

The Impact of Sodium Hyaluronate TMJ Injection on Pain and Mandibular Movements in Patient With Temporomandibular Disorders. (Clinical Study)

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ABSTRACT

AIMS: In this part of study we assess the effect of HA in pain & mandibular movements.

MATERIALS AND METHODS: This study include 21 patients with TMDs were diagnosed clinically and confirmed by Trans cranial radiography. The age range was from 18 to 50 years old, with a mean of 30.03 years. Three cycles of intra articular injections of 0.6 ML sodium hyaluronate were performed weekly for three successive weeks. Pain intensity was measured by the visual analog scale. Maximal mouth opening, clicking joint noise, and lateral movements were measured before and one week after first ,second & third injections.

RESULTS: This study include 21 patients 5 males & 16 females , with age ranged 18-50 years ,the majority of patients were at age ranged between 21-40 years which represent 66.6% of, concerning gender distribution female to male ratio was 3:1. only 7 patients(33.3%) have osteoarthritis .High significant relation between pain & OA. Firedman test 44.406 df,3 , significance 0.00 osteoarthritis were more frequent in female which represent 85.8% (6 patients) than male patient which represent 14.2% (one patient) there is no significant relation between osteoarthritis & sex, Friedman test = .527 , $p \geq 0.005$. The minimum maximum, means & standard deviation of visual analogue scale(VAS) before & one week after the first ,second & third injections of HA were recorded, VAS value before treatment was 6.28 & it decrease gradually to 3.3 ,2.2 till it become 0.8 in group c (one week after the third injection) . High significant difference $p \leq 0.001$ in VAS before & one week after the first ,second & third injections of HA. A significant difference in VAS one week after the first & second injections of HA.& one week after the second & third injections of HA. $P \leq 0.005$, while highly significant difference one week after the first & third injections of HA $P \leq 0.001$.The minimum maximum, means & standard deviation of interincisal distance ID in millimeters before & one week after the first ,second & third injections of HA were recorded. The mean interincisal distance was 35.4 mm before injection & it become 42.7 mm one week after the third injection. A a significant difference in ID before & one week after the first & second injections of HA. $P \leq 0.005$ while highly significant difference $p \leq 0.001$ in ID before & one week after the third injection of HA.Non significant difference in ID one week after the first, second & third injections of HA $p \geq 0.005$.The minimum maximum, means & standard deviation of the lateral right & left madibular movements in millimeters before & one week after the first ,second & third injections of HA.,it shows that the mean right lateral movement is 7.619 mm before the injection & it become 8.8mm one week after the third injection ,while the mean of left lateral movement is 7.3 mm which become 8.8 mm one week after the third injection of HA. . High significant difference $p \leq 0.001$ in lateral movements before & one week after the first ,second & third injections of HA, except before & one week after the second & third injections in right lateral movement which show significant difference $P \leq 0.005$.Non significant difference $p \geq 0.005$ in lateral movements one week after the first , second & third injections & one week after the second & third injections of HA.

CONCLUSION:The intra articular injection of HA in TMJ in a patients with TMDs is an effective & safe method in reducing pain & improving vertical & horizontal movements of mandible & their effect appear obviously after the first injection. So this treatment modalities can be considered as the best reversible type of treatment as it is a safe ,effective with no complications, not costly as compared with other modalities like bite palates , no side effect as with pharmacological therapy, & an immediate relief of signs & symptoms can be gained.

KEY WORDS: Hyaluronic acid, Pain, Mandibular Movements, TMJ, Intra articular injection.

INTRODUCTION

Temporomandibular disorders (TMDs) refer to cluster of disorders characterized by pain in preauricular area , the temporomandibular joint ,or the muscles of mastication, limited or deviations in the mandibular range of motion ,& noises in the TMJ during mandibular function. in addition pain elicited by function & by palpation of the muscles of mastication & abnormal static & dynamic occlusal relationship⁽¹⁾.

Masticatory pain is a discomfort about the face & mouth induced by chewing & other jaw use , it is the symptom that causes patient greatest concern to seek treatment⁽²⁾.

