Evaluation of Arthrocentesis with hyaluronic acid injections for management of temporomandibular disorders: a systematic review and case series

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Although arthrocentesis is an accepted safe treatment modality for the management of temporomandibular disorders (TMD) in symptomatic patients, the benefit of hyaluronic acid (HA) injections remains uncertain. The aim of this study was to evaluate whether intra-articular HA injections adjunctive to arthrocentesis can be more effective than other medications for the improvement of TMD associated symptoms. Additionally, the impact of HA injections on quality of life of TMD patients was assessed with SF-36® questionnaire in a cohort of patients. An electronic search of Medline, Scopus and Cochrane databases was performed up to March 2020. The following search terms were used: "arthrocentesis", "hyaluronic acid", "intra-articular injections", "visco-supplementation", "temporomandibular disorders". Prospective and retrospective studies that reported the application of HA injections compared to other intra-articular drugs for the treatment of temporomandibular disorders were included. Systematic or narrative reviews and pre-clinical studies were excluded. Additionally, a retrospective clinical study was performed for evaluation of changes in quality of life before and after arthrocentesis with HA injections. In the systematic review, the initial search yielded 1327 articles. After screening of the titles, abstracts, and full texts, 29 studies were selected (26 randomized studies, 2 controlled clinical trials, 1 retrospective report). In the clinical study, 12 patients were included. Intra-articular injections of HA and other medications together with arthrocentesis seemed to be beneficial for improvement of functional symptoms of TMD and pain. The case series also supported the efficacy of HA injections showing an improvement of quality of life of these patients. However, from literature review, it was impossible to identify an optimum drug or a protocol for predictably improving the pain and/or functional symptoms of temporomandibular problems, due to different etiologies, diversity of treatment modalities and conflicting results. In conclusion, there is no consensus in the literature that HA injections shows better results in comparison with other treatment modalities. According to the results of the present clinical study, HA injections with/without arthrocentesis seems to be beneficial in terms of clinical symptoms and quality of life of the TMD patients.

Arthrocentesis of the temporomandibular joint (TMJ) was first described by D. W. Nitzan (1) in 1991, as the lavage of the joint space without viewing by means of hydraulic pressure of the irrigating solution. It is considered as a safe, simple and minimally surgical approach for treatment of temporomandibular

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disorders (TMD) with pain that fail to respond to conventional conservative therapies (2-3). Arthrocentesis treatment can reduce pain by washing out inflammatory mediators through irrigation of the upper chamber of the TMJ. Additionally, mandibular movements can be improved by removing, reducing or eliminating intra-articular adhesions between the surface of the disc and the joint fossa (1, 4-10).

In cases of inflammatory TMDs, mediators of inflammation such as cytokines, can cause enzymatic degradation of the extracellular matrix in joint tissues. Additionally, alterations in intra-articular pressure and biochemical components of the synovial fluid can cause a failure of lubrication. As a result, symptoms such as pain, clicking and limitation of mandibular movements can be seen in such patients (5,11). The rationale for application of arthrocentesis procedures in TMD patients is based on the elimination of inflammatory cells within the joint and removing the negative pressure from the joint space (1, 4-5, 7, 9-10, 12).

As an adjunctive treatment modality to arthrocentesis lavage, administration of various agents, such as hyaluronic acid (HA), platelet rich plasma (PRP), corticosteroids and sodium hyaluronate were proposed by several authors to decrease intracapsular inflammation and to improve outcomes (13-16).

HA injections with or without arthrocentesis were reported in literature, as effective in decreasing pain produced by symptomatic joints (13, 17-23). Hyaluronic acid is a natural glycosaminoglycan produced by synovial cells that is naturally present in the synovial fluid (24-25). HA is considered an essential component of synovial fluid, participating in joint lubrication, and the degradation of HA is usually observed in cases of TMJ degeneration (24-25). HA helps relieving joint pain by decreasing levels of inflammatory mediators (26). The exact mechanism of action of HA is not clear, although the positive effects are thought to result from the increase in viscosity of the synovial fluid, restoration of nutrition, and reduction of inflammatory mediators (27-28).

TMDs are directly correlated with a decrease in quality of life of the patients (29). Pain is the most common TMD symptom and it often leads to various forms of psychological distress like anxiety, social impairment, reduced working capacity, social costs, physical disability (29). The most common used methods of assessment of TMDs are quality of life questionnaires such as, standard 36-Item Short Form Health Survey (SF-36©) and OHIP-14© questionnaires to monitor the disease (29). The SF-36© questionnaires are widely used in health research for evaluating Health-Related Quality of Life of the patients (30). SF-36© questionnaires can detect medical and social relevant differences in health status and changes in health status over time using a small number of statistically efficient dimensions (29-30).

The purpose of this study was to assess the efficacy and benefits of intra-articular injections of hyaluronic acid as an adjunct therapy with arthrocentesis for the improvement of symptoms associated with temporomandibular disorders. In the systematic review section of this work, the effect of HA injections on TMDs was compared to other medications and different protocols (including injections of other therapeutic substances/frequency of HA injections/ total number of HA injections/different dosages of HA injections/placebo) were assessed.

MATERIALS AND METHODS

Review question

The question addressed is: "In patients with temporomandibular disorders, are intra-articular injections of hyaluronic acid effective as an adjunctive therapy with arthrocentesis for the improvement of symptoms?"

