Hyaluronic Acid In the Treatment of TMJ Disorders: A Systematic Review of the Literature

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ABSTRACT: Hyaluronate acid (HA) injections are gaining attention as a treatment option to manage symptoms of temporomandibular joint (TMJ) disorders, but updated evidence-based data on their effectiveness are actually lacking. The present paper aims to summarize and review systematically the clinical studies on the use of hyaluronic acid injections to treat TMJ disorders performed over the last decade. On November 9, 2009, a systematic search in the National Library of Medicine's PubMed (*http://www.ncbi.nlm.nih.gov/pubmed*) database was performed by means of a combined MeSH and word terms to identify all peer-reviewed papers published in the English literature dealing with the hyaluronic acid infiltration in patients affected by TMJ disorders. The selected papers were assessed according to a structured reading of articles format, which provided that the study design was methodologically evaluated in relation to four main issues, viz., population, intervention, comparison, and outcome. Nineteen (N=19) papers were selected for inclusion in the review, 12 (N=12) dealt with the use of hylauronic acid in TMJ disk displacements and seven (N=7) dealt with inflammatory-degenerative disorders. Only nine groups of researchers were involved in the studies, and less than half of the studies (8/19) were randomized and controlled trials (RCTs). All studies reported a decrease in pain levels independently by the patients' disorder and by the adopted injection protocol. Positive outcomes were maintained over the follow-up period, which was varied among studies, ranging between 15 days and 24 months. The superiority of HA injections was shown only against placebo saline injections, but outcomes are comparable with those achieved with corticosteroid injections or oral appliances. The available literature seems to be inconclusive as to the effectiveness of HA injections with respect to other therapeutic modalities in treating TMJ disorders. Studies with a better methodological design are needed to gain better insight into this issue and to draw clinically useful information on the most suitable protocols for each different TMJ disorder.

Temporomandibular disorders (TMD) are a heterogeneous group of pathologies affecting the temporomandibular joints, the masticatory muscles, or both.[1] The disorders are characterized by a classically described triad of clinical signs: muscle and/or temporomandibular joint (TMJ) pain; TMJ sounds; and restric-

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tion, deviation or deflection of mouth opening path.[2] TMDs are considered the most common orofacial pain condition of nondental origin, with a prevalence at population level ranging from 1% to 75% for objective signs and from 5% to 33% for subjective symptoms,[3] even though the percentage of subjects who actually need treatment is about 16%.[4,5]

Intracapsular disorders of the TMJ, viz., disk displacements and inflammatory-degenerative disorders, account for a large part of TMD patient populations[6] and may be

managed with a number of approaches that aim to relieve pain and to improve function.[7] Among them, intra-articular injections of sodium hyaluronate, viz., hyaluronic acid (HA), are gaining attention as a potentially effective technique, alone or combined with joint lavage.[8]

In physiological conditions, hyaluronic acid plays an important role in maintaining intra-articular homeostasis; it favors the elasticity and viscosity of the synovial fluid, providing a cushion against any shocks; HA has a lubricating, anti-inflammatory and pain-relieving action and enables activation of the tissue repair process in the cartilage, with a normalizing action on the synthesis of endogenous acid by the synovial cells.[9,10] It has been hypothesized that abnormalities of the joint lubrication system may play a role in the onset of TMJ disorders,[11,12] thus providing a rationale for the visco-supplementation with HA in patients with TMJ internal derangements and inflammatory-degenerative disorders. Early uses of HA in TMJ disorders date back two decades,[13,14] but despite the number of investigations which have been done on this issue, there is little evidence-based information gleaned by a systematic review of the literature.[15]

Considering these drawbacks, the present paper aims to summarize and review systematically the clinical studies done over the last decade on the use of hyaluronic acid injections to treat TMJ disorders.

Materials and Methods

On November 9, 2009, a systematic search in the National Library of Medicine's PubMed (*http://www.ncbi.nlm.nih.gov/pubmed*) database was performed to identify all peer-reviewed papers in the English literature dealing with the hyaluronic acid infiltration as a treatment for TMJ disorders using the search strategy described below. The studies included for review were assessed on the basis of a structured reading of articles, which is also described in detail in the following sections.