Clinical descriptions of pain vary considerably ranging from dull ache to sharp & acute oftenly unilateral but a bilateral pain is also common, the location of pain may range from back of head & neck posteriorly ,to the temporal area superiorly & to the angle of the jaw anteriorly⁽³⁾ .But the most cited pain location is the area in front the ear⁽⁴⁾.

Mandibular movement values are an important parameter within the clinical evaluation of the temporomandibular joint⁽⁵⁾ .The normal maximum mouth opening is 40 mm while the normal lateral movements are 7mm⁽⁶⁾.

The symptoms of restricted mandibular movements could be classified into two categories ,restricted mouth opening (trismus) limited lateral movement & deviation during mandibular movements⁽²⁾. When muscles tissue have been compromised by fatigue & spasm, any contraction or stretching of muscle increases the pain, therefore to maintain the comfort the person restricts movement within range that does not increase pain level. Clinically this seen as inability to open mouth to normal range⁽⁷⁾.

Hyaluronic acid (HA) is a mucopolysaccharide acid present in ground substance in animal tissues. It is the major component of the synovial fluid and has an important role in lubrication, nutrition, homeostasis and load absorption of articular tissues.^(8,9,10) In cases of inflammatory and degenerative changes of joints, the concentration and molecular weight of HA is reduced.^(11,12) Viscosupplementation with sodium hyaluronate increases the concentration and molecular weight of HA in the synovial fluid,⁽¹³⁾ restoring tissues lubrication and nutrition as well as minimizing mechanic stress^(10,14) .Moreover, intra-articular SH injection presents an analgesic effect by blocking receptors and endogenous substances that cause pain in synovial tissues. In addition, it promotes a release of adhesion areas between the articular disc and the mandibular fossa, increasing joint mobility and allowing better synovial fluid circulation.⁽¹⁴⁾

At first, the intra-articular sodium hyaluronate injection was used in race horses with traumatic arthritis.⁽¹⁵⁾ Afterward, it was based on studies on the osteoarthritis model, induced in animals, and combined with the inhibition of osteoarthritis development.⁽¹⁶⁾ In the mid-70's, viscosupplementation with sodium hyaluronate began to be used in humans for osteoarthritis treatment of large joints such as knee, hip and shoulder,⁽¹⁷⁾ being indicated for the internal derangements of TMJ after 1979.⁽¹⁸⁾

HA injections are gaining attention as a treatment option to manage symptoms of TMDs ,but update evidence –based data on their effectiveness are actually lacking⁽¹⁹⁾, repeated intra –articular TMJ injections of HA appear to be safe & effective way of inhabiting the progression of osteoarthritic changes in the joint through the development of articular cartilage & reducing fibrous tissue proliferation⁽²⁰⁾.

AIMS OF STUDY

The aims of this study is to evaluate the effects of TMJ intra articular injection of high molecular weight Hyaluronic acid on TMJ pain & mandibular movements in patients with TMDs.

MATERLIS AND METHODS

1- Materials:

- 1- Patient sample .twenty one patients collected from Dentistry College Oral & Maxillofacial surgery Department University of Mosul & from private clinic were complain from temporomandibular disorder⁽¹⁾ including pain &/or clicking with or without limitation of mouth opening. The information was registered in special case sheet Figure (1),
- 2- Hyaluronic acid sodium salt (Hylgan) 20mg/2 ml Fidia Farmaceutici S.P.A-Abano Terme (PD) Italy. Figure (2),
- 3- Local anesthesia (Lidocain 2% with Epinephrine 1:180000) Antiqia – Colombia.,
- 4- Dental needle 27 G Dentject Korea.,
- 5- Vernier.,
- 6- Millimeter roller.
- 7- Soft pen.,
- 8- Gauze,
- 9- Antiseptic chlorohexidine gluconate (Hebetene 4%) Sahab-Gorden, 10- Stethoscope.

2-Methods

A special case sheet (Figure 1) was used to record the information from the patients. Trans cranial view was taken to check the osteoarthritic changes (decrease intrarticular spaces, spure formation, flattening of the articular surfaces & sub cortical radiolucency Elye`s cyst)⁽²¹⁾

A twenty-one patients were participated in this study, their age ranged 18-50 years & sex distribution 16 females & 5 males as shown in Table (1). All patients in the study sample were with no systemic diseases. All patients were examined by the same examiner to provide standardization, inspection to see any asymmetry of face, scar formation on chin, then digital examination of TMJ & muscles of mastication to evaluate the tenderness, maximum inter incisal distance were recorded by vernier , a stethoscope was used to detect any clicking in TMJ. All selected patients have clicking, pain with or without limitation of mouth opening.

