J Oral Res
research in oral sciences

Review

Effectiveness of hyaluronic acid in the treatment of degenerative diseases of the temporomandibular joint: Literature Review.

Efectividad del ácido hialurónico en el tratamiento de enfermedades degenerativas de la articulación temporomandibular. Revisión de Literatura.

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Receipt : 06/08/2020 Revised: 11/23/2020
Acceptance: 04/30/2021

Abstract: Objetive: The degenerative diseases of the tempo-romandibular joint (TMJ) are characterized by a progressive destruction of the articular tissues of the condyle and the glenoid fossa. The main aim of this review is to describe the effectiveness of the hyaluronic acid (HA) in the treatment of degenerative diseases of the TMJ in accordance with the available scientific evidence. **Material and Methods:** A literature search was made in the following databases *EBSCO*, *Pubmed*, *Cochrane* and *Trip Database*, using the keywords *hyaluronic*, *hyaluronan*, *NaH*, *hyaluronate*, *TMJ*, *TMD*, *CMD*, *craniomandibular*, *orofacial pain* and *temporomandibular*. There were no date or language restrictions applied. **Results:** After applying inclusion and exclusion criteria, 14 studies were included in this review (11 randomized controlled clinical trials and 3 non-randomized clinical trials). **Conclusion:** The studies reported a decrease in pain and improvement in functional parameters after treatment of TMJ osteoarthritis with HA. The use of arthrocentesis associated with the administration of HA provides effects synergistic, reaching a superiority the protocols with multiple injections with respect to those of a single session. The adverse effects related to the injection of HA with or without associated arthrocentesis were minor and transitory.

Keywords: *temporomandibular joint; osteoarthritis; dejenerative joint disease; orofacial pain; hyaluronic acid; arthrocentesis; viscosupplementation.*

Resumen: Objetivo: Las enfermedades degenerativas de la articulación temporomandibular (ATM) se caracterizan por una destrucción progresiva de tejidos articulares en el cóndilo y la fosa glenoidea. El objetivo principal de esta revisión es describir la efectividad del uso de ácido hialurónico en el tratamiento de enfermedades degenerativas de la articulación temporomandibular de acuerdo con la evidencia científica disponible. **Material y Métodos:** Se realizó una búsqueda de la literatura en las bases de datos electrónicas *EBSCO*, *PubMed*, *Cochrane* y *Trip Database*, utilizando las palabras claves *hyaluronic*, *hyaluronan*, *NaH*, *hyaluronate*, *TMJ*, *TMD*, *CMD*, *craniomandibular*, *orofacial pain* y *temporomandibular*, sin límite de fecha ni de idioma hasta Mayo del año 2020, complementada con una búsqueda retrógrada. **Resultados:** Con base en los criterios de inclusión y exclusión, 14

Cite as: Fernandez-Vial D, Silva-Arce F & Renner N.
Effectiveness of hyaluronic acid in the treatment of degenerative diseases of the temporomandibular joint: Literature Review.
J Oral Res 2021; 10(2):1-10.
Doi:10.17126/joralres.2021.008

estudios fueron incluidos en esta revisión (11 ensayos clínicos controlados aleatorizados y 3 ensayos clínicos controlados no aleatorizados). **Conclusión:** Los estudios reportaron una disminución del dolor y mejora en los parámetros funcionales luego del tratamiento de osteoartritis de la ATM con AH. El uso de artrocentesis asociada a la administración del AH provee efectos sinérgicos, alcanzando una superioridad los protocolos con múltiples inyecciones con respecto a aquellos de una sola sesión. Los efectos adversos relacionados con la inyección de AH con o sin artrocentesis asociada fueron menores y transitorios.

Palabra Clave: *articulación temporomandibular; osteoartritis; enfermedad degenerativa de las articulaciones; dolor orofacial; ácido hialurónico; artrocentesis; viscosuplementación.*

INTRODUCTION.