Search Strategy and Literature Selection

A search with Medical Subjects Headings (MeSH) terms was used initially, and the following terms were used to identify a list of potential papers to be included in the review:

Temporomandibular joint disorders: A variety of conditions affecting the anatomic and functional characteristics of the temporomandibular joint. Factors contributing to the complexity of temporomandibular diseases are its relation to dentition and mastication and the symptomatic effects in other areas, which account for referred pain to the joint and the difficulties in applying traditional diagnostic procedures to temporomandibular joint pathology where tissue is rarely obtained and x-rays are often inadequate or nonspecific. Common diseases are developmental abnormalities, trauma, subluxation, arthritis, and neoplasia. Year introduced: 1997 (Previous indexing: temporomandibular joint diseases 1982-1996).

Hyaluronic Acid: A natural high-viscosity mucopolysaccharide with alternating beta (1-3) glucuronide and beta (1-4) glucosaminidic bonds. It is found in the umbilical cord, in vitreous body and in synovial fluid. A high urinary level is found in progeria. Year introduced: 2002.

The search was limited to papers on adult populations (+19 years) in the English language and published later than 01/01/1999. The inclusion criterion for admittance in the systematic review was the type of study viz., clinical studies on humans, assessing the effectiveness of hyaluronic acid injections in the treatment of any TMD disorders. The inclusion in the review was based on consensus decision by all three authors, who reached a perfect inter-examiner agreement in all cases.

Systematic Assessment of Papers

The selected papers were assessed according to a structured reading of articles format (PICO format), which provided that the study design was methodologically evaluated in relation to four main issues, viz., population, intervention, comparison, and outcome, for each of which specific questions were constructed.

For each article, the study population ('P') was described in light of the criteria for inclusion, the demographic features of the sample, and the sample size. The study design was described in the section reserved for questions on study intervention: protocol, reference variables, follow-up and statistical analysis. The comparison criterion ('C') assessed the presence of any comparison groups, viz., a control group or a specific comparison subgroup within the patient population. The study outcome ('O') was described based upon the results reported by the authors.

Results

The combination of the two MeSH terms, which alone yielded 4863 and 2080 citations, respectively, allowed identification of 51 citations, the abstracts of which were read to select articles for retrieval of full-text. After reading the abstracts, 37 papers were excluded from further assessment, and the remaining 14 papers were retrieved in full-text and assessed for possible admittance in the review. All 14 papers retrieved were included in the review. Also, the PubMed search was expanded to articles related to the ones selected and the reference lists of the full-text papers were read carefully to search for other

studies, which had potential for inclusion in the review.

After examination of the full-text articles, 19 papers were selected for inclusion in the review, twelve (N=12) of which dealt with the use of hylauronic acid in TMJ disk displacements and seven (N=7) of which dealt with inflammatory-degenerative disorders.

Summary of Findings from Studies on TMJ Disk Displacement

Twelve studies on the use of hyaluronic acid in patients with TMJ disk displacement were performed by seven different research groups (**Table 1**) and accounted for a total of 487 joints in 433 patients (348 females, 52 males, 33 unspecified gender; mean age was between 27 and 42 years), 20 of whom took part to two studies.[16,17] Twenty-five joints (N=25) were affected by unspecified internal derangements, 89 were diagnosed disk displacement with reduction and 373 disk displacement without reduction. Five studies were performed by the same research group,[18-20] and two were duplication studies, presenting different results from the same investigation.[16,17] Another research group accounted for the other two studies.[21,22]

The study protocols were different among the various investigations, ranging from single HA injections with or without arthrocentesis[21] to five HA injections (one per week) following arthrocentesis.[23] Other protocols included five HA injections without arthrocentesis (one per week),[16-20] three HA injections,[24] three HA injections either in the upper or in the lower joint space,[25] two injections (one[26] or two weeks apart),[27] one HA injection two weeks later than either arthrocentesis or arthrocentesis plus HA injection.[22] As a general rule, the number of injections is dependent upon the HA molecular weight, viz., the lower the molecular weight the higher the number of injections, even though it was specified only in a minority of studies. An active control group was recruited in four studies, adopting either saline injections,[26] arthrocentesis,[21] or other HA injection protocols/sites of injections,[25,22] and passive control groups of untreated patients were included in the five studies of the same research group.[16-20] All studies based outcome assessment on measurement of jaw range of motion and pain levels at rest and while chewing, as measured on a VAS scale. Additional radiological,[18] kinesiographic,[16] or electromyographic[17] evaluations were provided in three studies, the last two of which were performed on the same study population. Follow-up spans ranged between 15 days[22] to 24 months,[19,21] even though in the majority of studies, patients were followed up for one year.[17,18,20,24]

