Int. J. Morphol.,
41(3):699-704, 2023.

Differences According to the Type of Exogenous Hyaluronic Acid and its Frequency of Infiltration in the Treatment of Temporomandibular Osteoarthritis

Diferencias Según el Tipo de Ácido Hiaurónico Exógeno y su Frecuencia de Infiltración en el Tratamiento de la Osteoartritis Temporomandibular

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WEN, S.; ITURRIAGA, V.; VÁSQUEZ, B.; SANTANDER, J.; BARRÍA, D. & DEL SOL, M. Differences according to the type of exogenous hyaluronic acid and its frequency of infiltration in the treatment of temporomandibular osteoarthritis. *Int. J. Morphol., 41(3)*:699-704, 2023.

SUMMARY: One of the most important minimally invasive treatments today in temporomandibular joint osteoarthritis (TMJ-OA) is the intra-articular exogenous hyaluronic acid (HA) injection, which has yielded good results in pain relief and improves mandibular function with few side effects. However, the effectiveness of HA continues to be controversial, partly due to the heterogeneity in the injection protocols in their molecular weight, viscosity and frequency of infiltration, among other properties. The aim of this review is to identify the differences in the histological and clinical effects of the different types of HA and the frequency of infiltration on TMJ-OA treatment. Materials and methods: A bibliographic search was performed in the PubMed, Web of Science and Scopus databases. The search was limited up to September 2022. Search terms included "osteoarthritis", "hyaluronic acid, "molecular weight", "concentration", "viscosity", "dose" and "temporomandibular", using AND/OR as Boolean terms. Results: Exogenous HA in its different molecular weights offers an improvement in histological and clinical characteristics. Apparently, low and medium molecular weight HA presents better results. No clinical studies related to the degree of HA viscosity were found. Respect to the frequency of infiltration, single injection, weekly injections for 3 weeks, weekly injections for 5 weeks and other protocols are used. However, their comparison is complex. There seems to be differences in the effects of the different HA preparations for the treatment of TMJ-OA, mainly in their molecular weight. However, the evidence remains scant.

KEY WORDS: Molecular weight; Viscosity; Frequency of infiltration; Temporomandibular joint; Osteoarthritis

INTRODUCTION

Osteoarthritis (OA) of the temporomandibular joint (TMJ) is a degenerative joint disease characterized by joint pain, limitation of mandibular movements and joint noises (Schiffman *et al*., 2014). According to a recent epidemiological report, about 11% of the population suffered from TMJ-OA, of which 86% were women and the average age was 51 (Kalladka *et al*., 2014). The etiology of TMJ-OA is multifactorial and the pathogeny is characterized by a complex mechanism involving progressive degradation of the cartilage, remodeling of the subchondral bone and chronic synovial inflammation (Wang *et al*., 2015; Li *et al*., 2021). Osteoarthritic changes in the joints are characterized by fibrillation and erosion in cartilage, chondrocyte proliferation and osteophyte formation at the joint margins, and sclerosis of the subchondral bone (Chen *et al*., 2017). The earliest indication of articular cartilage degeneration is the overproduction of proteoglycans and other extracellular matrix molecules, and the appearance of chondrocyte clusters. It has been reported that hypocellularity related to apoptotic cell death and cartilage erosion with exposure to subchondral bone is observed in the late stage (Cledes *et al*., 2006). The minimally invasive treatment of TMJ-OA is described as including the intra-arti-

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Received: 2022-01-22 Accepted: 2022-03-28

cular injection of drugs such as anti-inflammatories, viscosupplements and even platelet concentrates (Wieland *et al*., 2005; de Souza *et al*., 2012). Among these, the exogenous hyaluronic acid (HA) injection is usually the treatment of choice due to good results in pain relief and the improvement of mandibular function with few side effects (Honvo *et al*., 2019; Manfredini, Piccotti & Guarda-Nardini, 2010; Liu *et al*., 2020). In addition, the injection of HA is considered the most complete treatment in terms of viscosupplementation, immunomodulating effects and improvement in the repair of the TMJ (Bergstrand *et al*., 2019; Lin *et al*., 2020; Iturriaga *et al*., 2021). Although not fully understood, it has been demonstrated that intra-articular HA injections inhibit inflammation, reduce cartilage degradation and induce extracellular matrix (ECM) synthesis (Aggarwal & Sempowski, 2004; Kelly, Moskowitz & Lieberman, 2004). However, the effectiveness of HA in the treatment of TMJ-OA continues to be controversial (Gokçe Kutuk *et al*., 2019). This may be due, in part, to the heterogeneity in HA preparations, injection protocols, varying in molecular weight (MW), viscosity and number of applications (Ferreira *et al*., 2018). In addition, the therapeutic use of HA preparations as a viscosupplement is based on their rheological viscoelastic properties that can be explained from a physical, chemical and biomechanical point of view, taking into consideration the relation between the frequency dependences of the modulus of elasticity (G) and the modulus of viscosity, and it has been observed that the rheology varies depending on the preparation (Balazs 2004; Falcone & Berg, 2008). Table I shows the main characteristics of HA preparations.