The pretragus area was disinfected by hebeten, then 0.5 ml of a local anesthesia was injected in pretragus area while the patient open the mouth to block the auricotemporal nerve. waiting 3-5 minutes, cartridges were emptied to be used for injection of hyaluronic acid, then 10 mm front & 2 mm below from mid trago-canthus line was marked by soft pen which denote the upper compartment of the TMJ. Then the cup of the prefilled HA syringe was withdrawn, then 5ml syringe needle was tighten & 0.6ml of HA was pushed into the emptied cartridge then the drug was injected into the upper compartment of the TMJ at 45 degree⁽²²⁾ (Figure 3). A sterile gauze with hebeten was placed at the injected site for 1minute, the patient was instructed to open & close the mouth several times to allow distribution of the drug. Any immediate complications like severe pain, facial paralysis, fainting earache & bleeding were recorded. The remaining HA was stored in refrigerator at 20°C, the patients were instructed not to open their mouth widely & eat on both sides , analgesic was prescribed to be taken only on severe pain.

The second & the third injections were given with the same manner after one & two weeks respectively. The visual analogue scale 0-10 was used to assess the pain intensity were as the clicking was checked by stethoscope during opening & closing & the inter incial distance & the lateral movements were measured by the vernier at each visit, before & one week after the first, second & third injections.

Statistical Analysis.

Data was processed in computer with use of slandered program (SPSS 11.5 for windows), the statistical calculation of differences was done with the paired T test & Friedman tests. The following symbols were used for different levels of significance in tables. NS not significant, $p \geq 0.005$. significant $p \leq 0.005$. highly significant $p \leq 0.001$.

RESULTS

This study include 21 patients 5 males & 16 females, with age ranged 18-50 years ,the majority of patients were at age ranged between 21-40 years which represent 66.6% of the sample, concerning gender distribution female to male ratio was 3:1 (Table 1).

Table (2) revealed that only 7 patients (33.3%) have osteoarthritis. High significant relation between pain & OA. Firedman test 44.406 df,3, significance 0.00

Tables (3) showed that osteoarthritis were more frequent in female which represent 85.8% (6 patients) than male patient which represent 14.2% (one patient) there is no significant relation between osteoarthritis & sex, Friedman test = .527, $p \geq 0.005$.

Table (4) reveals the minimum maximum, means & standard deviation of visual analogue scale(VAS) before & one week after the first, second and third injections of HA., VAS value before treatment was 6.28 & it decrease gradually to 3.3 ,2.2 till it become 0.8 in group c (one week after the third injection). High significant difference $p \leq 0.001$ in VAS before & one week after the first, second and third injections of HA. as shown in (Table 5).

(Table6) Demonstrate a significant difference in VAS one week after the first & second injections of HA.& one week after the second & third injections of HA. $P \leq 0.005$, while highly significant difference one week after the first & third injections of HA $P \leq 0.001$.

(Table7) reveals the minimum maximum, means & standard deviation of interincisal distance ID in millimeters before & one week after the first ,second & third injections of HA.,The mean interincisal distance was 35.4 mm before injection & it become 42.7 mm one week after the third injection. A a significant difference in ID before & one week after the first & second injections of HA. $P \leq 0.005$ while highly significant difference $p \leq 0.001$ in ID before & one week after the third injection of HA. as shown in (Table8).

Table(9) Demonstrate non-significant difference in ID one week after the first, second & third injections of HA $p \geq 0.005$.

(Table10) reveals the minimum maximum, means and standard deviation of the lateral right & left madibular movements in millimeters before & one week after the first ,second & third injections of HA.,it shows that the mean right lateral movement is7.619 mm before the injection & it become 8.8mm one week after the third injection ,while the mean of left lateral movement is 7.3 mm which become 8.8 mm one week after the third injection of HA. . High significant difference $p \leq 0.001$ in lateral movements before & one week after the first, second & third injections of HA, except before & one week after the second & third injections in right lateral movement which show significant difference $P \leq 0.005$ as shown in Table(11).