As to findings, all studies reported a decrease in pain levels, and positive outcomes also considered parameters of condylar mobility,[18] kinesiographic,[16] and electromyographic recordings,[17] as well as a reduction in the Helkimo clinical dysfunction index.[25] Range of motion improved in the majority of studies, but a couple of papers[24,27] reported the absence of significant changes in mouth opening. Results from studies with an active control group suggested that arthrocentesis plus HA injection is superior to arthrocentesis alone in patients with closed lock,[21] that a protocol of two HA injections at weekly intervals is more effective than placebo injections of saline,[26] that a protocol of injections within the lower joint space is superior to injections in the upper joint space,[25] and that joint catabolyte levels decreased more significantly with a supplemental HA injection.[22]

Summary of Findings from Studies On TMJ Inflammatory Disorders

Seven studies (**Table 2**) on the use of hyaluronic acid injections in patients with inflammatory-degenerative disorders were performed by three different research groups and accounted for a total of 171 patients (87 females, eight males, 76 unspecified sex), 20 of which were included in the same investigation which was described in two different papers.[28,29] Four studies were performed by the same research group[30-33] and two others were conducted by another group and presented different data gathered on the same study population.[28,29] Patients were given a diagnosis of osteoarthritis according to the Research Diagnostic Criteria for TMD (RDC/TMD)[34] in almost all studies (6/7), confirmed radiologically in one study.[29]

The study protocols adopted by the three research groups provided either a single HA injection,[35] two injections (two weeks apart),[28,29] or a cycle of five HA injections (one per week) following arthrocentesis.[30-33] Also in this case, molecular weight of the hyaluronic acid was reported only in some cases. An active comparison group was recruited in three investigations; in one study control group, patients received the same injection protocol as the study group by using corticosteroids instead of HA.[28,29] In another study controls underwent a four-week treatment with oral drugs (methocarbamol plus paracetamol),[35] and in another one, an active control group undergoing occlusal appliance therapy and a passive untreated control group were recruited.[32] In all studies, parameters used for outcome assessment were based on the evaluation of jaw range of motion and pain levels (VAS), with an additional CT evaluation performed in one study.[28] Follow-up periods ranged between three months[35] to one year,[31] with 5/7 studies[28-30,32,33] following up patients for six months after the end of treatment.

Findings from the studies suggested that marked improvement was achieved in all studies in all outcome