Search strategy

An electronic search was performed on the following databases: MEDLINE using Pubmed search engine (http://www.ncbi.nlm.nih.gov/sites/pubmed), Scopus (http://www.scopus.com), Cochrane Central Register of Controlled Trials (CENTRAL). Grey literature databases were searched: HealthInfonet (http://www.healthinfonet.ecu.edu.au), Closing the Gap Clearinghouse (http://www.aihw.gov.au/closingthegap) and OpenGrey (http://www.opengrey.eu). The last search was performed on 12/03/2020. The search terms (medical subject heading (MESH) terms) included "TMJ arthrocentesis", "hyaluronic acid", "intra- articular injections", 'visco-supplementation', with 'temporomandibular disorder'. These terms were used alone or in combination using

Boolean operators AND, OR. The reference list of the retrieved literature reviews and of the included studies as well as related articles suggested by PubMed was also manually checked for possible additional eligible studies not identified by the electronic search.

Inclusion criteria

For being included, studies had to report clinical results of HA injections and comparison of HA with other treatment modalities and comparison of HA injection protocols for the management of temporomandibular disorders or arthritis (osteoarthritis or rheumatoid arthritis) or inflammatory joint disorders.

The search was limited to clinical studies involving human subjects. Restrictions were not placed regarding the language and the year of publication. Both prospective and retrospective studies were included. No limitation on sample size was placed. The studies had to provide details on the type and dosage of intra-articular injections, the indication for TMD therapy, and the duration of the treatment. They also had to provide clear definitions of the clinical outcomes for considering success or failure of the procedure.

Publications that didn't meet the above inclusion criteria and those that were not dealing with original clinical cases (e.g., reviews, technical reports, expert opinions) were excluded. Multiple publications of the same pool of patients were also excluded. When papers from the same group of authors, with very similar databases of patients, materials, methods and outcomes were identified, the authors were contacted for clarifying if the pool of patients was indeed the same. In case of multiple publications relative to consecutive phases of the same study or to enlargements of the original sample size, only the most recent data (those with the longer follow-up and the larger sample size) were considered.

Selection of the studies

The articles retrieved through the electronic and manually search was initially evaluated for relevance based on their titles and abstracts by two reviewers independently (MDF and FG). The concordance between reviewers was assessed by means of the Cohen's Kappa coefficient. In case of disagreement, a joint decision was taken by discussion. The same two reviewers assessed independently all the full text of eligible studies, in order to check if they met all inclusion criteria. Cases of disagreement were discussed together until agreement was reached. For articles excluded at this stage, the reason for exclusion was recorded. The identified suitable articles were subject to data extraction and analysis, and were also assessed for their methodological quality, and for their suitability to inclusion in a meta-analysis.

Data analysis

Data were extracted by two reviewers independently (MDF and FG), using an *ad hoc* data collection form. Cases of disagreement were subject to joint evaluation until an agreement was reached.

Studies were divided into two groups for evaluation (TMID group and Arthritis group). TMID group mainly consisted of temporomandibular internal derangement publications, other than studies that reported outcomes in arthritis patients. Arthritis group consisted of publications that evaluated TMJ osteoarthritis and osteoarthrosis.

The main variables extracted from each study included: study design, sample size, patients' gender and age, type and dosage of drug injected, reason for treatment, duration of treatment, and follow-up period.

Quality assessment and risk-of-bias assessment

The following methodological parameters were recorded: for randomized studies only, the random sequence generation method and allocation concealment; for all studies: clear definition of inclusion and exclusion criteria, clear definition of outcomes assessment and success criteria; completeness of the outcome data reported, recall rate (it was assumed adequate if dropout <20%), explanation for dropouts/withdrawal (when applicable), sample size (it was assumed adequate if >20 patients treated), and length of follow-up period (it was assumed adequate if the mean duration was ≥6 months).

The methodological quality of the selected studies was evaluated independently and in duplicate by two reviewers (MDF and FG) according to the above methodological parameters. All the criteria were assessed as adequate, unclear, or inadequate. The authors of the included studies were contacted for providing clarifications or missing information as needed. Studies were considered at low risk of bias if more than 2/3 of the parameters were judged as adequate.

Clinical case series protocol

The clinical case series of this present study was

conducted between 15/05/2019 and 15/03/2020 in the Department of Oral Science and Maxillofacial surgery, University of Milan, Granda Ospedale Maggiore Policlinico, Milan, Italy. The study was in compliance with the principles laid down in the Declaration of Helsinki on medical protocol and ethics. A signed informed consent form was obtained from all subjects for the arthrocentesis procedure.

This retrospective clinical study included 12 TMD patients who received hyaluronic acid (HA) injections after arthrocentesis. The diagnosis of TMJ disc disorder was based on anamnesis, clinical and radiologic examination. The clinical examination was done including the evaluation of the maximal mouth opening which was measured by a caliper as the distance between the incisal edges of the upper and lower incisors. The range of the lateral and protrusive mandibular movements were additionally checked.

Inclusion criteria

Inclusion criteria was set as patients with recent history of arthralgia associated with one of the following:

- acute and chronic closed lock of the TMJ in internal derangement;
- disc adhesions, either next to the fossa and/or the upper aspect of the articular tubercle, with mouth opening restrictions;
- patients with painful mouth opening and/or closing with joint noises;
- pain with dislocation of the disc without reduction if patient did not get better following the use of distraction bite for 40-50 days;
- patients who are not responding to nonsurgical treatment;
- limited mouth opening of less than 30 mm;
- impeded lateral movement towards unaffected side;
- deviation towards affected side;
- patients with internal TMDs not responding to conservative clinical treatment;
- at least 18 years of age;
- ability to give informed consent;
- arthralgia, disc displacement or degenerative joint.

Exclusion criteria:

- The patients who had invasive procedures recently;
- an inflammatory abscess or cellulitis at the site of the needle insertion;
- bacteremia;
- adjacent osteomyelitis;
- coagulopathy;
- malignant tumor;
- history of bony or fibrous adhesion;
- condylar fractures;
- patients with psychological problems;
- cervical or myofascial pain dysfunction as the sole or primary source of pain;
- systemic arthropathy (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis);
- fibromyalgia;
- nonsteroidal anti-inflammatory drug use within the previous 48 hours;
- declaration of allergy to any of the medications;
- limited mouth opening secondary to extra- articular pathology;
- pregnancy or breast-feeding.