Table(12) shows non significant difference $p \geq 0.005$ in lateral movements one week after the first , second and third injections & one week after the second & third injections of HA.

Table 1: Sample distribution.

Age years	Sex					
	Male	%	Female	%	Total	%
11-20	2	9.5	3	14.2	5	23.8
21-30	2	9.5	6	28.5	8	38.0
31-40	1	4.7	5	23.8	6	28.5
41-50	0	0	2	9.5	2	9.5
Total	5	23.8	16	76.2	21	100

Table 2: Osteoarthritis of TMJ in Trans cranial view.

Osteoarthritis	+ ive	%	- ive	%	Total
Number	7	33.3	14	66.6	21

Friedman test = 44.407 df=3 p= 0.000

Table 3: Gender distribution of Osteoarthritis of TMJ.

Sex	Male	%	Female	%	Total
Osteoarthritis	1	14.2	6	85.8	7

Friedman test = .527 df=1 p= 0.127 NS

Table 4: VAS Mean, & SD before & one week after first, second & third injections of Hyaluronic acid in TMJ.

Groups	Minimum	Maximum	Mean	Standard deviation
O	0	10	6.2857	2.79540
A	0	10	3.3810	2.80136
B	0	8	2.0476	2.01187
C	0	2	0.809	0.60159

O= VAS before injection of Hayluronic acid.,A= VAS one week after first injection of Hayluronic acid,B= VAS one week after second injection of Hayluronic acid,C= VAS one week after third injection of Hayluronic acid.

Table 5: Relation of VAS before & one week after first, second & third injections of Hyaluronic acid in TMJ.

Groups	Mean	Standard deviation	Paired t test	df	P
O-A	2.9048	2.36442	5.630	20	0.000**
O-B	4.2381	2.62479	7.399	20	0.000**
O-C	5.4762	2.50238	10.028	20	0.000**

O= VAS before injection of Hayluronic acid.,A= VAS one week after first injection of Hayluronic acid,B= VAS one week after second injection of Hayluronic acid,C= VAS one week after third injection of Hayluronic acid, $P \leq 0.001$ **= highly significant difference.

Table 6: Relation of VAS one week after first ,second & third injections of Hyaluronic acid in TMJ.

Groups	Mean	Standard deviation	Paired test	t	df	P
A-B	1.333	1.79815	3.398		20	0.003*
A-C	2.5714	2.46113	4.788		20	0.000**
B-C	1.2381	1.72930	3.281		20	0.004*

O= VAS before injection of Hayluronic acid.,A= VAS one week after first injection of Hayluronic acid,B= VAS one week after second injection of Hayluronic acid,C= VAS one week after third injection of Hayluronic acid,* significant difference= $P \leq 0.005$,** = highly significant difference $p \leq 0.001$.

Table 7: ID in mm Mean, & SD before & one week after first, second & third injections of Hyaluronic acid in TMJ.

Groups	Minimum	Maximum	Mean	Standard deviation
O	20	50	35.4286	9.74973
A	32	52	41.5714	5.93777
B	32	51	42.333	6.08550
C	32	51	42.7143	6.06748

O= ID before injection of Hayluronic acid.,A=ID one week after first injection of Hayluronic acid,B= ID one week after second injection of Hayluronic acid,C= ID one week after third injection of Hayluronic acid.

Table (8) Relation of ID before & one week after first ,second & third injections of Hyaluronic acid in TMJ.

Groups	Mean	Standard deviation	Paired test	t	df	P
O-A	6.1429	8.38621	- 3.357		20	0.003*
O-B	6.9048	9.03828	- 3.501		20	0.002*
O-C	7.2857	9.03960	- 3.170		20	0.001**

Table (9) Relation of ID one week after first ,second & third injections of Hyaluronic acid in TMJ.