Degenerative joint diseases (DJD) are pathologies of the temporomandibular disorders (TMD) that affect the temporomandibular joint (TMJ), and correspond primarily to osteoarthritis and osteoarthrosis.[1,2] Clinical studies have shown that they affect between 8% and 16% of the world population, being more common in women.[3] These are pathologies traditionally associated with age, which result in a progressive destruction of joint tissues in the condyle and glenoid fossa of the TMJ.[3,4] One of the main reasons for the development of this type of disorder is the overload of the TMJ due to various factors, but in the majority of cases the causes for the destruction of joint tissues have not been clearly determined yet.[3]

It has been observed that the severity of the disorder is correlated with the quality of life of patients,[3] which is the reason why it is essential to seek a treatment protocol that helps to eliminate or at least alleviate the symptoms of these pathologies. Throughout time, several conservative therapeutic approaches have been proposed, including interocclusal devices, physiotherapy, pharmacotherapy, and occlusal treat-ments, among others.[5,6]

A lack of lubrication of the articular surfaces has been described as having a potential role as a risk factor for intra-articular disorders and the subsequent inflammatory-degenerative disorder, providing an antecedent for TMJ viscosupplementation.[7]

It has been suggested that the direct administration of exogenous HA could have anti-inflammatory and analgesic effects, while at the same time activates a cascade of biochemical events that could ultimately lead to the repair of the articular cartilage tissue, which would normalize the synthesis of endogenous HA by synovial cells and would ultimately reduce the friction coefficient of the joint.[8] Another hypothesis proposed is that HA should also have an analgesic effect by reducing the afferent could might information from the affected region, thus helping to desensitize nociceptive nerve endings.[9,10]

The main aim of this review is to describe the effectiveness of the use of hyaluronic acid in the treatment of degenerative diseases of the tempo-romandibular joint according to the available scientific evidence.

MATERIALS AND METHODS.

A strategic search was carried out by two of the authors of this study, of the scientific articles available until May 2020 in the following electronic databases: EBSCO (Dentistry and Oral Sciences Source), PubMed, Cochrane and Trip Database. The keywords were: *hyaluronic*, *hyaluronan*, *NaH*, *hyaluronate*, *tmj*, *tmd*, *cmd*, *craniomandibular*, *orofacial pain*, and *temporomandibular*. Use of Boolean terms AND and OR. There were no date or language restrictions. It was complemented by a retrograde search. The articles were selected according to the following inclusion criteria:

- **Population:** individuals that fulfilled the diagnostic criteria for degenerative joint diseases of the TMJ (osteoarthritis; osteoarthrosis) according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD (13)) version 1.0 (Axis I subgroups IIIb and IIIc) classification, or according to Diagnostic Criteria for Temporomandibular Disorders (DC/TMD (2)) (Axis I, group I.1.3.A).
- **Intervention:** intra-articular administration of hyaluronic acid or its derivatives in the TMJ, either isolated injection or associated with arthrocentesis, regardless of the number and/or intervals between applications nor the molecular weight of HA.
- **Comparison:** placebo treatment, active agents or other therapy modality.

ISSN Print 0719-2460 - ISSN Online 0719-2479.

- Outcome: at least one of the following: variations in joint pain at rest and/or function; functional limitations; range of mandibular movements; joint noises; evaluation of structural changes of the TMJ by means of imaging testing (Cone Beam Computed Tomography (CBCT), conventional Computed Tomography or Magnetic Resonance); subjective effectiveness of treatment; adverse effects; tolerability of treatment.

- Study design: clinical trials carried out in humans. The analysis of the levels of evidence and the grades of recommendation of the articles was carried out based on the guidelines proposed by the Center for Evidence-Based Medicine of the University of Oxford.[11] The reporting quality of randomized clinical trials was evaluated with the CONSORT guideline[12] and non-randomized ones with the TREND guideline.[13] For the risk of bias assessment of clinical trials, the guideline proposed by The Cochrane Collaboration[14] was used.

RESULTS.

A total of 561 articles were obtained in the search; of which 14 were selected to be included in this review (Figure 1). From the total of articles, 11 correspond to randomized controlled clinical trials and 3 to non-randomized controlled clinical trials. The results of the level of evidence and grades of recommendation evaluation, reporting quality and risk of bias are found in Table 1. Table 2 shows a summary of the included studies.

Figure 1. Search and selection flow chart.