All patients underwent arthrocentesis followed by an intra-articular injection of HA. A SF-36 questionnaire was obtained from all subjects before interventions. After the procedure the patients were instructed to apply jaw exercises over the next 2 weeks and to resume a soft-mild diet. All the patients were prescribed with post-operative analgesics with no antibiotics administered pre- or post-operatively.

A standardized follow-up protocol, including clinical examinations and a second SF-36© questionnaire was planned as 15 days.

Surgical procedures

Arthrocentesis procedures were performed under local or general anesthesia, or intravenous conscious sedation, depending on the patient variables. After proper preparation of the target site and disinfecting the preauricular area with 10% povidone iodine solution. External auditory was protected from accumulation of blood and fluid using medical cotton pledget. The auriculotemporal nerve block was given with local anesthetic (4% articaine with 1:100,000 adrenalin), and the areas of joint penetration was infiltrated. Anesthetic solution was also injected and aspirated into the TMJ area to anesthetize and wash out the space with pumping felt. At this point, 5 mL syringe containing 4 mL of local anesthetic and a 22-gauge needle were used for the joint injection.

The classical technique of arthrocentesis was used in this study, which utilizes the insertion of two needles into

the upper joint compartment, one for injecting and the other for aspirating the solution, permitting more effective lavage of the joint as described by Nitzan *et al.* in 1991 (1).

The landmarks for the insertion of needles were located by using one of the following methods: 1- a line was drawn from the middle of the tragus to the outer canthus. The first posterior needle's entrance point was located along the canthotragal line, 10mm from the middle of the tragus and 2mm below the line. The second needle entrance point was 10mm farther along the line and 10mm below the first needle, or 2- The patient is asked to open the mouth and deviate it to the opposite side for distracting the condyle from the glenoid fossa, in order to increase the joint space. The articular fossa and eminence for entering TMJ joint capsule was indicated for first needle entrance. This was the approximate area of the maximum concavity of the glenoid fossa. This first entrance point was for pumping the saline into the upper compartment to increase the hydraulic pressure within the joint. 18-gauge needles were utilized for lavage.

In brief, the first needle was inserted (with the patient's mouth open) into the superior joint space in the most posterior point directing upward, forward, and inward to a depth of about 20–25 mm, after the tip of the needle has come into contact with the posterior wall of the articular eminence, behind the condyle and beneath the zygoma. This was followed by administration of irrigating physiological saline solution through the first needle with the aim of distending the superior joint space.

The second needle was introduced in front of the first needle and about 20 mm in front of tragus and 10 mm below. This point is site of the eminence of TMJ and it is for allowing the outflow of the solution from the joint cavity. Following the insertion of two needles, physiological saline solution was connected to one of the needles with sufficient pressure to assure the free flow of 500ml solution.

On termination of the procedure an ampule containing 1 mL of HA (Hyalgan; Fidia Pharma USA, Parsippany, NJ, USA; 10 mg/mL) was connected to the needle and injected into the joint space, which was followed by the removal of needle. The patient was then instructed to move his/ her mandible with or without manipulation by the operator. Postoperative analgesics with muscle relaxants for 1 week were prescribed. Follow up of the patient was done after 2 weeks.

Data collection and outcome evaluation

Data collection included demographics, medical history, magnetic resonance imaging findings, and SF-36® Questionnaire forms. A brief questionnaire SF-36® was given to all patients before the procedure and after 15 days. The SF-36® is a validated oral health QoL tool that is used to record specific domains. The primary outcome variables of the clinical part of this study based on SF-36® Quality of life Questionnaire form taken before operation and at the follow-up visits.

The success rate of arthrocentesis was evaluated with SF-36® Questionnaire comparing before and after treatment. Statistical analyses were done between these two variables using multiple statistical tests, with a P value less than 0 .05 considered significant.

Statistical analysis

It was planned to undertake a meta-analysis of the studies included in the review only in case of sufficient homogeneity in the clinical protocols, populations, outcome measures, type of comparison, follow-up on at least three different studies. Otherwise, qualitative evaluation of the included studies was to be performed by summarizing the cases treated with each approach and the main outcomes. Risk of bias of the included studies was assessed by using the criteria recommended by the Cochrane Collaboration (31).

Descriptive statistics of the case series was done using mean values and standard deviation (SD) for quantitative variables normally distributed. Normality of distributions was assessed using the d'Agostino and Pearson omnibus test. Each subscale of the preoperative and postoperative SF-36® questionnaires was compared by using the paired Student's t-test. For each subscale, all the items were averaged, so as to have a single value. $p=0.05$ was considered as the significance threshold. Statistical analysis was performed using GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA, USA).

RESULTS

Study selection for the review

The initial search resulted with 1465 articles in total (Fig. 1). After duplicate removal, 1327 titles and abstracts of the studies were evaluated, and the articles that fulfilled the inclusion criteria were included. Twenty-nine articles were found eligible and were assessed according to the Risk of

Bias criteria listed on Table I. Twenty-six RCTs were finally included in this review. However, after a careful assessment of protocols, study populations, patient characteristics, and outcome measures, it was decided not to undertake any meta-analysis because of the wide clinical diversity between the studies. Only a qualitative evaluation of the selected studies is presented.

Characteristics of the included studies

The reports included in this review had a total of 1356 participants for both groups (697 TMD, 659 osteoarthritis). Female patients were the majority, though some of the studies gave no information regarding gender of the participants. Mean age of the population was 40.6 (SD 11.7) years (TMD group mean age- 28 (SD 1.4) years old and osteoarthritis group mean age- 49 (SD 2.6) years old). Follow up periods ranged between 1.5 to 24 months with a mean value of 8.7 (SD 9.7) months.