Groups	Mean	Standard deviation	Paired test	t	df	P
O-A	6.1429	8.38621	- 3.357		20	0.003*
O-B	6.9048	9.03828	- 3.501		20	0.002*
O-C	7.2857	9.03960	- 3.170		20	0.001**

O= ID before injection of Hayluronic acid.,A= ID one week after first injection of Hayluronic acid,B= ID one week after second injection of Hayluronic acid,C= ID one week after third injection of Hayluronic acid, *,*= significant difference $p \leq 0.005$, * = highly significant difference $p \leq 0.001$.

Table 10: Lateral movements in mm ,Means & Standard deviations before & one week after first, second & third injections of Hyaluronic acid

Groups	Right side				Left side			
	Minimum	Maximum	Mean	SD	Minimum	Maximum	Mean	SD
O	4	12	7.6190	2.24669	4	12	7.3810	2.17890
A	5	12	8.2381	1.97243	5	12	8.1905	2.01542
B	6	12	8.4762	1.69172	6	12	8.4762	1.69172
C	7	12	8.8571	1.65184	7	12	8.8571	1.65184

O= variables before injection of Hayluronic acid., A= variables one week after first injection of Hayluronic acid , B= variables one week after second injection of Hayluronic acid, C= variables one week after third injection of Hayluronic acid.

Table 11: Relation of lateral movements in mm , before & one week after first, second & third injections of Hyaluronic acid.

Groups	Right side				Left side					
	Mean	SD	Paired t test	df	P	Mean	SD	Paired t test	df	P
O – A	-0.619	0.74001	-3.833	20	0.001**	-0.8095	0.6019	-6.167	20	0.000**
O – B	-0.8561	1.19523	-3.286	20	0.004*	-1.0952	1.0952	-4.600	20	0.000**
O – C	-1.2381	1.54612	-3.670	20	0.002*	-1.4762	1.4762	-4.830	20	0.000**

O= variables before injection of Hayluronic acid., A= variables one week after first injection of Hayluronic acid , B= variables one week after second injection of Hayluronic acid, C= variables one week after third injection of Hayluronic acid. *= significant $P \leq 0.005$, **=high significant $P \leq 0.001$.

Table 12: Relation of lateral movements in mm one week after first, second & third injections of Hyaluronic acid.

Groups	Right side				Left side					
	Mean	SD	Paired t test	df	P	Mean	SD	Paired t test	df	P
A – B	-0.2381	0.16768	-1.420	20	0.171 NS	-0.2857	0.78376	-1.671	20	0.110 NS
A – C	-0.6190	1.07127	-2.248	20	0.015 NS	-0.6667	1.06458	-2.870	20	0.009 NS
B – C	-0.3810	0.66904	-2.609	20	0.017 NS	-0.3810	0.66904	-2.609	20	0.017 NS

A= variables one week after first injection of Hayluronic acid , B= variables one week after second injection of Hayluronic acid, C= variables one week after third injection of Hayluronic acid. NS = non significant $P \geq 0.005$.

TMJ Case sheet					
Name:					
Age:					
Sex:					
Chief complaint:					
TMJ sound:	right:	left:	both:		
Injection :	Date:				
Pain:	0 1 2 3 4 5 6 7 8 9 10				
Joint sound:	Improved	slightly	well	no clicking	Worsen
Interincisal distance:	lateral right		lateral left		
x-Ray report:					
complications:					

Figure 1: TMJ Case sheet.