Table

Svstematic Review of Studies On the Use of Hvaluronic Acid In Patients with Disk

Study's first author and year	Population	Intervention	Comparison	Outcome
Guarda-Nardini, 2009 [23]	31 patients with DDR and arthralgia (RDC/TMD) and history of pain from > 4 months 25 F, 6 M; m.a. 42.4 yrs., a.r. 24-61	Protocol: Arthrocentesis with 1 ml HA injection (once a week for 5 weeks) Outcome variables: Pain at rest and at chewing (VAS), MAMO, MVMO (mm), functional limitation and subjective efficacy FU: 1 week, 1, 3 months Statistical analysis: T test, Wilcoxon	No control group	Marked improvements with respect to baseline values in all the outcomes variables Significant changes in almost all subjective parameters, with the only exception of minimum pain at rest and chewing
Long, 2009 [24]	112 patients with DDnR 104 F, 8 M; m.a. 28 yrs.	Protocol: 2 random groups (3 HA injections into upper joint space vs. 3 HA injections into lower joint space) Outcome variables: MO (mm), pain levels (VAS), modified Helkimo CDI FU: 3, 6 months Statistical analysis: ANCOVA	Two study groups	MMO, VAS and Helkimo CDI all improved in both the superior and the inferior joint space injection groups at the 3 and 6 month FU At the 3 and 6 month FU inferior joint space injection group better results in all variables than superior joint space injection group
Basterzi, 2008 [24]	40 joints of 33 patients (20 TMJ with DDR, 20 TMJ with DDnR) 29 F, 4 M, m.a. – 31 yrs.	Protocol: injection of 2ml HA at weekly intervals for 3 weeks Outcome Variables: MO (mm), pain levels (VAS) FU: 1, 6, 12 months Statistical analysis: T test, Wilcoxon	No control group	DDR: Significant reduction in VAS pain levels, no significant changes in MO DDnR: Significant reduction in VAS pain levels, no significant changes in MO
Sato, 2006 [18]	55 patients with DDnR (MR confirmation) 47 F, 8 M; m. a. 34.1	Protocol: 1 ml HA (one injection per week for 5 weeks) Outcome variables: condylar mobility, condylar position at MMO (posterior, under, anterior to the eminence), condylar erosions FU: 12 months Statistical analysis: Wilcoxon	42 TMJ in 21 subjects without TMD (16 F, 5 M; m.a. 35.4 yrs.)	Frequencies of patterns of condylar movement in patients at FU significantly different from baseline (Type I, posterior, decreased; Type III, anterior, increased) Frequencies of patterns of condylar movement in patients at FU were significantly different from those in controls Significant improvement in severity of bony changes at FU vs. baseline

Legends: **F**, females; **M**, males; **DDR**, disk displacement with reduction; **MAMO**, maximum assisted mouth opening; **MVMO**, maximum voluntary mouth
FU, follow up; **DDnR**, disk displacement without reduction; **MO**, mouth opening; **CDI**, clinical dysfunction index; **ANCOVA**, analysis of covariance; **EMG**,
tromyography; **ANOVA**, analysis of variance; **MR**, magnetic

Table 1

Systematic Review of Studies On the Use of Hyaluronic Acid In Patients with Disk

Yeung, 2006 [27]	34 TMJ of 27 patients with DDnR 20 F, 7 M; m.a. 39.3 yrs., a.r. 21-63	Protocol: 2 injections of 2ml HA (two weeks apart) Outcome variables: Pain levels (VAS), jaw range of motion (mm) FU: 1, 2, 3, 4 weeks, 3 and 6 months - Statistical analysis: T test	No control group	Significantly decreased VAS pain levels No significant changes in MO (slight decrease after injections) Significant decrease in frequency of clicking sounds
Sato, 2003 [16]	20 patients with DDnR 20 F; m.a. 30.1 yrs; a.r. 16-59	Protocol: 1 ml HA (one injection per week for 5 weeks) Outcome variables: mandibular kinesiography FU: mean 19 months Statistical analysis: X^2 test, Fisher's exact test, T-test	23 female volunteers without TMJ dysfunctions (m.a. 27.7 yrs., a.r. 18-43)	Patterns of patients became similar to those of normal volunteers after treatment Improvement in patients' masticatory efficiency after treatment
Hepguler, 2002 [26]	19 patients with DDR 13 F, 6 M; m.a. 31.9 yrs.	Protocol: 2 HA injections (1 week apart) Outcome variables: pain levels (VAS), modified Helkimo CDI (blind observer) FU: 1 and 6 months Statistical analysis: Mann-Whitney, X^2	Placebo injection of saline in 19 patients with DDR (13 F, 6 M; m.a. 31.1. yrs.)	HA group: improvement with total or partial remission in 89.5% (17/19) at 1 month and 63% (12/19) at 6 months vs. 21% and 26% of placebo group
Sato, 2002 [17]	20 patients with DDnR 20 F; m.a. 30.1 yrs; a.r. 16-59	Protocol: 1 ml HA (one injection per week for 5 weeks) Outcome variables: pain levels (VAS), MO (mm), EMG FU: 12 months Statistical analysis: T test	23 female volunteers without TMJ dysfunctions (m.a. 27.7 yrs., a.r. 18-43)	Improvement in all clinical as well as EMG parameters
Alpaslan, 2001 [31]	19 TMJ in 16 patients with DDR and 22 TMJ in 15 patients with DDnR 25 F, 5 M; m.a. 27	Protocol: 2 random groups, receiving arthrocentesis without or with HA injection Outcome variables: pain intensity and subjective jaw function (VAS), presence of TMJ sounds, jaw range of motion (mm) FU: 1, 2, 3, 4, 5, 6, 9, 12, 18, 24 months Statistical analysis: ANOVA with Tukey test	Two study groups (arthrocentesis alone vs. arthrocentesis plus HA)	Increase in maximal mouth opening, lateral movements, and function, and reduction of TMJ pain and noise with both techniques Arthrocentesis with HA slightly superior to arthrocentesis alone (especially in closed lock)