The main characteristics of the studies such as author and year of publication, study design, sample size, mean age of the population, intervention, diagnosis for TMD therapy, follow up duration of the treatment and risk of bias are listed on Table II for TMID groups and on Table III for arthritis groups. The study groups of the same studies and treatment outcomes are listed on Table IV for TMID groups and on Table V for arthritis groups. Regarding the clinical diagnosis for HA injections, 13 studies were found eligible for TMD group (after discussion among authors FG and MDF, Bouloux et al., 2017a-b (32-33) and Møystad et al., 2008a-b (34-35) were reconsidered as 1 article instead of 2, because both articles by the same group included the same study population), and 16 articles were found eligible for osteoarthritis group. One of the studies in TMJ osteoarthritis group included osteoarthrosis or an inflammatory joint disorder (21). Detailed and additional information for all of these studies is listed in Table II-V.

Study characteristics for SF-36© clinical evaluation

A total of 12 patients (10 Female, 2 Male) were included in this study. The mean age of the study population at the time of arthrocentesis was 45.9

Table I. *Risk of Bias of the selected 29 studies.*

AUTHOR /year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Completeness of the outcome data reported	Selective Reporting	Comparability of control and treatment groups at entry	Clear definition of inclusion and exclusion criteria	Clear definition of outcomes assessment and success criteria	Recall follow-up (<3monthH, 3-6 month M,> 12 month L)	Sample size(<20H,20-50M, >50L)
Gencer et al.[36] 2014	L	M	L	L	M	L	M	M	M	M	L
Emes et al.[39] 2014	H	M	H	H	M	M	M	M	M	M	H
Manfredini et al.[27] 2012	H	H	H	L	H	L	M	M	M	H	L
Bjørnland et al.[38] 2007	M	L	L	L	M	L	M	M	M	H	M
Kopp et al.[22] 1991	L	L	L	L	M	M	M	M	M	M	M
Kopp et al.[21] 1987	L	L	L	L	M	L	M	M	M	M	M
Kopp et al.[20] 1985	L	L	L	L	M	L	M	M	M	M	M
Møystad et al.[34-35] 2008	L	L	L	L	M	L	M	M	M	M	M
Ozdamar et al.[40] 2017	L	L	L	L	H	L	M	M	M	L	M
Bouloux et al.[32-33] 2017a-b	L	L	L	L	H	L	M	M	M	M	L
Alpaslan et al.[12] 2001	M	H	H	H	M	L	M	M	M	M	M
Bertolami et al.[41] 1993	L	L	L	L	L	L	M	M	M	M	L
Giraddi et al.[37] 2015	M	H	H	H	M	L	M	M	M	M	H
Hepguler et al.[42] 2002	L	L	L	L	L	L	M	M	M	M	M
Korkmaz et al.[26] 2016	L	L	H	L	L	L	M	M	M	M	L
Sharma et al.[44] 2013	M	H	H	H	M	L	M	M	M	M	M
Guarda-Nardini et al.[45] 2004	M	H	H	H	M	L	M	M	M	M	M
Guarda-Nardini et al.[46] 2005	M	H	H	M	M	M	M	M	M	M	L
Guarda-Nardini et al.[47] 2012	M	M	L	L	L	L	M	M	M	M	M
Guarda-Nardini et al.[49] 2015	M	H	H	L	L	L	M	M	M	M	M
Guarda-Nardini et al.[48] 2014	H	H	H	H	H	M	M	M	M	M	L
Hegab et al.[55] 2015	M	H	H	H	M	L	M	M	M	L	L
Tang et al.[50] 2010	M	M	L	L	M	L	M	M	M	H	M
Yilmaz et al.[43] 2019	M	M	M	M	M	M	M	M	M	M	L
Kutuk et al.[54] 2019	M	M	M	M	M	M	M	M	M	M	L
Comert-Kilic et al.[56] 2016	M	M	M	M	M	M	M	M	M	L	M
Fernandez-Ferro et al.[53] 2017	M	M	M	M	M	M	M	M	M	L	L
Berstrand et al.[51] 2019	M	M	M	M	L	M	M	M	M	L	M
Oliveras-Moreno et al.[52] 2008	M	H	H	H	L	L	M	M	M	M	M