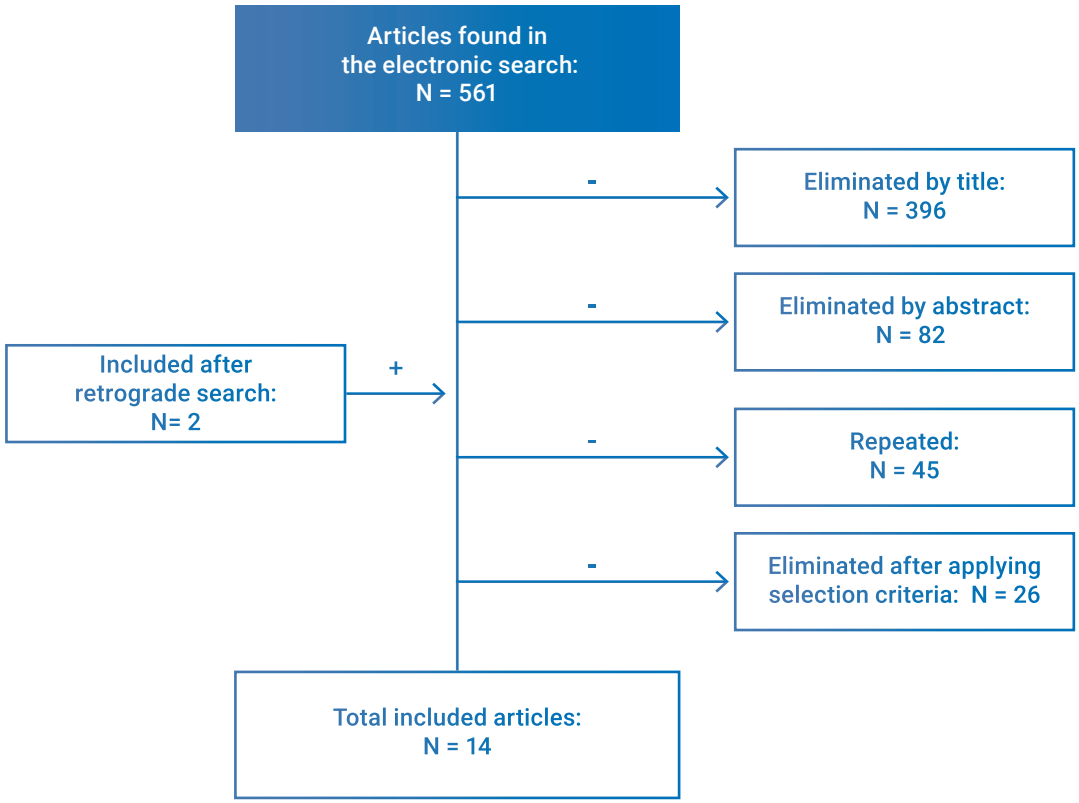

Table 1. Included articles and analysis of level of evidence, grade of recommendation, reporting quality and risk of bias.