Therefore, the aim of this review is to identify the differences in histological and clinical effects of different types of HA and the frequency of their injections in TMJ-OA treatment.

MATERIAL AND METHOD

A bibliographic search was performed in the PubMed, Web of Science and SCOPUS databases. The search was limited up to September 2022. Search terms included "osteoarthritis", "hyaluronic acid, "molecular weight", "concentration", "viscosity", "dose" and "temporomandibular", using AND/OR as Boolean terms. The search strategy was adapted to each database.

RESULTS

In TMJ-OA there is an imbalance between the anabolic and catabolic processes of the cartilage structures (Poole *et al*.,1993), where the viscosity of the synovial fluid is also reduced, causing evident joint deterioration (Chen *et al*., 2012). Consequently, the expression of enzymes like hyaluronan synthase 2 and 3 decreases, promoting the degradation and fragmentation of its endogenous HA, reducing its MW and acting as a molecular pattern associated with damage that activates antigen-presenting cells and triggers the immunoinflammatory response (Alvarez *et al*., 2019). In this sense, HA in physiological synovial fluid has a MW of 2-3 x 10^6 Da approximately, but in osteoarthritic processes HA presents a MW of 0.6×10^6 Da or less. Given that HA is a linear polysaccharide, its MW is significantly reduced by only a few ruptures in the molecule, being highly susceptible to degeneration by free radicals (Kim *et al*., 2001).

On the other hand, an increase in the joint friction coefficient is a main risk factor for degenerative joint pathologies and HA, which is an essential component for joint lubrication, may help in reducing joint friction (Kawai *et al*., 2004). Next, the results obtained regarding the histological and clinical effect of the different types of exogenous HA according to their MW and viscosity are described, as well as the frequency of injections in the treatment of TMJ-OA.

Table I. Characteristics of exogenous hyaluronic acid.

Source	Avian	Rooster comb
	Bacterial biofermentation	*Streptoccocus zooepidermicus*
Synthesis	Hyaluronans	Long-chain molecules, avian origin or biofermentation
	Hilanos	Chemically modified hyaluronan molecule via cross-linking
Molecular weight *	Low molecular weight	0.5-1.2 x 10^6 Dalton
	Medium molecular weight	1-4.5 x 10^6 Dalton
	High molecular weight	6-7 x 10^6 Dalton
Viscosity**	Low viscosity	≈ 30 mPA
	High viscosity	≈ 80 mPA

* Molecular weight of physiological hyaluronic acid: 0,5-6 × 10^6 Dalton.

** Viscosity is in millipascals. It is directly proportional to MW. However, there are commercial preparations of medium molecular weight with high and low viscosity presentation.

I. Molecular weight of hyaluronic acid

The MW of exogenous HA is an important factor for determining its biological activity (Ghosh & Guidolin, 2002). It has been suggested that the ideal MW of the preparations must be between 0.5 and 4.0 × 10^6 Da, assimilating endogenous HA. This allows easier access of the exogenous HA to the cells through an unusual endocytic pathway and interaction with specific intracellular proteins (Ghosh & Guidolin, 2002; Tammi *et al*., 2001).

Tolba *et al*. (2020) demonstrated that the intra-articular injection of exogenous medium MW HA (MMW-HA) between 2.3-2.5 × 10^6 Da has been effective in the repair of the condyle, articular disc and synovial membrane in rats with induced TMJ-OA, observing a reduction in inflammatory cells and extravasated red blood cells, in addition to strong glycosaminoglycan (GAG) staining in the ECM. It is important to note that the authors describe the HA used as high MW HA (HMMW-HA), but when reviewing its MW it corresponds to a MMW-HA according to the classification. Duygu *et al*. (2011) compared the histological effects of the HMW-HA injection (6 × 10^6 Da) to that of physiological solution in induced TMJ-OA in rabbits. Although the HMW-HA had a significantly more effective improvement than the physiological solution in terms of joint repair at the control 4 weeks after treatment, at 6 and 8 weeks no differences were observed between the two groups.

Tang *et al*. (2010) also described the MMW-HA (1.5-2.5 × 10^6 Da) as being more effective in the treatment of TMJ-OA than physiological saline solution, significantly reducing the activity of enzymes and receptors involved in the activation of metalloproteins (MMP) responsible for the degradation of the ECM in the cartilage during the pathogeny of TMJ-OA. For their part, Iturriaga *et al*. compared the effects of HMW-HA and low MW HA (LMW-HA) in the treatment of TMJ-OA induced in rabbits, observing an improvement in both groups compared to the untreated group. However, LMW-HA produced a significantly greater improvement in the cartilage and the articular disc, achieving similarity with the healthy control group. They observed that the TMJ in the group treated with LMW-HA at 30 days presented an articular cartilage with a continuous superficial zone, collagen fibers parallel to the surface, with no abrasions or deep fibrillations. They also provided evidence of improvements in the articular disc, rearranging the order of its collagen fibers and chondrocytes.