***H**=high risk of bias; **M**=medium risk of bias; **L**=low risk of bias.*

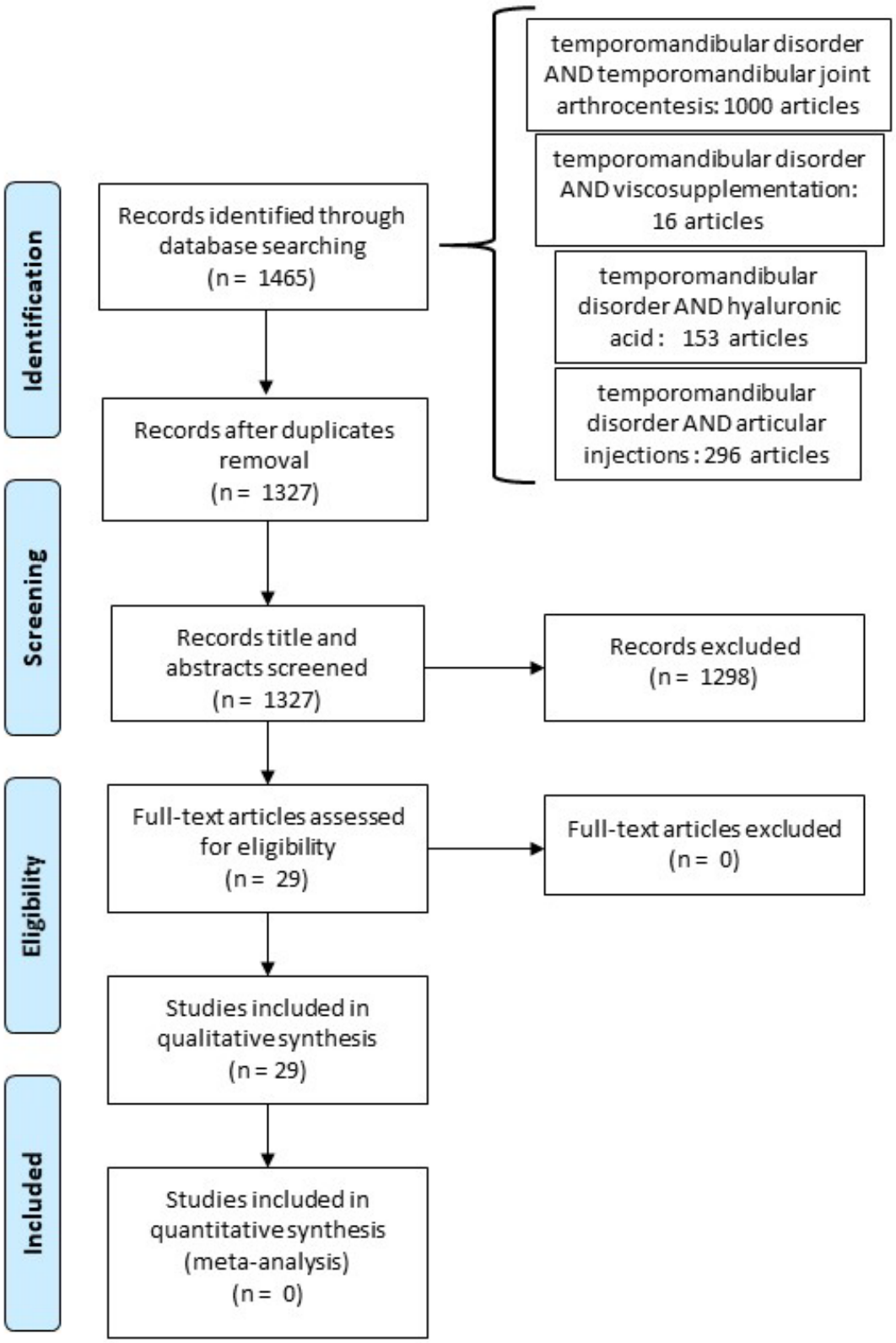

Fig. 1. *Flowchart of the articles retrieved with the electronic search and subsequently screened.*

(SD 18.17) years, ranging from 20 to 79 years. All patients were diagnosed for temporomandibular disorders. Five patients had a history of occlusal appliance therapy. The SF-36© results from this clinical study are listed in Table VI. Items related to patients' Bodily pain and General health showed a significant improvement after treatment, while other parameters did not significantly change.

DISCUSSION

Arthrocentesis consists of the lavage of the upper TMJ space with a lavage fluid and can be performed under local anesthesia. Following arthrocentesis irrigation, administration of various agents, such as HA, PRP, steroids or sodium hyaluronate were proposed by several authors to decrease intracapsular

Table II. *The main characteristics of the 13 studies for TMID groups.*

AUTHOR /year	Study design	Sample size	Mean Age	Intervention	Diagnosis	Follow up months	ROB
Gencer et al.[36] 2014	DB RCT	100	42.5	efficacy of HA, corticosteroid and NSAID injections on pain relief	Wilkes stage IV and V disease	1.5	M
Bouloux et al.[32-33] 2017a-b	DB RCT	51	45.23	efficacy of HA and corticosteroid injections on various clinical symptoms	internal derangements of the TMJ	3	L
Giraddi et al.[37] 2015	RCT	14	30.42	comparison betamethasone and sodium hyaluronate (combination) with betamethasone (CO) alone after arthrocentesis using single puncture technique into the upper joint space	TMJ internal derangement	6	M
Ozdamar et al.[40] 2017	DB RCT	24	26.87	effects of arthrocentesis procedure, either alone or in combination with hyaluronic acid (HA) injection on the prognosis	Wilkes stage III and over	6	L
Alpaslan et al.[12] 2001	RCT	31	27	efficacy of arthrocentesis with and without injection of sodium hyaluronate	internal derangements of the TMJ	24	M
Bertolami et al.[41] 1993	RCT	121	38.35	sodium hyaluronate in treating temporomandibular joint disorders	internal derangements of the TMJ	6	L
Hepguler et al.[42] 2002	DB RCT	38	31.52	the efficacy of intra-articular hyaluronic acid (HA) treatment	TMJ disc displacement with reduction.	6	L
Korkmaz et al.[26] 2016	Pros CC	51	31.33	the efficacy of intra-articular hyaluronic acid (HA) treatment	TMJ disc displacement with reduction.	6	L
Sharma et al.[44] 2013	RCT	20	15-25	arthrocentesis alone and arthrocentesis with sodium hyaluronate	TMJ disc displacement with reduction.	6	M
Yilmaz et al.[43] 2019	RCT	90	33.9	effectiveness of hyaluronic acid (HA) injection	TMDs	6	M
Emes et al. [39] 2014	Retro	16	30.8	efficacy of arthrocentesis associated with HA and NSAID injections on various clinical symptoms	Wilkes stage I to V disease	3	M
Fernandez-Ferro et al.[53] 2017	RCT	100	35.5	HA vs PRP	TMDs	18	M
Oliveras- Moreno et al. [52] 2008	RCT	41	29	HA vs Methocarbamol + Paracetamol tablets	Wilkes stage II	3	M

