Int. J. Oral Maxillofac. Surg. 2016; 45: 1531–1537
http://dx.doi.org/10.1016/j.ijom.2016.06.004, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review
TMJ Disorders

Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review

M. C. Goiato, E. V. F. da Silva, R. A. de Medeiros, K. H. L. Túrcio, D. M. dos Santos
Department of Dental Materials and Prosthodontics, Aracatuba Dental School, Sao Paulo State University (UNESP), Aracatuba, Sao Paulo, Brazil

M. C. Goiato, E. V. F. da Silva, R. A. de Medeiros, K. H. L. Túrcio, D. M. dos Santos: Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review. Int. J. Oral Maxillofac. Surg. 2016; 45: 1531–1537.

Abstract. This systematic review aimed to investigate whether intra-articular injections of hyaluronic acid (HA) are better than other drugs used in temporomandibular joint arthrocentesis, for the improvement of temporomandibular disorder (TMD) symptoms. Two independent reviewers performed an electronic search of the MEDLINE and Web of Science databases for relevant studies published in English up to March 2016. The key words used included a combination of 'hyaluronic acid', 'viscosupplementation', 'intra-articular injections', 'corticosteroids', or 'non steroidal anti inflammatory agents' with 'temporomandibular disorder'. Selected studies were randomized clinical trials and prospective or retrospective studies that primarily investigated the application of HA injections compared to other intra-articular medications for the treatment of TMD. The initial screening yielded 523 articles. After evaluation of the titles and abstracts, eight were selected. Full texts of these articles were accessed and all fulfilled the inclusion criteria. Intra-articular injections of HA are beneficial in improving the pain and/or functional symptoms of TMDs. However, other drug therapies, such as corticosteroid and non-steroidal anti-inflammatory drug injections, can be used with satisfactory results. Well-designed clinical studies are necessary to identify an adequate protocol, the number of sessions needed, and the appropriate molecular weight of HA for use.

Key words: hyaluronic acid; viscosupplementation; intra-articular injections; temporomandibular disorder.

Accepted for publication 6 June 2016
Available online 30 June 2016

0901-5027/01201531 + 07

Temporomandibular joint disorder (TMD) is a widely researched disease in the literature, since it has a high prevalence and is often associated with chronic pain and limited function of the temporomandibular joint (TMJ), resulting in decreased quality of life for the patient.[1–5] The joint disorders include disc displacement and degenerative and/or inflammatory disorders. Due to its complex aetiology and varied classification, different conservative and surgical treatments have been studied in an attempt to improve clinical symptoms and restore function for the affected patients.[1,6–10]

Conservative treatments include rest, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, botulinum toxin injections, bite splints, and physical therapy.[1,8,11–16] Arthrocentesis is among the surgical alternatives performed when there is no effective response to conservative treatment; this is a simple and minimally invasive procedure, commonly used to remove inflammatory mediators associated with nociceptive processes within the synovial fluid.[2,9,17–19] The procedure can be associated with the injection of various drugs, such as sodium hyaluronate (SH), which can also be used separately, with the aim of increasing the treatment efficacy.[17,20,21]

The use of intra-articular injections of SH (viscosupplementation), which is a viscous, high molecular weight polysaccharide, allows the lubrication and subsequent protection of the joint cartilage.[1,5,7,9,22–26] This substance consists of a sodium salt of hyaluronic acid (HA), a physiological component of synovial fluid, which is responsible for the lubrication of synovial joints including the TMJs.[2,22,27–30]

There is still controversy in the literature regarding the benefits of the use of intra-articular HA injections in the treatment of TMD,[1] as well as in establishing an ideal protocol and technique to restore function and promote pain relief for patients.[31,32] The aim of this study was to evaluate, through a systematic review, whether intra-articular injections of HA are better than other drugs used in TMJ arthrocentesis, for the improvement of TMD symptoms. The null hypothesis was that there is no difference in the improvement of TMD symptoms treated with HA injections when compared to other intra-articular medications.

Materials and methods

A systematic literature review was performed following the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The protocol for this systematic review was registered in the PROSPERO database (International Prospective Register of Systematic Reviews; registration number CRD4201603348). The first step in the systematic review was to use the PICO format to define a clinical question for comparative studies involving patients with a TMD (P, population) who were treated with HA injections (I, intervention), compared to other types of intra-articular drug therapy (C, comparison), regarding the improvement in TMD symptoms (O, outcome).