Legends: **F**, females; **M**, males; **DDR**, disk displacement with reduction; **MAMO**, maximum assisted mouth opening; **MVMO**, maximum voluntary mouth
FU, follow up; **DDnR**, disk displacement without reduction; **MO**, mouth opening; **CDI**, clinical dysfunction index; **ANCOVA**, analysis of covariance; **EMG**,
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Table 1

Systematic Review of Studies On the Use of Hyaluronic Acid In Patients with Disk

Sato, 2001 [19]	60 patients with DDnR 56 F, 4 M; m.a. 30.3 yrs., a.r. 13-74	Protocol: 1 ml HA (one injection per week for 5 weeks) Outcome variables: pain levels (VAS), MO (mm), muscle palpation FU: every month for 24 months Statistical analysis: Cox hazard	76 patients with DDnR not receiving any treatment 70 F, 6 M; m.a. 28.4 yrs., a.r. 11-61	Pumping injection of HA favourable effect when compared with the control group
Alpaslan, 2000 [22]	25 patients with ID 20 F, 5 M; m.a. 25.8 yrs., a.r. 17-50	Protocol: arthrocentesis plus HA injection 15 days later (10 patients) vs. arthrocentesis and HA plus additional HA injection 15 days later (15 patients) Outcome variables: Pain levels (VAS), jaw range of motion (mm), nitrite and nitrate levels in synovial fluid FU: 15 days Statistical analysis: T test	Two study groups	Improvement of symptoms in both groups Joint catabolytes levels decreased significantly only with an additional HA injection
Sato, 1999 [20]	22 TMJ with DDnR in 21 patients 18 F, 3 M; m.a. 33.6 yrs., a.r. 17-74	Protocol: 1 ml HA (one injection per week for 5 weeks) Outcome variables: pain levels (VAS), MO (mm), muscle palpation, condyle morphology (MR) FU: 12 months Statistical analysis: Descriptive comparison	30 TMJ in 15 TMD-free subjects (7 F, 8 M; m.a. 29.3 yrs., a.r. 24-47)	Improvement in patients' clinical signs and symptoms during the follow up period Persistence of disk displacement and deformity

Legends: **F**, females; **M**, males; **DDR**, disk displacement with reduction; **MAMO**, maximum assisted mouth opening; **MVMO**, maximum voluntary mouth
FU, follow up; **DDnR**, disk displacement without reduction; **MO**, mouth opening; **CDI**, clinical dysfunction index; **ANCOVA**, analysis of covariance; **EMG**,
tromyography; **ANOVA**, analysis of variance; **MR**, magnetic