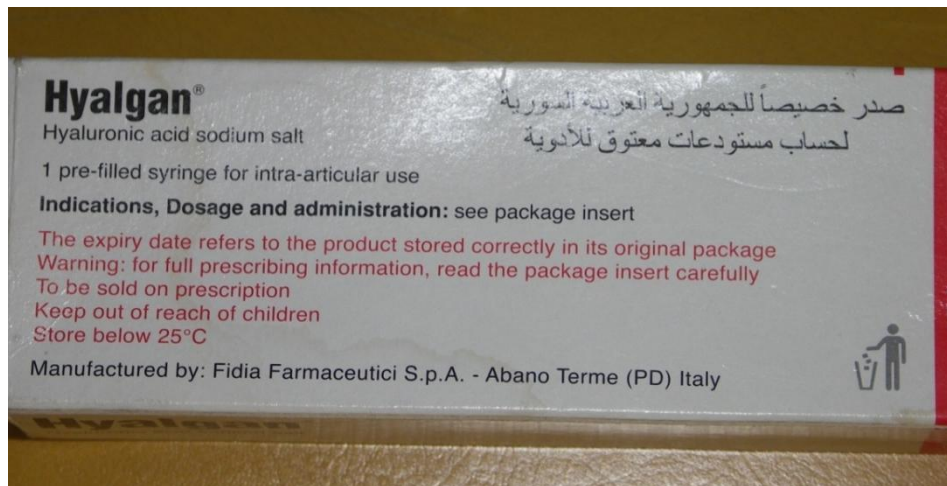


Figure 2: Hyaluronic Acid Sodium Salt, Italy.

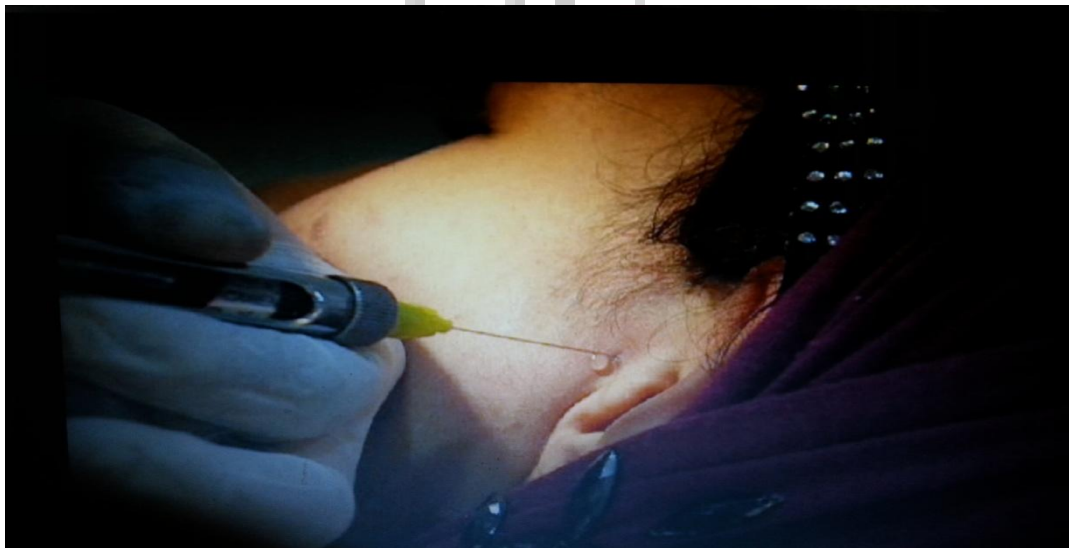


Figure 3: Intra articular injection of Hyaluronic Acid into upper TMJ space.

DISCUSSION

The development and use of sodium hyaluronate, especially high molecular weight hyaluronate, in the treatment of TMJ internal derangement is an exciting therapeutic prospect that deserves further thorough investigation⁽²³⁾. In this study a 2ml of high molecular weight of HA was used. Sodium hyaluronate, the sodium salt of hyaluronic acid, is a high molecular weight Polysaccharide and a major natural component of synovial fluid. The importance of hyaluronate to the lubrication of synovial tissue has been established but its function in relation to the occurrence of joint disease is not precisely known⁽²³⁾. In 1939 Mayer et al.⁽²⁴⁾ first identified it in synovial fluid. Hyaluronic acid is a glycosaminoglycan made of the periodic repeat of d-glucuronic acid and N-acetylglucosamine disaccharides units. It plays a role in the regulation of synovial fluid⁽²³⁾.

In this study the majority of the patients were at age ranged 21- 40 years & this result is consistent with other studies^(25,26,27).

Regarding sex, female to male ratio was 3:1 and it agree with other studies^(26,28).

The reason why women make up the majority of patients presented for treatment is still unclear⁽²⁸⁾, however physiological & hormonal factors should also be considered as possible components of remarkable gender distribution among TMD patients⁽²⁵⁾, recently they found that the testosterone level help to explain the lower prevalence of TMJ pain & also show that testosterone reduces TMJ pain at sub physiological level⁽²⁹⁾

There is high relation between OA & pain, this result agrees with other study⁽³⁰⁾ & this is due to a lower viscosity of HA in synovial fluid resulted from inflammation⁽³¹⁾.