Search strategy and study selection

An electronic search of the MEDLINE (PubMed search form) and Web of Science databases was performed for relevant studies published in English up to March 2016. A double-blind screening of all titles and abstracts, obtained through the electronic search, was conducted for possible inclusion in the study by two independent reviewers. The key words (medical subject heading (MeSH) terms) included a combination of 'hyaluronic acid', 'viscosupplementation', 'intra-articular injections', 'corticosteroids', or 'non steroidal anti inflammatory agents' with 'temporomandibular disorder'. The titles and abstracts were selected according to the inclusion criteria. Two reviewers (EVFS, RAM) were calibrated for the identification of eligible studies and any disagreement was resolved by discussion. A third reviewer (MCG) acted as the moderator.[33] The Cohen kappa method was used to calculate agreement between reviewers. The full texts of potentially relevant articles were accessed for selection according to pre-established inclusion and exclusion criteria.

Inclusion and exclusion criteria

The following studies were selected: randomized clinical trials (RCTs) and prospective or retrospective studies that primarily investigated the application of HA injections compared to other intra-articular medications for TMDs.

Animal and *in vitro* studies, case reports, duplicate articles, interviews, comments, and literature or systematic reviews were excluded. Furthermore, studies that did not comparatively evaluate HA injections with other intra-articular medications for TMD treatment were also excluded.

Quality analysis of studies

The selected studies were classified according to the Jadad scale and were categorized as low quality (score between 0 and 2) or high quality (score between 3 and 5).[34]

Data analysis

Several factors were extracted from the selected studies and analyzed. These included the study design, number of patients, sex (male and female), mean age (years), and method of TMD diagnosis (clinical, by imaging, and/or through the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)). The pathology diagnosed in the patients, type of treatment used, follow-up period, and results found were also recorded.

Results

Study selection

The initial screening yielded a total of 771 articles. After the removal of duplicate studies, 523 articles remained, of which eight texts were selected after the evaluation of their titles and abstracts (kappa score = 1.00). The full texts of these articles were accessed and all articles fulfilled the inclusion criteria and were included in the study (kappa score = 1.00) (Fig. 1).

According to the Jadad scale, four studies had a score of 5, three had a score of 4, and one had a score of 3, for a total of eight high quality studies (Table 1).

Study characteristics

The main characteristics of the studies included are detailed in Table 2.

Among the eight studies, seven were RCTs[2,7,10,16,24,26,31] and one was a retrospective study.[1] The total number of patients treated was 350, ranging from 16 to 100; 275 were female and 75 were male.

Regarding the clinical diagnosis, four studies evaluated patients with osteoarthritis,[7,16,24,31] one study evaluated patients with osteoarthrosis or an inflammatory joint disorder,[10] two studies classified patients according to Wilkes classification, with internal derangements ranging from I to V,[1,2] and one study evaluated patients with rheumatoid arthritis (RA).[26]

Concerning the types of treatment performed, four studies compared the use of HA with corticosteroids,[7,10,16,24] one study evaluated an additional group of