Table

Systematic Review of Studies On the Use of Hyaluronic Acid In Patients with Disk

Study's first author and year	Population	Intervention	Comparison	Outcome
Manfredini, 2009 [30]	76 patients with OA (RDC/TMD) Unspecified age and sex	Protocol: Arthrocentesis with 1 ml HA injection (once a week for 5 weeks) Outcome Variables: Pain at rest and at chewing (VAS), MAMO, MVMO (mm), functional limitation and subjective efficacy FU: 1 week, 1, 3, 6 months Statistical analysis: Pesarin Method (permutation test)	No control group	Decreasing trend in all outcome variable from the beginning of therapy to the end of follow-up
Møystad, 2008 [28]	20 patients with OA (clinical, radiological) 19 F, 1 M; m.a. 53.4 yrs.	Protocol: 2 injections of either HA or CO (two weeks apart) Outcome variables: CT signs from 2 dental radiologists (prospective and randomized blinded clinical trial) FU: 6 months Statistical analysis: T test, Wilcoxon (within group); T test, Mann-Whitney, X^2 (between group)	Active group: CO injections (15 F, 5 M; m.a. 50 yrs.) Passive group: untreated controlateral TMJ	No statistically significant differences between the 2 study groups with regard to any variables No statistically significant difference both in the HA-group and CO-group between the treated and the untreated joints (regression, progression or no change of osteoarthritic abnormalities independent by the administration of any drug)
Oliveras-Moreno, 2008 [35]	20 patients with Wilkes stage II disease 16 F, 4 M; m.a. 25 yrs.	Protocol: randomization - injection of 1ml HA vs. Oral methocarbamol 380mg plus paracetamol (2 tablets every 6 hours for 4 weeks) Outcome variables: pain levels (VAS), jaw function (VAS), treatment tolerability FU: 2, 4, 8, 12 weeks (HA group), 2, 4, 12 weeks (control group) Statistical analysis: Mann-Whitney, generalized linear model	Active control group (oral drugs, N=21) 16 F, 5 M; m.a. 33 yrs.	Significant difference in favour of the HA group from week 8 onward for the TMJ pain at rest; from week 2 onward for pain on jaw opening, at weeks 4 and 8 for pain at mastication. TMJ function statistically significantly better in the test group at all follow-up visits
Bjørnland, 2007 [29]	20 patients with OA (clinical, radiological) 19 F, 1 M; m.a. 53.4 yrs.	Protocol: 2 injections of either HA or CO (two weeks apart) Outcome variables: jaw range of motion (mm), pain levels (VAS) FU: 3, 6 months Statistical analysis: T test, Wilcoxon (within groups); T test, Mann-Whitney, X^2 (between groups)	Active group: CO injections (15 F, 5 M; m.a. 50 yrs.)	Improvement in all outcome variables, independently by the administered drug

Legends: **OA**, osteoarthritis; **CT**, computerized tomography; **CO**, corticosteroids; **F**, females; **M**, males; **DDR**, disk displacement with reduction; **MAMO**, assisted mouth opening; **MVMO**, maximum voluntary mouth opening; FU, follow up; **DDnR**, disk displacement without reduction; **MO**, mouth opening; **CDI**, dysfunction index; **ANCOVA**, analysis of covariance; **EMG**, electromyography; **ANOVA**, analysis of variance; **MR**, magnetic

Table 2

Systematic Review of Studies On the Use of Hyaluronic Acid In Patients with TMJ Inflammatory-Degenerative

Guarda- Nardini, 2007 [31]	25 patients with OA (RDC/TMD)	Protocol: Arthrocentesis with 1 ml HA injection (once a week for 5 weeks) Outcome Variables: Pain at rest and at chewing (VAS), MAMO, MVMO (mm), functional limitation and subjective efficacy FU: 1 week, 1, 3, 6, 12 months Statistical analysis: Pesarin method (permutation test)	No group control	Marked improvements in all outcome variables, maintained during the follow-up period
Guarda-Nardini, 2005 [32]	20 patients with degenerative TMJ disease (clinical, radiological) 20 F, 5 M; m.a. 49.8 yrs.	Protocol: Arthrocentesis with 1 ml HA injection (once a week for 5 weeks) Outcome Variables: Pain at rest and at chewing (VAS), MAMO, MVMO (mm), functional limitation and subjective efficacy FU: 1 week, 1, 3, 6 months Statistical analysis: T test, Wilcoxon	Active control group: 20 patients undergoing a bite-plane treatment for at least 6 months (19 F, 1 M; m.a. 51.4 yrs.) Passive control group: 20 patients refusing any treatment (16 F, 4 M; m.a. 46.4 yrs.)	Significant improvements in all outcome parameters in both HA and bite-plane groups No outcome differences between active groups
Guarda-Nardini, 2002 [33]	10 patients with degenerative TMJ disease (clinical, radiological) 9 F, 1 M; m.a. 49.3 yrs., a.r. 39-68	Protocol: Arthrocentesis with 1 ml HA injection (once a week for 5 weeks) Outcome Variables: Pain at rest and at chewing (VAS), MAMO, MVMO (mm), functional limitation and subjective efficacy FU: 1 week, 1, 3, 6 months Statistical analysis: T test	No control group	Significant improvement in all outcome parameters maintained over time