High significant difference in pain intensity before & one week after the first ,second & third injections of HA ,this result disagree with other study^(23,30,31) & agree with Bertolami et al.study⁽³²⁾ .The elimination of pain is mainly because of the analgesic, anti-inflammatory, and lubricating properties of the hyaluronic acid⁽²³⁾ .Moreover, intra-articular SH injection presents an analgesic effect by blocking receptors and endogenous substances that cause pain in synovial tissues⁽¹⁴⁾ . Balazs2002⁽³³⁾ commented that the analgesic effect was directly proportional to the molecular weight and, therefore, to the elastoviscosity of the solution, which was first reported by Miyazaki et al.⁽³⁴⁾ .

It has been reported that synovial fluid aspirated from inflammatory joint disease or rheumatoid arthritis has a lower viscosity than patients with no disease⁽³⁵⁾ . This was found to be correlated to either increased degradation of high molecular weight hyaluronate and/or a decrease in the concentration of high molecular weight hyaluronate in inflammatory disease. ⁽³⁶⁾ . Therefore, Viscosupplementation with sodium hyaluronate increases the concentration and molecular weight of HA in the synovial fluid⁽¹³⁾ restoring tissues lubrication and nutrition as well as minimizing mechanic stress^(10,14) .the improvement in symptomatology and function were most likely linked with the intrinsic properties of high molecular weight of hyaluronic acid which is used in the this study.

Regarding ID, high significant difference before & one week after the third injection of HA. were as significant difference before & one week after first & second injections of HA were found , & this result is consistent with other studies^(23,32) & disagree with other study⁽³¹⁾ .

The significant increase in mouth opening due to reduction in frictional coefficient⁽³⁶⁾ also it may be due to a reduction in pain because of analgesic, anti-inflammatory & lubricating properties of HA^(14,23,33) .

There is a difference in ID one week after first , second & third injections of HA & this can be explained by the improvement of ID after the first injection of HA as reduction of frictional coefficient & pain due to lubricating & analgesic effect of HA^(23,33) . Which appear one week after the first injection , so one injection of HA is effective for relieving pain as revealed by this study.

We found in this study a significant improvement of lateral movements before & one week after the first, second & third injections of HA & this result disagree with the result of Shi etal.2002,⁽³¹⁾ &Yeung et al.2006⁽²³⁾ , the latter use only two injections of HA at two weeks interval , & this difference in result may be due to the number of injection , periods between injections & the type of HA. Viscosupplementation with sodium hyaluronate increases the concentration and molecular weight of HA in the synovial fluid,⁽¹³⁾ restoring tissues lubrication and nutrition as well as minimizing mechanic stress.^(10,14) Moreover, intra-articular SH injection possess analgesic effect by blocking receptors and endogenous substances that cause pain in synovial tissues. In addition, it promotes a release of adhesion areas between the articular disc and the mandibular fossa, increasing joint mobility and allowing better synovial fluid circulation⁽¹⁴⁾ .

Because of these actions of HA , the reduction of pain & the improvement of ID & lateral movements of TMJ in this study , after the injection of HA can be explained.

No complications to this procedure were found only one patient developed syncope due to fear.

What is new in this study:

- 1- We use a dental needle 27 G instead of syringe needle 21 G & this allow good & rapid penetration of tissue ,less pain ,less tissue trauma, less opportunity to infection.
- 2- Only one prefilled 2ml of HA was used in this study i.e. low cost to patient.

CONCLUSIONS

The intra articular injection of HA in TMJ in a patients with TMDs is an effective & safe method in reducing pain & improving vertical & horizontal movements of mandible & their effects appear obviously after the first injection. So this treatment modalities can be considered as the best reversible type of treatment especially in patient with disc displacement without reduction , it is safe, effective with no complications, not costly as compared with other modalities like bite palates , no side effect as with pharmacological therapy, & an immediate relief of signs & symptoms can be gained.

SUGGESTIONS

- 1- Study of single injection of high molecular weight of HA on signs & symptoms of TMDs.
- 2- Long term study for 6 months & 1 year.

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