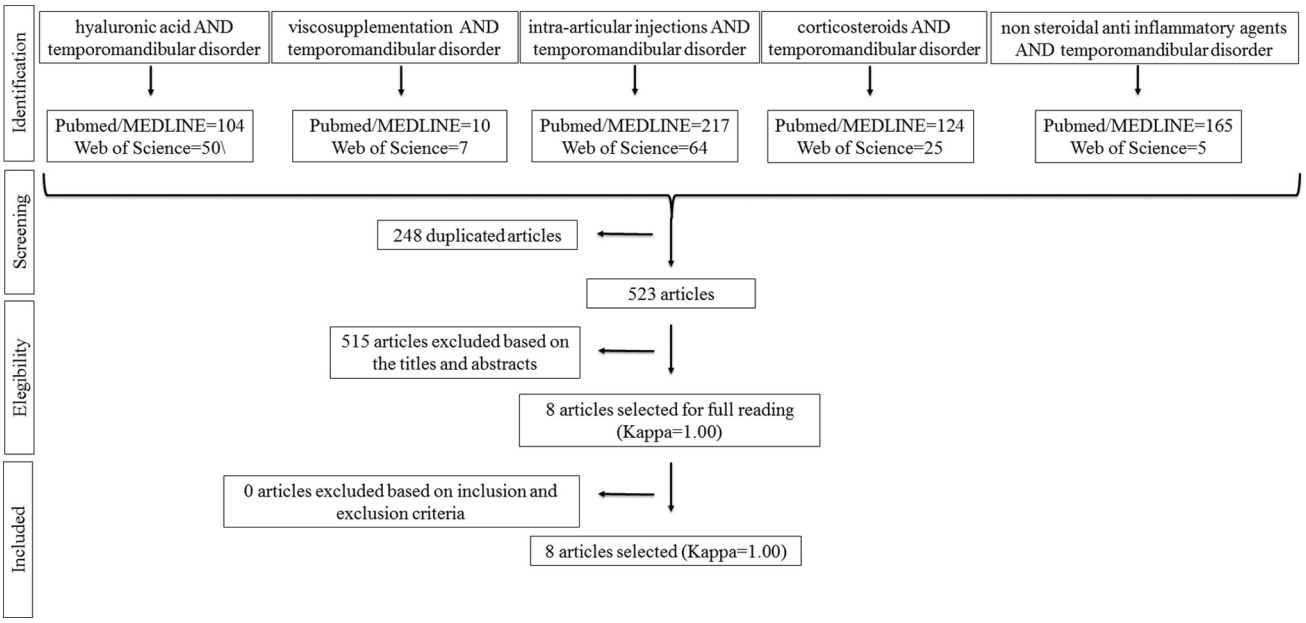

Fig. 1. Flow chart of the screening process.

saline solution,[26] and one study added the analysis of NSAID therapy.[2] Two studies used drugs in association with arthrocentesis: HA was compared to corticosteroids in one study[31] and to NSAID therapy in one study.[1] The follow-up period ranged from 1 month to 24 months.

There was no consensus in the studies that HA injections showed better results than the intra-articular use of other medications for the treatment of TMD (Table 2). In the studies by Bjørnland et al. and Gencer et al., the groups of patients who received intra-articular HA injections exhibited better results in terms of pain relief[2,7] and/or joint function[7] than the other groups analyzed. In the study performed by Manfredini et al., all groups showed improvements in pain relief and joint function, with no statistical difference between them.[31] However, patients who underwent arthrocentesis followed by high molecular weight HA injection showed unsatisfactory results. In the study by Emes et al., no significant reduction in pain or improvement in joint function was observed using HA injections.[1] On the other hand, Møystad et al.[24] and Kopp et al.[10,16,26] found no statistical difference in the use of corticosteroids or HA, but reported benefits of both techniques.

Although seven RCTs were included in this review, no meta-analysis was performed due to the wide clinical diversity between the studies.

Discussion

According to the Jadad scale, all of the studies included in this systematic review (100%) had a well-designed methodology with appropriate randomization and blinding for a clinical trial analyzing the efficacy of intra-articular injections of HA compared to other intra-articular medications for the improvement of TMD symptoms. The null hypothesis proposed initially was rejected, since there was no consensus in the studies included in this review that HA injections had similar results in the improvement of TMD symptoms when compared to other intra-articular medications.

Although the best results were found for groups of patients undergoing HA injections,[2,7] several RCTs found no superiority in the results achieved with this substance when compared to corticosteroid injections regarding the different clinical symptoms studied.[10,16,24,26]

TMD consists of a TMJ disorder related to pain in the joint or surrounding tissues and functional limitations associated or not with joint sounds during movement.[2] Wilkes proposed a classification for internal derangement of the TMJ with categories of early (I), early intermediate (II), intermediate (III), late intermediate (IV), and late (V) stages, which vary according to the clinical and radiological progression, as well as the pathology of the disorder.[35]

The literature reports that conservative treatments, such as the use of oral medications for the treatment of TMD, should precede more invasive procedures.[1,8,22] In some studies included in this review, the

Table 1. Quality assessment of the selected studies.

Jadad scale	Kopp et al.[10]	Kopp et al.[16]	Kopp et al.[26]	Bjørnland et al.[7]	Møystad et al.[24]	Manfredini et al.[31]	Gencer et al.[2]	Emes et al.[1]
Was the study described as randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the randomization described and appropriate?	No	No	No	Yes	Yes	Yes	Yes	Yes
Was the study described as double-blind?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was the double-blind method appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was there a description of withdrawals and drop outs?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Result	4	4	4	5	5	5	5	3
Quality of study	High	High	High	High	High	High	High	High

Table 2. Characteristics of studies included in the review.