***RCT**= Randomized controlled trial; **DB**= Double blind; **Pros**= Prospective; **Retro**= Retrospective; **CC**=Case-control; **TMJ**=Temporomandibular joint; **TMD**= Temporomandibular disorder; **HA**= Hyaluronic acid; **PRP**= Platelet rich plasma; **NSAID**= Nonsteroidal anti-inflammatory drugs; **CS**= Corticosteroids; **ROB**= Risk of bias; **H**=High risk of bias; **M**=Medium risk of bias; **L**=Low risk of bias.*

Table III. *The main characteristics of the 16 studies for TMJ arthritis groups.*

AUTHOR /year	Study design	Sample size	Age	Intervention	Follow up months	ROB
Manfredini et al.[27] 2012	DB RCT	60	50.1	Efficacy of arthrocentesis with or without other drugs (Cortison)	3	M
Møystad et al.[34-35] 2008	DB RCT	36	49.9	Bone changes after HA and corticosteroid injections	6	M
Bjørnland et al.[38] 2007	DB RCT	40	51.7	Efficacy of HA and corticosteroid injections	6	M
Kopp et al.[22] 1991	DB RCT	41	60.5	Efficacy of HA and saline injections	1	M
Kopp et al.[21] 1987	DB RCT	24	50	Efficacy of HA and corticosteroid injections on various clinical symptoms	24	M
Kopp et al.[20] 1985	DB RCT	33	46	Efficacy of HA and corticosteroid injections	1.5	M
Guarda-Nardini et al.[45] 2004	RCT	27	53.9	HA on clinical features	3	M
Guarda-Nardini et al.[46] 2005	RCT*	60	49.2	sodium hyaluronate effect	6	M
Guarda-Nardini et al.[47] 2012	RCT	40	50.3	comparison of low– or medium–molecular weight HA after arthrocentesis	3	M
Guarda-Nardini et al.[49] 2015	RCT	30	45-65	HA different protocols comparison	6	M
Guarda-Nardini et al.[48] 2014	CC	50	40-60	effectiveness of viscosupplementation with HA	6	M-H
Hegab et al.[55] 2015	RCT	50	38.6	HA vs PRP	12	M
Tang et al.[50] 2010	RCT	40	42.6	HA effect	1.25	M
Kutuk et al.[54] 2019	RCT	60	35.6	comparison of CS, HA, and PRP	3	M
Comert-Kilic et al.[56] 2016	RCT	31	30.48	HA vs PRP	12	M
Berstrand et al.[51] 2019	RCT	37	51	Arterocentesis with versus without HA	47	M

RCT*=Randomized controlled trial;* ***DB****=Double blind;* ***CC****=Case-control;* ***TMJ****=Temporomandibular joint;* ***HA****= Hyaluronic acid;* ***PRP****= Platelet rich plasma;* ***NSAID****= Nonsteroidal anti-inflammatory drugs;* ***CS****= Corticosteroids;* ***ROB****= Risk of bias;* ***H****=high risk of bias;* ***M****=medium risk of bias;* ***L****=low risk of bias. *except control group.*

inflammation and to increase the effects (13-15).

In literature, several authors compared HA injections with injections of different other substances and with different protocols. According to the results of the present systematic review, concerning the types of treatment performed, 3 study groups compared the use of HA with CO (corticosteroids) in TMID group (Table II, IV) (32-33,35-37). Gencer et al. (36) reported HA injections and Giraddi et al. (37) (HA+ CO versus corticosteroid) reported HA injection in combination with CO as more efficient. However, another study group found no significant difference among groups (32-33). In arthritis group, 6 studies compared the use of HA with CO (Table III, V) (20,22,27,34-35,38). All these studies found beneficial results for HA and CO injections, while two of the study groups reported a significant difference in pain reduction for HA groups when compared to control groups (34-35,38).

A study by Emes et al. (39) evaluated NSAID and HA injections and reported no significant benefits for either technique (39). There were 7 studies in TMID group comparing HA injections with saline /placebo/ occlusal appliance (12, 26,40-44). Five of these articles reported better results for HA

Table IV. *The study groups and treatment outcomes of the studies for TMID groups.*

