (SD) for normally distributed numerical variables and median and interquartile range (IQR) for non-normally distributed variables, while numbers and percentages are used for the categorical variables.

Data tabulated and statistically analyzed using Statistical Program for Social Science (SPSS) version 26.0 (Ibm, New York, USA), and P-value <0.05 is considered statistically significant.

RESULTS

Twenty participants were included in this study, among them 17 (85%) were females and only 3 (15%) were males. Their ages ranged from 20 to 40 with a mean of 26.4. All patients were diagnosed with bilateral ID of TMJ (total of 40 joints). Anterior disc displacement without reduction (DDNR) represented 57.5% while anterior disc displacement with reduction (DDR) represented 42.5% (table 1).

Paired samples t-test was used for the MUMO comparison in each time point versus the preceding one and the Bonferroni method was used for the p-value adjustment to avoid type I error and false rejection of the null hypothesis. Additional comparison between the mean of MUMO at baseline and 1 week after the second injection to detect the first improvement. There was a statistically significant improvement in MUMW one week after the second injection when compared to baseline (table 2). In addition, there was a significant increase in maximum mouth opening over time as tested using mixed repeated measured ANOVA (p-value<0.001).

Descriptive data	Total (N=20)					
Sex						
Female	17 (85%)					
Male	3 (15%)					
Age (years)						
Range	20-40					
Mean±SD	26.4±6.26					
Sides affected						
Bilateral	lateral 20 (100%)					
Diagnosis						
DDNR	23 (57.5%)					
DDR	17 (42.5%)					

TABLE (1) Descriptive data of the patients.

TABLE (2) Comparison of MUMO at each time interval versus the preceding one.

MUMO		Mean	±SD	Adjusted p-value	
After 1 st injection – Preoperative	After 1 st injection	29.85	7.49	- 0.222	
	Preoperative 26.84 7.3		7.32	0.222	
After 2 nd injection – Preoperative	After 2 nd injection	31.83	5.17	- 0.003	
	Preoperative	reoperative 26.84 7.32		0.005	
After 2 nd injection - After 1st injection	After 2 nd injection	31.83	5.17	0.225	
	After 1 st injection	29.85	7.49	- 0.235	
After 3 rd injection - After 2 nd injection	After 3 rd injection	33.17 4.43		- 0.064	
	After 2 nd injection	31.83	5.17	0.004	
1 week after 4 th injection - After 3 rd injection	1 w. after 4 th injection	33.18	4.00	- >0.000	
	After 3 rd injection	33.17	4.43	20.339	
1 month after 4 th injection - 1 week after 4 th injection	1 m. after 4 th injection	^h 34.76 4.09		- ~0 001	
	1 w. after 4 th injection	33.18	4.00	<0.001	

МИМО		Mean	±SD	Adjusted p-value
3 months. after 4 th injection - 1 month after 4 th injection	3 ms. after 4 th injection	35.22	4.15	0.002
	1 m. after 4 th injection	34.76	4.09	0.003
6 months after 4 th injection - 3 months after 4 th injection	6 ms. after 4 th injection	35.36	4.05	0.000
	3 ms. after 4 th injection	35.22	4.15	- >0.999

Wilcoxon signed-rank test was used for the modified Helkimo's score and VAS score comparisons in each time point versus the preceding one and the Bonferroni method was used for the p-value adjustment. In comparison to the baseline, the statistically significant improvement in both scores could be noted one week after the first injection. In addition, there was a statistically significant improvement when comparing VAS scores one month to one week following the fourth injection (table 3).

TABLE (3) Comparison of modified Helkimo and VAS scores at each time interval versus the preceding one.

		Modified Helkimo's score			VAS		
		Median	IQR	Adjusted P-Value	Median	IQR	Adjusted P-Value
After 1 st injection - Preoperative	Preoperative	12	7	- 0.007 -	7.3	3.4	- 0.002
	After 1 st injection	7	8		5.85	3.3	
After 2 nd injection - After 1 st injection	After 2 nd injection	2.5	10	- 0.010 -	3.7	2.4	- 0.001
	After 1 st injection	7	8		5.85	3.3	
After 3 rd injection - After 2 nd injection	After 3 rd injection	2	4	- 0.011 -	2.55	2.2	- 0.001
	After 2 nd injection	2.5	10		3.7	2.4	
1 w. after 4 th injection - After 3 rd injection	1 w. after 4 th injection	1	2	- 0.068 -	1.85	1.7	- 0.109
	After 3 rd injection	2	4		2.55	2.2	
1 m. after 4 th injection - 1 w. after 4 th injection	1 m. after 4 th injection	1	1	- 0.162 -	0.75	1.6	- 0.001
	1 w. after 4 th injection	1	2		1.85	1.7	
3 ms. after 4 th injection - 1 m. after 4 th injection	3 ms. after 4 th injection	1	1	- >0.999 -	0.25	1.3	- 0.177
	1 m. after 4 th injection	1	1		0.75	1.6	
6 ms. after 4 th injection - 3 ms. after 4 th injection	6 ms. after 4 th injection	1	1	- >0.999 -	0	1	- 0.832
	3 ms. after 4 th injection	1	1		0.25	1.3	