Legends: **OA**, osteoarthritis; **CT**, computerized tomography; **CO**, corticosteroids; **F**, females; **M**, males; **DDR**, disk displacement with reduction; **MAMO**, assisted mouth opening; **MVMO**, maximum voluntary mouth opening; FU, follow up; **DDnR**, disk displacement without reduction; **MO**, mouth opening; **CDI**, dysfunction index; **ANCOVA**, analysis of covariance; **EMG**, electromyography; **ANOVA**, analysis of variance; **MR**, magnetic

variables, and that improvement was kept constant over the follow-up period. Studies with control groups showed that a single HA injection was superior to oral administration of methacarbamil plus paracetamol,[35] and that a significant positive difference, with respect to untreated joints[28,29] or patients,[32] was observed. No significant differences were detected with respect to patients treated with corticosteroids[28,29] or occlusal appliances.[32]

Discussion

The issue of temporomandibular disorders treatment is one of the most controversial and intriguing aspects of the dental and orofacial pain literature. There is broad consensus among scientists that symptomatic management is currently the most effective approach to treatment of such disorders in terms of reversibility and benefit-to-risk ratio.[36] Such suggestion has led to the proposal of several conservative treatment modalities for both muscle and joint disorders, including oral appliances,[37] physiotherapy,[38] physical therapy,[39] artrocentesis and joint lavage,[40] drugs,[41] and behavioral therapies.[42] However, it seems that the level of evidence coming from the literature on the use of such different approaches is still insufficient, since very few systematic reviews have been performed on the issue of TMD treatment.[43,44]

Within this context, viscosupplementation with hyaluronic acid injections is gaining attention as a potentially useful technique to improve jaw function and achieve relief from pain in patients with TMD, as suggested by the literature on larger joints, such as the knee and hip joints.[45] The present review was only a systematic review performed to assess the effectiveness of intra-articular injection of hyaluronic acid, both alone and in combination with other remedies for TMJ disorders.[15] The review was limited to randomized or quasi-randomized controlled trials (RCTs), thus examining findings from very few studies from the year 1985 to 2002 (N=7) and concluded that there was positive but weak evidence for using hyaluronate to treat TMD and rheumatoid TMJ cases. Some methodological flaws and incomplete reporting were the main factors influencing validity and reproducibility of the conclusion. There is a need for further high quality RCTs of hyaluronate before drawing firm conclusions with regard to its treatment effectiveness.[15]

The aim of the present review was to update knowledge on this issue, by evaluating the literature produced over the last decade. Nineteen papers were selected for discussion, 12 of which dealt with patients with TMJ disk displacement (sometimes referred to as internal derangement) and seven of which dealt with TMJ inflammatory-degenerative disorders, with interesting emerging results.

Few papers provided a IIb level of evidence (randomized controlled trials),[46] since only 8/19 (42.1%) papers concerned with six different investigations provided the presence of an active control group, while all the other papers reported data from uncontrolled or passively controlled investigations, viz., case series thus providing a IIIb or IV level of evidence. All low-evidence papers reported encouraging findings as to the effectiveness of different hyaluronic acid injection protocols to improve jaw range of motion and to decrease pain levels. Notwithstanding, data from the RCTs suggested that such effects are not superior to those achieved with corticosteroids injections[28,29] or occlusal appliance therapy[32] in patients with inflammatory-degenerative disorders, they do seem to be superior to those achieved using placebo injections[26] or arthrocentesis[21] in subjects with disk displacement with reduction. Other findings from RCTs on disk displacement patients suggest that additional viscosupplementation with additional HA injections, compared with a single HA injection plus arthrocentesis is more effective in achieving symptom management,[22] and that injections in the lower joint space are more effective than the classical upper joint approach.[25] Unfortunately, there was no data provided on how to achieve a reproducible and accurate approach to the lower joint space.