Author	Study design	Objective	Number and sex of patients	Mean age, years (range)	Diagnostic method	Pathology diagnosed
Kopp et al.[10]	Double-blind RCT	Efficacy of HA and corticosteroid injections on various clinical symptoms	33 patients 4 M and 29 F	46 (26–77)	Clinical and imaging	Osteoarthrosis or inflammatory joint disorder
Kopp et al.[16]	Double-blind RCT	Efficacy of HA and corticosteroid injections on various clinical symptoms	24 patients 3 M and 21 F	50 (26–77)	Clinical and imaging	Osteoarthritis
Kopp et al.[26]	Double-blind RCT	Efficacy of HA, corticosteroid, and saline injections on various clinical symptoms	41 patients 2 M and 39 F	60.5 (17–84)	–	Rheumatoid arthritis
Bjørnland et al.[7]	Double-blind RCT	Efficacy of HA and corticosteroid injections on various clinical symptoms	40 patients 6 M and 34 F	51.7 (37–55)	Clinical and imaging	Osteoarthritis
Møystad et al.[24]	Double-blind RCT	Bone changes after HA and corticosteroid injections	36 patients 5 M and 31 F	49.9	RDC/TMD and imaging	Osteoarthritis
Manfredini et al.[31]	Double-blind RCT	Efficacy of arthrocentesis with or without other drugs on various clinical symptoms	60 patients 9 M and 51 F	50.1	RDC/TMD	Osteoarthritis
Gencer et al.[2]	Double-blind RCT	Efficacy of HA, corticosteroid and NSAID injections on pain relief	100 patients 45 M and 55 F	42.5 (20–65)	Clinical and imaging	Wilkes stage IV and V disease
Emes et al.[1]	Retrospective	Efficacy of arthrocentesis associated with HA and NSAID injections on various clinical symptoms	16 patients (18 TMJs) 1 M and 15 F	30.8 (19–57)	Clinical and imaging	Wilkes stage I to V disease

Author	Type of treatment	Follow-up	Outcome
Kopp et al.[10]	Group 1: two 0.5-ml HA injections (14 days apart) (18 patients) Group 2: two 0.5-ml corticosteroid injections (14 days apart) (15 patients)	6 weeks	Groups 1 and 2: improvement in clinical symptoms
Kopp et al.[16]	Group 1: two 0.5-ml HA injections (14 days apart) (12 patients) Group 2: two 0.5-ml corticosteroid injections (14 days apart) (12 patients)	24 months	Groups 1 and 2: improvement in clinical symptoms
Kopp et al.[26]	Group 1: two 0.7-ml saline injections (14 days apart) (13 patients) Group 2: two 0.7-ml HA injections (14 days apart) (14 patients) Group 3: two 0.7-ml corticosteroid injections (14 days apart) (14 patients)	4 weeks	Groups 2 and 3: improvement in clinical symptoms
Bjørnland et al.[7]	Group 1: two 0.7–1.0-ml HA injections (14 days apart) (20 patients) Group 2: two 0.7–1.0-ml corticosteroid injections (14 days apart) (20 patients)	6 months	Group 1: significantly more effective in reducing pain
Møystad et al.[24]	Group 1: two HA injections (14 days apart) (17 TMJs) Group 2: two corticosteroid injections (14 days apart) (19 TMJs)	6 months	Groups 1 and 2: no statistical difference observed between them
Manfredini et al.[31]	Group 1: 2-needle arthrocentesis (11 patients) Group 2: 2-needle arthrocentesis + 1.0 ml corticosteroid injection (9 patients) Group 3: 2-needle arthrocentesis + 1.0 ml low MW HA injection (11 patients) Group 4: 2-needle arthrocentesis + 1.0 ml high MW HA injection (5 patients) Group 5: 5 weekly 2-needle arthrocentesis + 1.0 ml low MW HA injection (12 patients) Group 6: 5 weekly 1-needle arthrocentesis + 1.0 ml low MW HA injection (12 patients)	3 months	Groups 1, 2, 3, 5, and 6: improvement in clinical symptoms
Gencer et al.[2]	Group 1: 0.5-ml saline injection (control) (25 patients) Group 2: 0.5-ml HA injection (25 patients) Group 3: 0.5-ml corticosteroid injection (25 patients) Group 4: 0.5-ml NSAID injection (25 patients)	6 weeks	Group 2: significantly more effective in reducing pain
Emes et al.[1]	Group 1: arthrocentesis + 1.0 ml HA injection (8 TMJs) Group 2: NSAID injection (10 TMJs)	3 months	No significant benefits for either technique

F, female; HA, hyaluronic acid; M, male; MW, molecular weight; NSAID, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial; RDC/TMD, Research Diagnostic Criteria for Temporomandibular Disorders; TMJ, temporomandibular joint.

patients included for surgical procedures had previously undergone conservative treatment but without success.[2,7,10,16]

According to Alpaslan and Alpaslan,[9] despite intra-articular injections of corticosteroids improving TMJ pain symptoms, the prognosis following their use is unpredictable, since adverse local effects can occur in the joint tissues. A similar reason was used by Kopp et al. to justify their studies.[10,16] The authors investigated whether HA injections were more effective than corticosteroid (betamethasone) injections in patients with TMJ pain and tenderness for at least 6 months. In these studies, the patients were evaluated 4 weeks after the second treatment session. Kopp et al. found that both procedures reduced the clinical symptoms and dysfunction of patients.[10] However, they stated that HA was a more suitable treatment since it is a physiological component of synovial fluid and therefore the risk of the progression of joint degeneration, which may be caused by corticosteroids, is reduced. In one of the studies by Kopp et al., patients who showed no improvement in symptoms (28% of patients in the HA injection group and 40% in the corticosteroid injection group) received two more injections of the alternative drug, with an interval of 2 weeks between injections, and this had no significant influence on the treatment effect.[16] The patients were evaluated at 12 and 24 months, and an improvement in clinical symptoms was verified for both drugs.