Author	Date of publication	Title	Journal	Type of study	Level of evidence; grade of recommendation	Quality	Risk of bias
Guarda-Nardini et al.[15]	2005	Conservative treatment of temporomandibular joint osteoarthrosis. intra-articular injection of sodium hyaluronate.	J. Oral Rehabil.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 81.8% (very adequate)	Low
Bjørnland et al.[16]	2007	Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injection compared with injection with sodium hyaluronate.	J. Oral Rehabil.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 97.1% (very adequate)	Low
Guarda-Nardini et al.[17]	2007	A one-year case series of arthrocentesis with hyaluronic acid injections for temporomandibular joint osteoarthritis.	Oral Surg, Oral Med, Oral Pathol, Oral Radiol	Non-randomized clinical trial	2b; B (favorable recommendation)	TREND: 81.8% (very adequate)	Moderate
Møystad et al.[18]	2008	Injection of sodium hyaluronate compared to a corticosteroid in the treatment of patients with temporomandibular joint osteoarthritis: clinical effects and computed tomography evaluation of osseous changes.	Oral Surg, Oral Med, Oral Pathol, Oral Radiol	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 94.2% (very adequate)	Low
Manfredini et al.[19]	2009	Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections.	J. Oral. Maxillofac. Surg.	Controlled non-randomized clinical trial	2b; B (favorable recommendation)	TREND: 93.0% (very adequate)	High
Tang et al.[20]	2010	Effects of intra-articular administration of sodium hyaluronate on plasminogen activator system in temporomandibular joints with osteoarthritis.	Oral Surg, Oral Med, Oral Pathol, Oral Radiol	Randomized controlled clinical trial	2b; B (favorable recommendation)	CONSORT: 63.3% (adequate)	Moderate
Guarda-Nardini et al.[21]	2012	Comparison of 2 hyaluronic acid drugs for the treatment of temporomandibular joint osteoarthritis.	J. Oral. Maxillofac. Surg.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 88.2% (very adequate)	Low
Manfredini et al.[22]	2012	Arthrocentesis with or without additional drugs in temporomandibular joint inflammatory degenerative di sease. Comparison of six treatment protocols.	J Oral Rehabil	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 84.8% (very adequate)	Low
Guarda-Nardini et al.[23]	2014	Effectiveness of treatment with viscosupplementation in temporomandibular joints with or without effusion.	J. Oral. Maxillofac. Surg.	Controlled non-randomized clinical trial	2b; B (favorable recommendation)	TREND: 95.3% (very adequate)	Low
Guarda-Nardini et al.[24]	2015	Single- or multiple-session viscosupplementation protocols for temporomandibular joint degenerative disorders: a randomized clinical trial.	J. Oral. Rehabil.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 94.1% (very adequate)	Low
Cömert Kilic et al.[25]	2016	Is arthrocentesis plus platelet-rich plasma superior to arthrocentesis plus hyaluronic acid for the treatment of temporomandibular joint osteoarthritis.	Int. J. Oral Maxillofac. Surg.	Randomized controlled clinical trial	2b; B (favorable recommendation)	CONSORT: 82.3% (very adequate)	High
Gurung et al.[26]	2017	Efficacy of arthrocentesis versus arthrocentesis with sodium hyaluronic acid in temporomandibular joint osteoarthritis: A comparison.	Natl. J. Maxillofac. Surg.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 76.4% (adequate)	Moderate
Gokçe et al.[29]	2019	Clinical and Radiological Comparison of Effects of Platelet-Rich Plasma, Hyaluronic Acid, and Corticosteroid Injections on Temporomandibular Joint Osteoarthritis.	J. Craniofac. Surg.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 62% (adequate)	Low
Bergstrand et al.[30]	2019	Long-term effectiveness of arthrocentesis with and without hyaluronic acid injection for treatment of temporomandibular joint osteoarthritis.	J. Oral. Sci.	Randomized controlled clinical trial	1b; A (extremely recommendable)	CONSORT: 80.6% (very adequate)	Low

ISSN Print 0719-2460 - **ISSN Online** 0719-2479.

Table 2. Article Analysis.