In relation to the clinical effects, a randomized trial on 35 patients with TMJ-OA compared two treatments of arthrocentesis plus intra-articular injection with exogenous HA of differing MW. The first group received MMW-HA (1.2 × 10^6 Da) and the second group LMW-HA (0.6 × 10^6 Da). In both groups, an improvement was noted in terms of pain when chewing, pain at rest, masticatory efficiency, functional limitation and mouth opening. Yet there were no significant differences (Guarda-Nardini *et al*., 2012). For their part, Manfredini *et al*. (2012) also obtained clinical results by comparing 6 treatment protocols in a total of 60 patients diagnosed with TMJ-OA. The protocols were: A) two-needle arthrocentesis in a single session, B) two-needle arthrocentesis in a single sessionplus corticosteroids, C) two-needle arthrocentesis in a single session plus LMW-HA, D) two-needle arthrocentesis in a single session plus HMW-HA, E) 1 two-needle arthrocentesis weekly for 5 weeks plus LMW-HA and F) 1 single-needle arthrocentesis weekly for 5 weeks plus LMW-HA. Pain when chewing, pain at rest, masticatory efficiency and mouth opening were evaluated. The D protocol (HMW-HA) was interrupted after five patients due to the appearance of unpleasant side effects, such as swelling of the TMJ and intense pain after the injection in two of the five patients. Therefore, the 5 remaining groups were analyzed at 3 months of follow-up. An improvement was noted in the mean baseline values in all treatment groups that completed the protocol in relation to the evaluated variables. There were no significant differences between the groups in any variable. Nevertheless, protocol E provided the greatest improvement.

II. Viscosity of hyaluronic acid

In the present review no experimental in animal model or clinical studies were found that evaluate the effect of the different viscosities of exogenous HA. The related studies refer mainly to *in vitro* conditions. Synovial fluid from osteoarthritic joints has a much lower elasticity and viscosity than that of normal joints. A decrease in the rheological properties of synovial fluid results from both a reduced molecular size and concentration of HA in the synovial fluid, which may lead to degeneration or remodeling of the articular cartilage and subchondral bone (Takahashi *et al*., 2004; Xinmin & Jian, 2005). Generally, it is described that HA solutions with higher MW have a greater viscosity, more elevated dynamic modules and greater shear thinning ratio. Rebenda *et al*. (2020) evaluated the changes in the friction of the cartilage in HA of differing MW. To this end, an *in vitro* study was conducted using samples of porcine femoral cartilage incubated in the different HA preparations and then subjected to friction. In their results they determined a strong dependency between the MW and the viscosity of the HA solutions. The highest viscosity was measured for HA with a MW of 2 × 10^6 Da and the lowest for HA of 0.7 × 10^6 Da in the entire the shear rate range. In this sense, when osteoarthritic synovial fluid is treated with viscosupplementation, it is expected to recover the

rheological properties of a synovial fluid returning to its normalcharacteristics, and it must be considered that the condition of the cartilage and the composition of the previous synovial fluid can significantly impact the effectiveness of the viscosupplementation (Rebenda *et al*., 2020).

III. Frequency of intra-articular injections of hyaluronic acid

The most recognized protocols of intra-articular injections are the single injection, protocols of a weekly injection for 3 weeks, or a weekly injection for 5 weeks. It is also possible to find studies where they combine these protocols with or without arthrocentesis.

At experimental level, Iturriaga *et al*. evaluated the use of a single injection of exogenous HA in the management of TMJ-OA induced in rabbits, using two types of HA according to their MW (LMW-HA and HMW-HA). In both cases, a repair of the mandibular condyle, mandibular fossa and articular cartilage was noted at 30 days post-injection. At the follow-up at 135 days, however, both groups relapsed in terms of joint repair, which suggests the possible need to repeat the dose in the short and/or medium term. Tolba *et al*. used models with a protocol of a weekly injection for three weeks (days 7, 14 and 21), assessing the results at 28 days compared to an untreated group. They found improvements in the articular cartilage and articular disc, evidencing a restoration of the structural components and recovery of the tissue organization. In addition, the concentration of MMP-3 in the treatment group decreased significantly compared to the untreated group.