Similar to Kopp et al.,[16] Bjørnland et al.[7] compared the efficacy of HA and corticosteroid (betamethasone) injections on different clinical symptoms in patients with TMJ osteoarthritis, but with a shorter follow-up period. Patients were evaluated 14 days, 1 month, and 6 months after the initial injection, and it was verified that those in the first group (HA injections) showed a greater reduction in pain and improvement in jaw function than the second group (corticosteroid injections). The joint sounds improved in both groups. Among the complications of treatment, temporary pain conditions related to HA injections were observed, possibly due to the amount of HA injected in the TMJ or to incorrect placement within the joint capsule.

Osteoarthritis is the most prevalent TMJ disease. Patients with this disorder tend to exhibit a reduction in intra-articular HA concentration due to depolymerization by reactive oxygen species and the production of acid molecules with a lower molecular weight than normal.[22] Consequently, a reduction in lubrication and an increase in joint mechanical stress occur, resulting in clinical and radiographic progression of the disease.[22]

For the imaging diagnosis of TMJ alterations, magnetic resonance imaging and computed tomography (CT) are the most commonly used methods for soft tissue and bone examinations, respectively.[24] Thus, Møystad et al. compared bone changes after HA and corticosteroid (betamethasone) injections in patients with TMJ osteoarthritis using CT Images 24. The contralateral TMJ with minor symptoms was used as the control, and radiographic signs of the disease were classified through a score (presence of erosions, sclerosis, osteophytes, and flattening of the condyle). After 6 months, there was no statistically significant difference between the groups or between the period before and 6 months after treatment. However, progression, regression, and no changes in osseous abnormalities were observed in both groups.

Arthrocentesis, which consists of joint lavage with Ringer's lactate solution or saline solution for the removal of intra-articular inflammatory components, can be combined with viscosupplementation with HA.[17,18,22] Several studies have evaluated the effectiveness of arthrocentesis associated or not with HA injections on pain intensity and jaw function in patients with TMDs.[9,11,19,23,25] The authors found that the combination treatments gained superior results. Alpaslan and Alpaslan stated that the HA provides a long-term lubricating effect, reducing the actions of inflammatory mediators and increasing joint mobility.[9] On the other hand, Aktas et al. suggested that arthrocentesis is sufficient for the treatment of patients with no degenerative changes on imaging examinations[17]; however, the association with HA is necessary when there is joint degeneration.

Emes et al. analyzed the effects of arthrocentesis associated with HA injections compared to NSAID (tenoxicam) injections in patients previously treated unsuccessfully with arthrocentesis associated with HA after 6 months of follow-up.[1] Patients were evaluated for the presence of pain and maximum and assisted mouth opening at 1 week, 1 month, and 3 months. In the first group (HA injections), the pain decreased between periods, although this was not statistically significant. In the second group (NSAID injections), the pain reduced in the first week, but increased after 1 and 3 months of follow-up; again, the difference was not statistically significant. A small improvement in the functional aspect was found in both groups, however without statistical significance. The authors stated that more invasive procedures, such as repeated injections, arthroscopy, and open joint surgery, are necessary in these cases.

Gencer et al. compared the effect of intra-articular injections of HA, corticosteroid (betamethasone), and NSAID (tenoxicam) on pain relief in patients with capsular or cartilage degeneration and TMD symptoms.[2] The study had a control group of patients who received saline injections, and the evaluation of pain relief was performed after 1 and 6 weeks. Although all groups had greater pain relief than the control group, the best results were observed for HA injections at 1 and 6 weeks. For patients using tenoxicam, pain relief was not maintained between these periods.

Guarda-Nardini et al., Sato and Kawamura, and Sato et al. extensively investigated the efficacy of five arthrocentesis sessions associated with viscosupplementation with HA in patients with TMD.[4,12,14,15,18,27,28,30,32] They observed that this protocol is beneficial regarding the improvement in subjective symptoms (such as pain at rest and in motion) and clinical signs (such as mouth opening and lateral movements), with these being maintained for long periods after the cessation of treatment.