AUTHOR /year	Study groups (G)	Result
Gencer et al.[36] 2014	Group 1: 0.5-ml saline, Group 2: 0.5-ml HA, Group 3: 0.5-ml CS, Group 4: 0.5-ml NSAID	0.5-ml HA injection significantly more effective in reducing pain
Bouloux et al.[32-33] 2017a-b	Arthrocentesis+ HA Group 1 mL (10 mg/l, 500-700 kDa) Cortison group: 1 mL of betamethasone (6 mg/mL), Placebo group: 1 mL of Ringer's lactate	All groups within-group improvements in JFLS score and MIO. No significant difference among the groups in pain, quality of life, functional limitation.
Giraddi et al.[37] 2015	HA+CS group:0.5 mL HA and 0.5 mL of betamethasone). CS group: 1 mL of betamethasone.	The HA + CO group showed a significant improvement in pain reduction, increase of the mouth opening and reduction of joint noises.
Ozdamar et al.[40] 2017	2 mL of sodium hyaluronate (Orthovisc"‡ 30 mg/2 mL Intra- articular Syringe) following arthrocentesis as HA group, & 2 mL of saline solution 0.9% as SS group	Arthrocentesis procedure improves both pain VAS and MIO but no significant difference between the groups.
Alpaslan et al.[12]2001	HA group 1 mL HA (15 mg/ mL, 1000 kDa) Control (with no HA)	There was a significant difference in improvement of the mouth opening, lateral movements, pain and mandibular function in the HA group.
Bertolami et al.[41] 1993	HA group (41. 1% sodium hyaluronate in physiologic saline Control group: physiologic saline.	Significant improvements in TMD patients in HA groups for the clinical and anamnestic index of dysfunction. Osteoarthritis: no statistical difference in any variable.
Hepguler et al.[42] 2002	HA group (n=19) (Orthovisc), placebo group (n=19)	HA group all measurements improved significantly, in the placebo group no change
Korkmaz et al.[26] 2016	Group 1: participants who refused treatment, Group 2: 1 injection of 1 mL HA (15 mg/mL -> 1000 kDa) (Orthovisc). Group 3: double injections of 1 mL HA at 1-month interval (Orthovisc). Group 4: occlusal appliance for 6 months.	HA groups had significant improvement in pain, mouth opening, and QoL compared to the occlusal appliance group. No difference between the two HA groups.
Sharma et al.[44] 2013	Group HA: 2 arthrocenteses plus 1 mL HA (20 mg/mL). Control group: 2 arthrocentesis treatments, 1 week apart.	No significant difference was found between groups.
Yilmaz et al.[43] 2019	group I (DDwR) and group II (DDwoR). Sub-groups were made depending on allocated treatment: group Ia (arthrocentesis plus HA), group Ib (single HA), group Ic (control), group IIa (arthrocentesis plus HA), group IIb (single HA), and group IIc (control).	At the 6-month follow- up, improvement in all parameters, except for TMJ sounds in all treatment groups, with no improvements in control (no HA) groups. Notably, arthrocentesis +HA superior improvement chewing efficiency and QoL compared to HA without arthocentesis. Both procedures improved the symptoms but arthrocentesis plus HA injection seemed superior.
Emes et al.[39] 2014	G1: arthrocentesis + 1.0 ml HA injection G2: NSAID injection (10 TMJs)	no significant benefits for either technique
Fernandez-Ferro et al.[53] 2017	Group A received an injection of PRGF, and Group B received an injection of HA.	Better results were observed in the group treated with PRGF, with a significant reduction in pain at 18 months, compared with HA treatment. For mouth opening, an increase in both groups, but no significant difference.
Oliveras-Moreno et al.[52] 2008	1 injection of 1 mL HA 1% (Ostenil mini) vs Control Group: 380 mg methocarbamol plus 300 mg paracetamol: 2 tablets every 6 hour for 4 weeks.	There was no significant difference between groups in resting pain. HA group showed significant improvement in pain during mouth opening, joint function and chewing pain, compared to the control group

TMD: *Temporomandibular disorder;* ***HA:*** *Hyaluronic acid;* ***PRP:*** *Platelet rich plasma;* ***PRGF:*** *Platelet rich in growth factors;* ***NSAID:*** *Nonsteroidal anti-inflammatory drugs;* ***CS:*** *Corticosteroids;* ***VAS:*** *Visual analog score for pain;* ***MIO:*** *Maximum mouth opening;* ***DDwR:*** *Disc displacement with reduction;* ***DDwoR****= Disc displacement without reduction.*

injection groups (12,26,41-43), while two reported no difference among the groups evaluated (40,44). In osteoarthritis group, seven studies evaluated HA injections versus saline / placebo / occlusal appliance / with or without arthrocentesis / different number of injections and periods (45-51). All these studies concluded on positive results in clinical parameters. Additionally, Tang et al. (50) and Guarda-Nardini et al. (49) reported significant positive result (significant result for five applications of arthrocentesis plus HA) in pain for HA groups (49-50). One study compared HA injections with 380 mg methocarbamol plus 300

Table V. *The study groups and treatment outcomes of the studies for TMJ arthritis groups.*