Article	Date of publication	N	Intervention / follow-up.	Results
Guarda-Nardini et al.[15]	2005	N= 60.	**Group A** (N = 20): 5 sessions of ATS with RL (2 needles) + HA (600 kDa). **Group B** (N = 20): Occlusal device for 6 months. **Control group** (N = 20): No intervention (refuses treatment). *Follow-up: in every session, 1, 3 and 6 months.	- Both protocols significantly improved the conditions of the patients in all the parameters considered. There were no significant differences between groups A and B. The only difference was regarding treatment tolerability, which proved to be significantly higher in group A. - No adverse effects were reported in the intervened groups.
Bjørnland et al.[16]	2007	N= 40.	**Group HA** (N = 20): 2 injections of 0.7 - 1 ml HA (6000 kDa) separated by 14 days.	- In both groups, there was reduction of crepitus. - Maximum opening and protrusion increased significantly in the HA group.
Møystad et al.[18]	2008		**Group CS** (N = 20): 2 injections with 0.7-1 ml of Betamethasone separated by 14 days. *Follow-up: 2 weeks, 1 month, 6 months.	- The injection was more effective in patients with joint pain only compared to those with myofascial and joint pain. - There were significant differences in pain reduction in the HA group compared to the CS group. There was no statistically significant difference between the groups regarding jaw movements or bone changes.
Guarda-Nardini et al.[17]	2007	N= 25.	5 sessions of ATS with RL + HA (500-730 kDa). *Follow-up: in every session and at 1 week, 1 month, 3 months, 6 months and 1 year.	- Significant improvements in all parameters evaluated, especially in pain at rest and chewing, chewing efficiency and functional limitations. - It does not mention the presence or absence of adverse effects.
Manfredini et al.[19]	2009	N= 76.	5 ATS with 2 needles with RL + 5 injections of 1 mL HA (500-730 kDa) at 1 week intervals. *Follow-up: 1 week, 1 month, 3 months and 6 months.	- The parameters of chewing efficiency, subjective efficacy of the treatment, functional limitation and pain when chewing showed the greatest improvements over time. - It does not mention the presence or absence of adverse effects.
Tang et al.[20]	2010	N= 40.	A previous synovial fluid sample was taken, for which 2 ml of SS was injected and then aspirated **Group A** (N = 20): 5 injections of 1 ml HA (1,500-2,500 kDa) intervals of 1 week. Healthy control group (N = 20): 5 injections of SS at 1 week intervals. * Follow-up: during each injection and 1 week after the last injection.	- Synovial fluid samples from patients with osteoarthritis (Group A + control) presented significantly higher PAS levels than the group of healthy volunteers. - Group A showed significant improvements regarding pain and the concentration of PAS in synovial fluid, compared to the control group. - It does not mention the presence or absence of adverse effects.
Guarda-Nardini et al.[21]	2012	N= 40.	**Group A** (N = 17): 5 sessions of ATS with SS of 1 needle + 1 ml HA (1200 kDa). **Group B** (N = 18): 5 sessions of ATS with SS of 1 needle + 1 m AH (600 kDa). *Follow-up: in every session and at 3 months.	- Both protocols were effective in improving symptoms up to 3 months of follow-up. There were no significant differences between the groups in any of the variables. - No adverse effects were reported; The only discomfort was found on the patient's behalf at the time of injecting the anesthetic solution.
Manfredini et al.[22]	2012	N= 72.	**Group A** (N = 11): 1 ATS session with SS. **Group B** (N = 9): 1 ATS session with SS + 1 mL Triamcinolone. **Group C** (N = 11): 1 ATS session with SS + 1 mL HA (600 kDa). Group D: (eliminated) 1 ATS session with SS + 1 mL HA (6000 kDa). **Group E** (N = 12): 5 ATS + HA sessions (600 kDa). **Group F** (N = 12): 5 ATS + HA sessions (600 kDa). *Follow-up: end of treatment and at 3 months.	- Improvements were observed in the parameters evaluated. There were no significant differences between the groups. Group E was the one that reported the greatest improvements in all parameters. The highest percentages of improvement belonged to the groups with more than 1 HA injection session. - For the intervention in group D, several patients presented joint inflammation and severe post-injection pain, which is why this intervention was discontinued. - There were no adverse effects in the rest of the groups.
Guarda-Nardini et al.[23]	2012	N= 50.	**Group A** with effusion in TMJ (N = 25): ATS with SS + 1 mL HA (1200 kDa). **Group B** without effusion in TMJ (N = 25): ATS with SS + 1 mL HA (1200 kDa). *Follow-up: in every session, 3 and 6 months.	- Both groups showed significant improvements in all the parameters evaluated, which was maintained during the 6 months of follow-up. There are no significant differences in the effectiveness of the treatment between groups A and B. However, in the period between 3 and 6 months, there was a partial tendency to decrease the effectiveness in joints with effusion. - There were no relevant adverse effects in any patient, except for minor inflammation in one patient in group B after the first injection.
Guarda-Nardini et al.[24]	2012	N= 30.	**Group A** (N = 10): 1 ATS + 1 injection of HA (7000 kDa) **Group B** (N = 10): 1 ATS + 1 injection of HA (1200 kDa) **Group C** (N = 10): 5 ATS + 5 injections of HA (1200 kDa) at 1 week intervals. *Follow-up: in every session, 3 and 6 months.	- Group C showed significant improvements in terms of pain and when assessing the overall effect of treatment, compared to the other groups. - No adverse effects were reported in the intervened groups.
Cömert Kilic et al.[25]	2016	N= 31.	PRP group (N = 18): initial ATS with RL together with injection of PRP and then 4 injections of PRP alone. HA group (N = 13): ATS with RL together with a single injection of 2 ml HA (500-700 kDa). *Follow-up: 12 months.	- No statistically significant difference was found in changes of pain level or maximum opening between the two groups, with both techniques resulting in improvements in both parameters. - No complications related to the injection or during the follow-up period were observed.