In 2015, Guarda-Nardini et al. compared two single-session protocols with high or medium molecular weight HA injections with the reference protocol of five arthrocentesis sessions associated with viscosupplementation with medium molecular weight HA.[20] The authors noted that the latter protocol was superior to the others after 6 months of follow-up.

In the study of Manfredini et al., different protocols for the treatment of osteoarthritis, lasting more than 6 months, were compared regarding the improvement of nociceptive and functional symptoms.[31] The drugs associated with arthrocentesis were corticosteroid (triamcinolone) (group 2), low molecular weight HA (groups 3, 5, and 6), and high molecular weight HA (group 4). The protocol used for group 4 was interrupted due to the unpleasant side effects experienced after treatment with the high molecular weight HA, which included excess TMJ pain. According to the authors, the high molecular weight HA results in higher viscosity and lower ease of diffusion thereof within the TMJ intra-articular space. All other groups showed improvements in the variables assessed (chewing efficiency, pain at rest and in motion, and improvement in mouth

opening values), with no statistically significant difference between them. However, group 5 showed the best results from a numerical point of view. Regarding the use of one or two needles for the application of the drug, no difference was observed between the groups, similar to the results of Guarda-Nardini et al.,[32] who also found no difference between the techniques in five sessions of arthrocentesis followed by HA injections. Regarding the molecular weight of HA, the results differ from those of Yeung et al., who assessed the clinical signs and symptoms in patients with disc displacement without reduction before and 6 months after treatment with two sessions of high molecular weight HA injections.[21] The authors observed an improvement in symptoms and proposed high molecular weight HA as the primary treatment for TMDs.

Rheumatoid arthritis is a chronic inflammatory disease that can compromise, among other joints, the TMJ.[26] Kopp et al. evaluated the short-term effects of HA, glucocorticoids (methylprednisolone), and saline solution injections in the TMJs of patients with RA, with the presence of symptoms for less than 1 year in this joint.[26] Patients in the first two groups (HA and glucocorticoid injections) exhibited significant positive results when compared to those who had saline injections; they showed a reduction in pain and clinical dysfunction, as well as increased maximum mouth opening.

Regarding the clinical diagnosis, no comparative studies on the use of HA for the treatment of articular disorders caused by disc displacement or by degenerative and/or inflammatory disorders were found. Patients in the studies included had only one type of clinical diagnosis, making it difficult to establish for what type of condition HA is more favourable.

Furthermore, this treatment is relatively expensive[2] and has, until now, been approved by the US Food and Drug Administration only for use in knee osteoarthritis.[36] Therefore, further studies with a larger number of patients and longer follow-up periods are necessary to identify a suitable protocol, number of sessions needed, and appropriate molecular weight of HA in order to ensure safe use in patients.

In conclusion, intra-articular injections of HA are beneficial for the improvement of the pain and/or functional symptoms of TMDs. However, other drug therapies, such as corticosteroid and NSAID injections, can be used with satisfactory results. Therefore, RCTs with longer follow-up periods and larger sample sizes are necessary to assess the actual effectiveness of this technique.

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

Patient consent

Not required.