AUTHOR /year	Study groups (G)	Result
Manfredini et al.[27] 2012	G1: 2-needle arthrocentesis, G2: 2-needle arthrocentesis + 1.0 ml corticosteroid injection, G3: 2-needle arthrocentesis + 1.0 ml low MW HA injection, G4: 2-needle arthrocentesis + 1.0 ml high MW HA injection, G5: 5 weekly 2-needle arthrocentesis + 1.0 ml low MW HA injection, G6: 5 weekly 1-needle arthrocentesis + 1.0 ml low MW HA injection.	Improvement in clinical symptoms in all groups
Møystad et al.[34-35] 2008	G1: two HA injections (Hylan G-F 20 (Synvisc®) (8 mg/mLe 6000 kDa) (14 days apart), G2: two corticosteroid injections (betamethasone (5.7 mg/mL) (Celestone Chronodose®) (14 days apart)	Significant difference in pain reduction in the HA group, when compared to the CS group. No statistical difference between groups
Bjørnland et al.[38] 2007	G1: two 0.7–1.0-ml HA injections (Hylan G-F 20 (Synvisc®) (8 mg/mLe 6000 kDa) (14 days apart), G2: two 0.7–1.0-ml corticosteroid injections (betamethasone (5.7 mg/mL) (Celestone Chronodose®) (14 days apart)	Significant difference in pain reduction in HA group, compared to CS group. No significant difference between groups regarding mandibular movements and bone changes.
Kopp et al.[22] 1991	G1: two 0.7-ml saline injections (14 days apart), G2: two 0.7-ml HA injections (14 days apart), G3: two 0.7-ml corticosteroid injections (14 days apart)	In Groups 3 and 2 improvement in clinical symptoms
Kopp et al.[21] 1987	G1: two 0.5-ml HA injections (14 days apart), G2: two 0.5-ml corticosteroid injections (14 days apart)	Groups 1 and 2- improvement in clinical symptoms
Kopp et al.[20] 1985	G1: two 0.5-ml HA injections (14 days apart), G2: two 0.5-ml corticosteroid injections (14 days apart)	in Groups 1 and 2 improvement in clinical symptoms
Guarda-Nardini et al.[45] 2004	HA group: 5 Arthrocentesis +2 mL HA, Control: 3 Arthrocentesis with Ringer's solution, 1 week apart	The HA group showed significant improvement in pain, functional limitation and masticatory efficiency. In control group, no significant difference between any variable.
Guarda-Nardini et al.[46] 2005	Group A: 5 arthrocentesis plus HA (20 mg/2 mL, 500 e700,000-Hyalgan®). Group B: occlusal appliance for 6 months. Control: patients who refused therapy	No significant difference was observed between groups A and B. Group A showed better treatment toleration compared to group B with a significant difference
Guarda-Nardini et al.[47] 2012	Five sessions of arthrocentesis with a single needle: Group A: 1 mL HA (16mg/2mL,1200kDa- Synovial®). Group B: 1 mL HA (20 mg/mL, 600 KDa - Hyalgan®).	The groups showed similar positive results with no significant difference in any variable.
Guarda-Nardini et al.[49] 2015	Group A: 1 arthrocentesis + injection of HA (7000 kDa Durolane SJ®). Group B (10): 1 arthrocentesis + HA (1200 kDae16 mg/ 2 mL, Synovial®). Group C: 5 arthrocentesis +HA (Synovial®).	Group C (5 arthrocentesis and HA) showed significant improvement in pain when evaluating the overall effect of treatment compared to the other groups.
Guarda-Nardini et al.[48] 2014	G1: HA in patients with effusion, G2: HA in patients without effusion	both groups showed significant improvements in all parameters
Hegab et al.[55] 2015	HA Group: 5 injections of 1 mL HA (1,500 e2,500 kDa; Sofast) at 1-week intervals. Control Group: 5 saline injections at 1-week intervals.	The HA group showed significant improvement in pain compared to the control group.
Tang et al.[50] 2010	A-group: arthrocentesis with lavage alone, AS-group: arthrocentesis combined with hyaluronic acid treatment	Both methods resulted in significant long-term improvements in pain and jaw function (no difference among groups). Joint sounds did not significantly improve within groups.
Kutuk et al.[54] 2019	Group 1 (PRP), Group 2 (HA), and Group 3 (CS)	intra-articular PRP injections decreased TMJ palpation pain more effectively when compared to HA and CS groups.
Comert-Kilic et al.[56] 2016	PRP group and HA group	No statistically significant difference was observed between the groups in VAS parameters or MIO measurements. Both treatment techniques resulted in significant improvements in clinical parameters
Berstrand et al.[51] 2019	3 arthrocentesis, followed by:PRP Group: 1 mL of autologous PRP. Group HA: 1 mL of HA (20 mg/2 mL, 500e730 kDa, Suplasyn®), 1 week apart.	The HA group showed significant improvement in mouth opening and pain over the PRP group after 1, 3 and 6 months but after 12 months the PRP group showed better results.

TMJ: *Temporomandibular joint;* ***HA:*** *Hyaluronic acid;* ***PRP:*** *Platelet rich plasma;* ***PRGF:*** *Platelet rich in growth factors;* ***NSAID:*** *Nonsteroidal anti-inflammatory drugs;* ***CS:*** *Corticosteroids;* ***MW:*** *Molecular weight;* ***VAS:*** *Visual analog score for pain;* ***MIO:*** *Maximum mouth opening.*

mg paracetamol tablets. As a result, they reported significant improvement in pain during mouth opening, joint function and chewing pain, in HA group compared to the control group (52).

PRP (Platelet-rich plasma) and PRGF (Platelet rich in growth factor) are products of autologous blood containing many growth factors with potential healing properties on new bone and cartilage. Various authors compared PRP/PRGF and hyaluronic acid injections. There were conflicting results: two studies found better results for PRP/PRGF (53-54) while another reported better results for HA (55),

Table VI. *SF 36® results and significance of the comparison between pre- and post-intervention evaluation done using paired Student's t-test.*

SF-36© Question groups	Pre %, mean (SD)	Post %, mean (SD)	p-value
HT (Health transition) (1 question)	45.8(23.4)	47.9(24.9)	0.34
PF (Physical functioning) (10 questions)	70.4(31.4)	73.8(32.3)	0.33
RP (Role limitations due to physical health) (4 questions)	75(36.9)	56.2(50.1)	0.08
RE (Role limitations due to emotional problems) (3 questions)	69.4(36.1)	58.3(42.9)	0.49
VT (Energy/ fatigue) (4 questions)	50.4(21.0)	52.5(19.5)	0.94
MH (Emotional well-being) (5 questions)	71.1(18.3)	72(15.1)	0.84
SF (Social functioning) (2 questions)	69.8(25.8)	66.7(23.4)	0.57
BP (Bodily Pain) (2 questions)	55.2(27.2)	71.9(23.7)	0.004*
GH (General health) (5 questions)	59.0(23.7)	51.7(23.8)	0.04*

**Statistically significant difference; SD=Standard Deviation.*

and one study reported no significant difference among groups (56).

According to the results of this review, there was no consensus in the studies showing either HA injections or intra-articular use of other medications are better for the treatment of TMD. The SF-36© questionnaire results from this study show an improvement in the quality of life of the patients following arthrocentesis with HA injections (Table VI). In particular, pain and general health (which are among the most relevant for patients' comfort) improved significantly, while other parameters did not show a significant change respect to pre-operative assessment.

Due to the great variety of applications and conflicting results among them, the results of this review must be cautiously interpreted. However, according to clinical application outcomes and results from the literature, HA injections with/ without arthrocentesis can be suggestive of possible benefits for management of TMD and osteoarthritis, especially in terms of pain and mouth opening. HA injections seem to be advantageous in terms of an increase in the quality of life of such patients. To confirm these results, further well-designed randomized controlled clinical studies with large sample size are necessary to identify an optimum drug or a protocol for intra-articular injections in the management of TMD symptoms.

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