Gurung et al.[26]	2017	N= 20.	**Group A** (N = 10): 5 ATS RL with 1 week intervals **Group B** (N = 10): 5 sessions of ATS with RL + HA with one week intervals. *Follow-up: first day, 5th day, one week, 1, 1 ½ and 3 months.	- Significant pain reduction in both groups. - Maximum opening, lateral movements and protrusion were significantly improved in both, although it was superior in the group with HA to that with ATS alone. - No imaging changes were observed. - 4 patients had transitory facial paralysis after anesthesia.
Gokçe et al.[29]	2019	N= 60.	**Group 1** (PRP): Infiltration of 1 ml of PRP with 1 month intervals. **Group 2** (HA: Infiltration of 1 ml of HA with 1 month intervals. **Group 3** (CS; Triamcinolone): Infiltration of 1 ml of CS with 1 month intervals. *Follow-up: 3 months.	- There were statistically significant changes in pain reduction with the use of PRP and CS between 2 and 3 months after treatment. - A greater efficacy of PRP was observed compared to HA and CS.
Bergstrand et al.[30]	2019	N= 37.	**Group A** (N = 17): ATS with RL. **Group B** (N = 20): ATS with RL + 1ml of HA (6000 kDa) *Follow-up: average 47 months (25-79 months).	- There was no significant difference between both groups. - There was a significant increase in maximum opening in both groups. - Significant decrease in pain in both groups. - There were no significant changes in joint sounds in both groups. - ATS reduces TMJ pain in the long term, but the use of HA does not generate significant changes.

HA: Hyaluronic acid. **ATS:** Arthrocentesis. **SS:** Saline solution. **CS:** Corticosteroid. **PRP:** Platelet rich plasma. **RL:** Ringer lactate solution. **PAS:** Plasminogen Activator System.

DISCUSSION.

Once the search was carried out, only studies regarding the evaluation of the use of hyaluronic acid in cases of osteoarthritis of the TMJ were found, and not of osteoarthrosis of the TMJ. This is possibly related to the fact that osteoarthritis involves pain, which implies a greater need for treatment and therefore it would imply a major research focus.

Furthermore, pain is a more feasible parameter to evaluate and more significant for patients. Nonetheless, we believe that the results obtained can be extrapolated to the use of HA in cases of osteoarthrosis, since multiple studies evaluated parameters such as increased ranges of mandibular movement and reduction of intra-articular friction,[26] which are common problems to both pathologies.

All studies included in this review used as inclusion criteria the diagnosis of osteoarthritis with the RDC/TMD criteria, with an exception for one study that used the DC / TMD.[25] This represents a very positive aspect in terms of the standardization of the patient inclusion criteria, allowing an adequate comparison between the studies.

1. Intra-articular administration protocols of HA:

Guarda-Nardini *et al.*,[17] carried out a non-randomized exploratory clinical trial, in which they performed a protocol of five arthrocentesis using two needles with Ringer lactate solution and five injection cycles of low molecular weight HA.

The patients were evaluated periodically up to 12 months of follow-up, and significant improvements were found in all the parameters evaluated, especially in terms of pain at rest and chewing, chewing efficiency and functional limitations. Likewise, Manfredini *et al.*,[24] conducted a clinical trial with similar characteristics during a 6-month follow-up period, also finding significant improvement in the reduction of symptoms.

Later in 2012, Manfredini *et al.*,[22] carried out a randomized controlled clinical trial, in which 72 patients were distributed into six groups, implementing different protocols; either the use of saline only, corticosteroids or HA (one or five injections of different molecular weights). Improvements in the parameters evaluated were observed in all groups (except for a group with high molecular weight HA application, which was eliminated due to the adverse effects that occurred after the first application), but in the groups with multiple HA injections the improvement was significantly greater.