DISCUSSION

Hyaluronic acid, which is a high-viscosity polysaccharide secreted intrinsically by B cells of the synovial membrane and forms the most volume of the synovial fluid, plays an important role in TMJ lubrication, protecting joint cartilage, and nourishing its avascular structures ⁽¹³⁾. Inflammation in the TMJ reduces the concentration and molecular weight of HA, thus reducing its physiological effects ⁽¹⁴⁾.

The viscoelasticity of the synovial fluid is affected by molecular weight of HA. Iturriaga et al. described three categories of molecular weight for extrinsic HA namely low molecular weight (LMW) HA 500–1000 kDa, medium molecular weight (MMW) HA 1200–4500 kDa, and high molecular weight (HMW) HA 6000–7000 kDa ⁽¹⁵⁾. However the choice of the best molecular weight of HA to be injected is a matter of controversy, it is evident that LMW is associated with more biological properties due to its stimulatory effect on synoviocytes and chondrocytes, and HMW is characterized by more biomechanical effects in terms of high viscosity, shock absorption, and lubrication ⁽¹⁶⁾. In this study, it was decided to use MMW-HA to get the maximum possible benefits.

All participants in this study showed clinically and statistically significant improvement after the first injection of MMW-HA regarding Helkimo's clinical dysfunction index and pain on VAS. On the other hand, MUMO needed another injection to show improvement. These improvements continued up to the 6 months of the follow-up period.

Intra-articular HA injection has successfully been used in the pain control of intra-articular TMD due to their anti-inflammatory and analgesic effects, such as scavenging free radicals, reducing vascular permeability, and inhibition of phagocytosis, chemotaxis, prostaglandin synthesis, metalloproteinase activity⁽¹⁷⁾. Gomis et al. interpreted the analgesic effect of HA by its ability to reduce nerve impulses and sensitivity of joint nociceptor nerve endings ⁽¹⁸⁾.

The increase in mouth opening is undoubtedly due to the mechanical effect of the HA injected into the joint. This high viscoelastic liquid causes an increase in the hydraulic pressure with consequent expansion of the intra-articular space. Increased knee joint space was observed by Jubb et al. one year after the HA injection as shown in pre and postoperative MRI⁽¹⁹⁾. HA injection provides lubrication that reduces the friction of the joint surfaces, thus increasing the movement capacity of the joint. Relief of pain and a decrease in the negative pressure also contribute to improving mouth opening. Extrinsic HA binds to chondrocytes via the CD44 receptor which in turn stimulates greater intrinsic production of HA by the synoviocytes, stabilizes the cartilaginous matrix, stimulates chondrocyte proliferation, increases type 2 collagen and aggrecan production by chondrocytes, and diminishes the degradation of type 2 collagen ⁽²⁰⁾. These pharmacological actions interpret continuous improvement regarding clinical parameters over time in this 6-month follow-up study. HA injection treatment should not be considered only as a lubricant and shock absorber but also as a valuable tool to re-establish the ideal environment for asymptomatic functioning TMJ.

The results of this study coincide with the results of Stasko et al. study that found a significant improvement in clinical symptoms regarding maximum mouth opening and pain on VAS in 99 patients after a series of a total of three intraarticular TMJ HA (800 – 1200 kDa) injections in one-week intervals ⁽²¹⁾.

This study showed very slow improvement in MUMO and pain after one week of the fourth injection. The lack of such statistically significant improvement can be interpreted by pain and trauma associated with four weekly consecutive injections. Similar results were obtained by Manfredini and his colleagues who found clinical improvement across five arthrocentesis plus HA injections at oneweek intervals. However, they noted a decrease in MUMO after the fourth injection that returned to be improved after the fifth injection ⁽²²⁾. Guarda-Nardini et al. reported superiority of five-session viscosupplementation over single-session protocol regarding pain although no difference noted in other clinical outcomes ⁽²³⁾.

These findings reinforce the opinion that decreasing the number of injections with expected clinical, psychological and social impact should be a priority for future research.

CONCLUSION

Viscosupplementation is an effective simple non-invasive treatment modality for the treatment of TMJ-ID in case of failure of the conservative treatment that is easily performed in the outpatient clinic. Two injections showed to be enough for clinical improvement, however randomized controlled trials are required to compare different protocols regarding the number and intervals of HA injections.

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