Duyu *et al*. used a protocol of a weekly injection for 3 weeks in TMJ-OA with initial degenerative changes. They used a HMW-HA and evaluated the results at 4, 6 and 8 weeks, compared to a group treated with physiological solution. They concluded that at 4 weeks the application of HMW-HA had statistically significant effects on the repair of the articular cartilage; however, there were no differences with the control group at 6 and 8 weeks. On the other hand, Neo *et al*. (1997) conducted a study on 6 sheep, where after the induction of TMJ-OA, they applied 5 LMW-HA (0.8×10^6 Da) (day 7, 10, 14, 17 and 21) injections in one joint versus the application of saline solution with the same protocol in the other joint. They observed a significant reduction in the extent of the osteoarthritic changes at one month and 3 months after the protocol in the group treated with HA compared to the control group.

From the clinical point of view, Guarda-Nardini *et al*., (2007) conducted a protocol of a weekly injection for 5 weeks of two-needle arthrocentesis plus LMW-HA ($0.5 - 0.73 \times 10^6$ Da) in a series of 25 patients, observing improvement and maintenance of this improvement at one year in all the variables studied, which included pain at rest and function, opening range, masticatory efficiency, treatment tolerability, and others. They mention that the improvement was significant from the second arthrocentesis plus HA. In 2012, Guarda-Nardini *et al*. provided a variation, applying a protocol of a weekly injection for 5 weeks of single-needle arthrocentesis plus HA (a group with LMW-HA and another with MMW-HA) in 40 patients with a 3-month follow-up period. They observed that there was also an improvement in all the evaluated variables for both types of MW. On the other hand, Manfredini *et al*. compared protocols of a single injection accompanied by arthrocentesis and protocols of 1 weekly injection for 5 weeks, also accompanied by arthrocentesis. They evaluated the results at a 3-month follow-up, where the authors found no statistically significant differences between the groups.

CONCLUSION

Most studies that compare the effects of exogenous HA have focused on its MW. Generally, all the MW have proven to be effective in the management of TMJ-OA from both the histological and clinical points of view, noting some differences mainly between the use of LMW-HA and HMW-HA in favor of the former. No evidence was found with respect to the effects of different viscosities of HA on the treatment of TMJ-OA. On the other hand, there is still no consensus on the frequencies of intra-articular injections of exogenous HA, likely due to the individual differences of each study and its clinical application for each patient. Generally, the trend has been to use injection protocols from other joints, mainly the knee, for the treatment of TMJ-OA. Yet the TMJ is a small joint that presents morphological, mechanical and functional differences from the others, which are important to take into consideration. Further research is required on experimental models and in clinical trials that compare the different types of exogenous HA, their rheological variables and frequencies of injection in the treatment of TMJ-OA.

WEN, S.; ITURRIAGA, V.; VÁSQUEZ, B.; SANTANDER, J.; BARRÍA, D. & DEL SOL, M. Diferencias según el tipo de ácido hiaurónico exógeno y su frecuencia de infiltración en el tratamiento de la osteoartritis temporomandibular. *Int. J. Morphol., 41(3)*:699-704, 2023.

RESUMEN: Uno de los tratamientos mínimamente invasivos más importantes en la actualidad en la artrosis de la articulación temporomandibular (OATM) es la inyección intraarticular

de ácido hialurónico (AH) exógeno, que ha dado buenos resultados en el alivio del dolor y mejora la función mandibular con pocos efectos secundarios. Sin embargo, la efectividad del AH continúa siendo controversial, en parte debido a la heterogeneidad en los protocolos de inyección en cuanto a su peso molecular, viscosidad y frecuencia de infiltración, entre otras propiedades. El objetivo de esta revisión fue identificar las diferencias en los efectos histológicos y clínicos de los diferentes tipos de HA y la frecuencia de infiltración en el tratamiento de TMJ-OA. Se realizó una búsqueda bibliográfica en las bases de datos PubMed, Web of Science y Scopus. La búsqueda se limitó hasta septiembre de 2022. Los términos de búsqueda incluyeron "osteoartritis", "ácido hialurónico", "peso molecular", "concentración", "viscosidad", "dosis" y "temporomandibular", utilizando AND/OR como términos booleanos. El HA exógeno en sus diferentes pesos moleculares ofrece una mejora en las características histológicas y clínicas. Aparentemente, el AH de bajo y medio peso molecular presenta mejores resultados. No se encontraron estudios clínicos relacionados con el grado de viscosidad del HA. Respecto a la frecuencia de infiltración, se utilizan inyecciones únicas, inyecciones semanales durante 3 semanas, inyecciones semanales durante 5 semanas y otros protocolos. Sin embargo, su comparación es compleja. Parece haber diferencias en los efectos de las diferentes preparaciones de HA para el tratamiento de la OA-TMJ, principalmente en su peso molecular. Sin embargo, la evidencia sigue siendo escasa.

PALABRAS CLAVE: Peso molecular; viscosidad; frecuencia de infiltración; articulación temporomandibular; osteoartritis

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