Likewise, Guarda-Nardini *et al.*,[24] carried out another clinical trial in which they divided 30 patients into three groups, from which two underwent a single application of HA with different molecular weights, and one to a protocol of five injections at weekly intervals. Similar results to the previous study were found, being the group with multiple injections the one with the greatest improvements. Therefore, the superiority of protocols with multiple injections in contrast to those with a single session is supported through the above mentioned clinical trials.[27,28]

ISSN Print 0719-2460 - **ISSN Online** 0719-2479.

Regarding the clinical technique, it should be noted that most of the protocols applied in TMJ osteoarthritis are derived from previous studies in other joints of the body, such as the knee and hip, where a synergistic effect has been observed when arthrocentesis is followed by the injection of HA, which would justify its combined use in TMJ osteoarthritis, giving a logical basis to carry out a lavage of the joint prior to each HA infiltration instead of performing the techniques alone.[22,27]

Related to the previously mentioned, in the clinical trial by Bergstrand *et al*.,[30] a group of 17 patients underwent arthrocentesis with Ringer lactate solution and another group received the same arthrocentesis with the subsequent administration of 1ml of HA, reporting the results at the six months evaluation and then a long-term with an average of 47 months. Both groups showed a reduction in pain, concluding that TMJ arthrocentesis is related to a reduction in pain and an improvement in function after a short and long-term observation, but that these results were not modified by the use of a medication (HA) during arthrocentesis. More long-term studies are required to evaluate the different existing treatment protocols with HA infiltration, assessing multiple administrations and molecular weights.

The effect produced by HA was compared with other interventions. In 2005 Guarda-Nardini *et al*.,[15] compared a protocol of five arthrocentesis sessions with HA injection versus the use of an occlusal device for six months (bite-plate), finding that both protocols were effective in improving symptoms, with no significant difference between any of the variables except for the treatment tolerability, for which the HA group resulted better. Møystad *et al*.,[18] and Bjørnland *et al*.,[16] compared the injection of HA without prior arthrocentesis *versus* the injection of betamethasone, reporting a decrease in pain relate to both interventions, being more significant in the case of the use of HA, but there was no significant difference between the groups regarding improvement in ranges of mobility or bone changes at six months.

In 2016, Cömert *et al*.,[25] compared a group with initial arthrocentesis with Ringer lactate together with an injection of platelet-rich plasma (PRP) and then four injections of PRP alone, *versus* a second group in which arthrocentesis was performed with Ringer lactate along with a single injection of HA (2ml; 500-700 kDa). No statistically significant difference was found regarding the level of pain nor maximum opening between the two groups, with both techniques resulting in improvements in these parameters, but the authors suggested that injection of HA should be preferred over PRP, since it seems to be more accepted by the patients.[25] Gokçe *et al*.,[29] compared the injection of HA, PRP and corticosteroid (triamcinolone) in cases of OA with a follow-up of three months, where there were positive changes in pain reduction in all groups, reporting that the intra-articular injection of PRP decreased pain more effectively compared to HA and corticosteroid.

Among the studies that compared protocols with different molecular weights of HA, in the study by Manfredini *et al*.,[22] published in 2012, HA of 600 and 6000 kDa were used combined with arthrocentesis. They reported joint inflammation and intense pain in the group with high molecular weight (6000 kDa), whilst there was an improvement in all the parameters of the group with low molecular weight (600 kDa). On the contrary, in 2008 Møystad *et al*.,[18] also used 6000 kDa HA in one of their groups with two direct injections of 0.7 to 1ml without arthrocentesis, registering a statistically significant improvement in pain reduction versus the group with corticosteroids, there was no report of cases with increased pain.

Guarda-Nardini *et al*.,[24] with the purpose of finding a protocol with fewer interventions, compared an arthrocentesis session with a single injection of HA of 7000 kDa and another of 1200 kDa, with a protocol of five sessions of arthrocentesis with HA of 1200 kDa, obtaining in all of them an improvement in the parameters evaluated when comparing medium and high molecular weight, and the only difference being the number of sessions, without reporting any adverse effects. Both, low and medium molecular weight seem to be the most suitable because in all studies they reported an improvement without adverse effects, unlike what is described with high molecular weight HA which offered more varied results.