References

1. Emes Y, Arpınar I.Ş., Oncü B, Aybar B, Aktaş I, Al Badri N, et al. The next step in the treatment of persistent temporomandibular joint pain following arthrocentesis: a retrospective study of 18 cases. *J Craniomaxillofac Surg* 2014;**42**:e65–9. http://dx.doi.org/10.1016/j.jcms.2013.06.010.
2. Gencer ZK, Özkiriş M, Okur A, Korkmaz M, Saydam L. A comparative study on the impact of intra-articular injections of hyaluronic acid, tenoxicam and betametazon on the relief of temporomandibular joint disorder complaints. *J Craniomaxillofac Surg* 2014;**42**:1117–21. http://dx.doi.org/10.1016/j.jcms.2014.01.041.
3. Su N, Yang X, Liu Y, Huang Y, Shi Z. Evaluation of arthrocentesis with hyaluronic acid injection plus oral glucosamine hydrochloride for temporomandibular joint osteoarthritis in oral-health-related quality of life. *J Craniomaxillofac Surg* 2014;**42**:846–51. http://dx.doi.org/10.1016/j.jcms.2013.12.003.
4. Guarda-Nardini L, Ferronato G, Favero L, Manfredini D. Predictive factors of hyaluronic acid injections short-term effectiveness for TMJ degenerative joint disease. *J Oral Rehabil* 2011;**38**:315–20. http://dx.doi.org/10.1111/j.1365-2842.2010.02164.x.
5. Tang YL, Zhu GQ, Hu L, Zheng M, Zhang JY, Shi ZD, et al. 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 Endod* 2010;**109**:541–7. http://dx.doi.org/10.1016/j.tripleo.2009.11.007.
6. Manfredini D, Favero L, Del Giudice A, Masiero S, Stellini E, Guarda-Nardini L. Axis II psychosocial findings predict effectiveness of TMJ hyaluronic acid injections. *Int J Oral Maxillofac Surg* 2013;**42**:364–8. http://dx.doi.org/10.1016/j.ijom.2012.10.033.
7. Bjørnland T, Gjaerum AA, Møystad A. Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injection compared with injection with sodium hyaluronate. *J Oral Rehabil* 2007;**34**:583–9. http://dx.doi.org/10.1111/j.1365-2842.2007.01759.x.
8. Babadağ M, Sahin M, Görgün S. Pre-and posttreatment analysis of clinical symptoms of patients with temporomandibular disorders. *Quintessence Int* 2004;**35**:811–4.
9. Alpaslan GH, Alpaslan C. Efficacy of temporomandibular joint arthrocentesis with and without injection of sodium hyaluronate in treatment of internal derangements. *J Oral Maxillofac Surg* 2001;**59**:613–8. http://dx.doi.org/10.1053/joms.2001.23368.
10. Kopp S, Wenneberg B, Haraldson T, Carlsson GE. The short-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint pain and dysfunction. *J Oral Maxillofac Surg* 1985;**43**:429–35.
11. Morey-Mas MA, Caubet-Biayna J, Varela-Sende L, Iriarte-Ortabe JI. Sodium hyaluronate improves outcomes after arthroscopic lysis and lavage in patients with Wilkes stage III and IV disease. *J Oral Maxillofac Surg* 2010;**68**:1069–74. http://dx.doi.org/10.1016/j.joms.2009.09.039.
12. Manfredini D, Bonnini S, Arboretti R, Guarda-Nardini L. Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections. *Int J Oral Maxillofac Surg* 2009;**38**:827–34. http://dx.doi.org/10.1016/j.ijom.2009.03.715.
13. Oliveras-Moreno JM, Hernandez-Pacheco E, Oliveras-Quintana T, Infante-Cossio P, Gutierrez-Perez JL. Efficacy and safety of sodium hyaluronate in the treatment of Wilkes stage II disease. *J Oral Maxillofac Surg* 2008;**66**:2243–6. http://dx.doi.org/10.1016/j.joms.2008.01.067.
14. Guarda-Nardini L, Stifano M, Brombin C, Salmaso L, Manfredini D. A one-year case series of arthrocentesis with hyaluronic acid injections for temporomandibular joint osteoarthritis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**103**:e14–22. http://dx.doi.org/10.1016/j.tripleo.2006.12.021.
15. Sato S, Oguri S, Yamaguchi K, Kawamura H, Motegi K. Pumping injection of sodium hyaluronate for patients with non-reducing disc displacement of the temporomandibular joint: two year follow-up. *J Craniomaxillofac Surg* 2001;**29**:89–93. http://dx.doi.org/10.1054/jcms.2000.0189.
16. Kopp S, Carlsson GE, Haraldson T, Wenneberg B. Long-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint arthritis. *J Oral Maxillofac Surg* 1987;**45**:929–35.
17. Aktas I, Yalcin S, Sencer S. Prognostic indicators of the outcome of arthrocentesis with and without sodium hyaluronate injection for

the treatment of disc displacement without reduction: a magnetic resonance imaging study. *Int J Oral Maxillofac Surg* 2010;**39**:1080–5. http://dx.doi.org/10.1016/j.ijom.2010.07.001.