A major concern with the literature on HA injections in TMJ disorders is that a large number of papers is accounted for by only a couple of research groups, which performed five studies each and were likely based upon the same patient population, followed up at different points in time. Such an observation is a concrete matter of concern when trying to discuss the overall external validity of the literature findings. Moreover, very little data exist comparing the different protocols of HA injections, alone or combined with arthrocentesis, since the studies from the different research groups are not consistent with each other with regard to the number and interval of HA injections. Even the more extreme examples of different protocols, viz., a cycle of five HA injections plus arthrocentesis (one week apart) vs. a single HA injection, seem to find a biologically plausible rationale and seem to be justified by the choice to adopt HA of different molecular weights. Uncertainties in the choice of the protocols are likely due to the absence of literature guidelines for this specific issue on which a clinician may base a treatment plan. Unfortunately, the present systematic assessment of the literature did not provide much useful information at the clinical (single patient) level. However, it must be kept in mind that there are some objective problems related to the need to do further research into this issue, the main one being the difficulty in designing methodologically correct studies. The different protocols that are usually

adopted for arthrocentesis (single session) and HA injections (five weekly injections) in other joints make it impossible to perform, e.g., a double-blind, randomized, and controlled clinical trial to test for the superiority of one treatment or the combination of the two over the other, or even to test for the relative effectiveness of different protocols.

From a methodological viewpoint, it should be pointed out that the inclusion criteria were here enlarged to studies with less than optimal evidence levels and poor quality designs. Such an approach may not be the most suitable when performing reviews at the highest levels, as suggested by some guidelines for the assessment of quality, methodological systematic reviews,[47] but it did accomplish the review's intention to gather as much data as possible on the argument. Inclusion was limited to English literature included in PubMed, which is the most diffuse and comprehensive medical database. However, there is a likelihood that some minor publications in other languages and included in other databases , even low, cannot be excluded and should be considered in future reviews. The problem of publication bias, viz., the likelihood that negative findings on the outcome of a particular treatment may be published less frequently than positive ones, has not been addressed. Even if consistency of findings from case series published by the different research groups suggest a good outcome with HA injections for TMJ disorders seems to rule out this potential problem. It should be noted that redundancy concerns, viz., duplication studies on the same study populations, cannot be ruled out due to the small number of few groups involved in this clinical research field, some of which contribute multiple papers with different follow-up periods.

In general, despite the fact that the literature supports the potential effectiveness of visco-supplementation to manage TMJ disorders, it seems that evidence-based data are still lacking to support its use in daily practice. The literature is still in a growing or preliminary phase, which is a striking observation if one considers that early studies on the issue date back almost 30 years.[48] Moreover, the clinical use of HA injections should also be supported by detailed benefit-to-cost ratio evaluations in future studies, because HA injections need to stand comparison with conservative approaches, such as occlusal splints, physiotherapy, and pain medication, before being definitively introduced within the daily armamentarium of the TMD specialist.

Conclusions

Temporomandibular joint disorders are commonly managed with a number of reversible an conservative approaches, among which visco-supplementation with hyaluronic acid injections is gaining attention as a potentially effective tool to improve jaw function and decrease pain levels. Nonetheless, evidence-based data appears to be lacking, and a systematic assessment of the available literature was performed to summarize current knowledge on the issue. Nineteen papers dealing with HA injections in patients with either disk displacement (N=12) or inflammatory-degenerative disorders (N=7) were published in the last decade, and their structured reading suggests that several shortcomings still affect the literature on this issue. So few papers have been done and by only nine research groups, with a couple of those accounting for more than half the published papers, thus limiting generalization of findings. Moreover, few randomized and controlled trials comparing the effectiveness of HA injections with that of other treatments have been performed. In general, despite the effectiveness shown by all case series, HA injections did not prove superior to other active treatments, such as corticosteroid injections or occlusal appliances. Some studies showed that viscosupplementation has an additional value with respect to joint lavage alone, viz., arthrocentesis. Strong evidence-based data to identify the best protocol (e.g., number and sites of the injections, HA molecular weight, combination with arthrocentesis) for the different clinical conditions (e.g., inflammatory-degenerative disorders, arthralgia, closed lock, other internal derangements) are needed before supporting the routine clinical use of HA injections to manage TMJ disorder symptoms.

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