Nine of the studies[16–21,25,26,29] do not mention whether there was a wash-out period established where no type of analgesic or anti-inflammatory medication was used prior to treatment, and/or later during follow-up. In the cases of Manfredini *et al*.,[22] in 2012 and Guarda-Nardini *et al*.,[21] 2014 and 2015,[23,24] they specified that all patients had a time of at least two weeks *prior* to the intervention (wash-out period) and during the follow-up time that was free of any medication that could have altered the results, allowing only the use of acetaminophen (paracetamol)

in doses no greater than 500mg - 1000mg immediately after injection or during the time after the intervention. Bergstrand *et al*.,[30] reported the use of acetaminophen (paracetamol) 500 mg up to three times a day if the patient felt it necessary.

The impossibility to rule out the factor related to the medications used by the patients during the follow-up period may have altered the results obtained.

2. Effects observed after intra-articular application of HA in patients with TMJ osteoarthritis

All the studies that used hyaluronic acid within their protocols reported a reduction in the level of pain at rest and function, in a short and medium term, with significant difference only regarding the number of applications and their association with arthrocentesis or not. This also occurs concerning improvements in range of motion and functional limitations. Regarding the presence of joint noises such as click and crepitus, the study by Cömert *et al*.,[25] showed a decrease in joint noises reported by patients; while Bergstrand *et al*.,[30] with an average follow-up of 47 months, reported that no significant change was found in the presence of joint noises.

Regarding the assessment of reparative changes in the articular surfaces by imaging evaluation after the use of HA, the studies of Gurung *et al*.,[26] and Møystad *et al*.,[18] evaluated this factor. The first study after exposing one group to five sessions arthrocentesis with Ringer lactate solution at one-week intervals and the other group to the same protocol but associated with the use of HA, reported no significant variations in the evaluation with CBCT at three months after the intervention, besides the disappearance of condyle erosion of a couple of patients. This could be attributed to the short follow-up period, since it is too short to find a radiological reparative change in the condyle or in the glenoid fossa. In the case of Møystad *et al*.,[18] they compared two injections of HA versus two of betamethasone without the use of arthrocentesis, in terms of the variation in pain and maximum opening and related imaging changes found in computed tomography at six months follow-up.

A decrease in the pain intensity and an increase in the range of mandibular opening were reported in most patients where a progression of bone changes was observed on CT, which indicates that the radiological evaluation of the progression of osteoarthritis does not always reflect clinical signs and symptoms.

Due to the mentioned above, we consider that longitudinal studies with a longer follow-up period are required.

3. Possible adverse effects or complications related to the intra-articular application of HA

Four studies[17,19,20,29] did not mention the presence or absence of adverse effects. In the study of Manfredini *et al*.,[22] in their group of one session arthrocentesis with saline solution together with 1ml of HA of very high molecular weight (6000 kDa), several subjects presented joint inflammation and intense pain after the first injection, which was the reason to eliminate that group from the study. The rest of the investigations did not report the manifestation of any adverse effects during the injection or during the follow-up period,[15,24,25] or were not relevant, such as: temporary facial paralysis after anesthesia,[26,30] and mild transient discomfort after joint injection.[21,23]

CONCLUSION.

The studies showed a decrease in pain and improvement in functional parameters after TMJ osteoarthritis treatment associated with the use of hyaluronic acid. The use of arthrocentesis associated with the administration of HA provides synergistic effects, prevailing a superiority in protocols with multiple injections compared to those of a single session. Adverse effects related to HA injection with or without associated arthrocentesis were minor and transitory. Studies with longer-term evaluation of radiological changes after HA interventions are required.

Conflict of interests: The authors report having no conflicts of interest
Ethics approval: Not required.
Funding: Self-financed
Authors' contributions: All authors contributed to the study ejecution. Fernandez-Vial D and Renner N, equal authorship.
Acknowledgements: None.

ISSN Print 0719-2460 - **ISSN Online** 0719-2479. **Attribution 4.0 International (CC BY 4.0). www.joralres.com/2021**

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