18. Guarda-Nardini L, Manfredini D, Ferronato G. Short-term effects of arthrocentesis plus viscosupplementation in the management of signs and symptoms of painful TMJ disc displacement with reduction. A pilot study. *Oral Maxillofac Surg* 2010;**14**:29–34. http://dx.doi.org/10.1007/s10006-009-0179-z.
19. Alpaslan C, Bilgihan A, Alpaslan GH, Güner B, Ozgür Yis M, Erbaş D. Effect of arthrocentesis and sodium hyaluronate injection on nitrite, nitrate, and thiobarbituric acid-reactive substance levels in the synovial fluid. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;**89**:686–90. http://dx.doi.org/10.1067/moe.2000.105518.
20. Guarda-Nardini L, Rossi A, Arboretti R, Bonnini S, Stellini E, Manfredini D. Single- or multiple-session viscosupplementation protocols for temporomandibular joint degenerative disorders: a randomized clinical trial. *J Oral Rehabil* 2015;**42**:521–8. http://dx.doi.org/10.1111/joor.12282.
21. Yeung RW, Chow RL, Samman N, Chiu K. Short-term therapeutic outcome of intra-articular high molecular weight hyaluronic acid injection for nonreducing disc displacement of the temporomandibular joint. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**102**:453–61. http://dx.doi.org/10.1016/j.tripleo.2005.09.018.
22. Triantaffilidou K, Venetis G, Bika O. Efficacy of hyaluronic acid injections in patients with osteoarthritis of the temporomandibular joint. A comparative study. *J Craniofac Surg* 2013;**24**:2006–9. http://dx.doi.org/10.1097/SCS.0b013e3182a30566.
23. Tuncel U. Repeated sodium hyaluronate injections following multiple arthrocenteses in the treatment of early stage reducing disc displacement of the temporomandibular joint: a preliminary report. *J Craniomaxillofac Surg* 2012;**40**:685–9. http://dx.doi.org/10.1016/j.jcms.2011.12.003.
24. Møystad A, Mork-Knutsen BB, Bjørnland T. Injection of sodium hyaluronate compared to a corticosteroid in the treatment of patients with temporomandibular joint osteoarthritis: a CT evaluation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008;**105**:e53–60. http://dx.doi.org/10.1016/j.tripleo.2007.08.024.
25. Bertolami CN, Gay T, Clark GT, Rendell J, Shetty V, Liu C, et al. Use of sodium hyaluronate in treating temporomandibular joint disorders: a randomized, double-blind, placebo-controlled clinical trial. *J Oral Maxillofac Surg* 1993;**51**:232–42.
26. Kopp S, Akerman S, Nilner M. Short-term effects of intra-articular sodium hyaluronate, glucocorticoid, and saline injections on rheumatoid arthritis of the temporomandibular joint. *J Craniomandib Disord* 1991;**5**:231–8.
27. Guarda-Nardini L, Manfredini D, Stifano M, Staffieri A, Marioni G. Intra-articular injection of hyaluronic acid for temporomandibular joint osteoarthritis in elderly patients. *Stomatologija* 2009;**11**:60–5.
28. Sato S, Kawamura H. Changes in condylar mobility and radiographic alterations after treatment in patients with non-reducing disc displacement of the temporomandibular joint. *Dentomaxillofac Radiol* 2006;**35**:289–94. http://dx.doi.org/10.1259/dmfr/92464710.
29. Guarda-Nardini L, Masiero S, Marioni G. Conservative treatment of temporomandibular joint osteoarthrosis: intra-articular injection of sodium hyaluronate. *J Oral Rehabil* 2005;**32**:729–34. http://dx.doi.org/10.1111/j.1365-2842.2005.01505.x.
30. Guarda-Nardini L, Tito R, Staffieri A, Beltrame A. Treatment of patients with arthrosis of the temporomandibular joint by infiltration of sodium hyaluronate: a preliminary study. *Eur Arch Otorhinolaryngol* 2002;**259**:279–84. http://dx.doi.org/10.1007/s00405-002-0456-z.
31. Manfredini D, Rancitelli D, Ferronato G, Guarda-Nardini L. Arthrocentesis with or without additional drugs in temporomandibular joint inflammatory-degenerative disease: comparison of six treatment protocols. *J Oral Rehabil* 2012;**39**:245–51. http://dx.doi.org/10.1111/j.1365-2842.2011.02265.x.
32. Guarda-Nardini L, Ferronato G, Manfredini D. Two-needle vs. single-needle technique for TMJ arthrocentesis plus hyaluronic acid injections: a comparative trial over a six-month follow up. *Int J Oral Maxillofac Surg* 2012;**41**:506–13. http://dx.doi.org/10.1016/j.ijom.2011.11.007.
33. Goiato MC, Pellizzer EP, Silva EV, Bonatto LR, Santos DM. Is the internal connection more efficient than external connection in mechanical, biological, and esthetical point of views? A systematic review. *Oral Maxillofac Surg* 2015;**19**:229–42. http://dx.doi.org/10.1007/s10006-015-0494-5.
34. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12. http://dx.doi.org/10.1016/0197-2456(95)00134-4.
35. Wilkes CH. Internal derangements of the temporomandibular joint. Pathological variations. *Arch Otolaryngol Head Neck Surg* 1989;**115**:469–77. http://dx.doi.org/10.1001/archotol.1989.01860280067019.
36. Food and Drug Administration (FDA). http://www.fda.gov [Accessibility verified December 26, 2015].

Address:
Marcelo Coelho Goiato
Department of Dental Materials and Prosthodontics
Aracatuba Dental School (UNESP)
José Bonifácio
1193
Vila Mendonça
CEP 16015-050
Aracatuba
Sao Paulo
Brazil
Tel: +55 18 36363287;
Fax: +55 18 36363245
E-mail: goiato@foa.unesp.br