

The use of sodium hyaluronate in the treatment of temporomandibular joint disorders*

O uso do hialuronato de sódio no tratamento das disfunções temporomandibulares articulares

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ABSTRACT

BACKGROUND AND OBJECTIVES: Temporomandibular disorder is a collective term involving clinical masticatory muscles, temporomandibular joints and/or associated structures changes. This study aimed at reviewing, using major databases, the effectiveness and safety of sodium hyaluronate in the treatment of temporomandibular joint disorders, aiming at recommending or discarding its clinical use.

CONTENTS: The following databases were queried: Medline, via Pubmed (1966-2013), Cochrane Central Registry of Controlled Trials (2012), Embase (1980-2013) and LILACS (1982-2013). The strategy was a search adjusted to each database to identify the largest possible number of studies involving sodium hyaluronate to manage joint temporomandibular disorders. Language was limited to articles published in English. The following keywords were crossed: temporomandibular joint management, versus sodium hyaluronate, versus acute or chronic reducing or nonreducing disk displacement, versus hyaluronic acid, versus osteoarthritis, versus viscosupplementation. Inclusion criteria were randomized, blind or double-blind studies, and case series with 15 or more participants. Exclusion criteria were open label-label studies, animal model studies and articles related to arthrogenous disorders not being treated with sodium hyaluronate infiltration of the temporomandibular joint. Methodological quality of such studies was evaluated and classified according to the level of evidence of the Oxford Center for Evidence Based Medicine.

CONCLUSION: According to this review, one may state that sodium hyaluronate is effective and safe, being recommended to manage the following conditions: acute and chronic reducing and nonreducing disk displacement, osteoarthritis and degenerative joint disease.

Keywords: Clinical treatment, Nonreducing disk displacement, Osteoarthritis, Reducing disk displacement, Sodium hyaluronate, Surgical treatment, Temporomandibular joint, Viscosupplementation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A disfunção temporomandibular compreende um termo coletivo que envolve alterações clínicas nos músculos da mastigação, das articulações temporomandibulares e/ou estruturas associadas. O objetivo deste estudo foi realizar uma análise crítica, utilizando as principais bases de dados, sobre a efetividade e a segurança do hialuronato de sódio no tratamento das disfunções temporomandibulares de origem articular, a fim de recomendar ou refutar seu uso na prática clínica.

CONTEÚDO: Os estudos foram obtidos através das seguintes bases de dados: Medline, via PubMed (1966 - 2013), Registro de Ensaios Controlados Cochrane, (2012), Embase (1980 - 2013) e LILACS (1982 - 2013). A estratégia utilizada foi a busca ajustada para cada base, a fim de identificar o maior número possível de estudos envolvendo o uso do hialuronato de sódio no tratamento da disfunção temporomandibular de origem articular. Houve limitação do idioma, buscando artigos em língua inglesa. Cruzaram-se os seguintes descritores: tratamento da articulação temporomandibular *versus* hialuronato de sódio *versus* deslocamento agudo e crônico do disco com e sem redução *versus* ácido hialurônico *versus* osteoartrite e osteoartrose *versus* viscosuplementação. Como critérios de inclusão foram analisados estudos randomizados, uni ou duplamente encobertos, série de casos, com 15 ou mais participantes. Excluíram-se relato de caso, estudos abertos "open-label", estudos em modelos animais e artigos relacionados a tratamento da disfunção artrogênica que não possuísem como uma das terapias a infiltração de hialuronato de sódio na articulação temporomandibular. A qualidade metodológica desses estudos foi avaliada e classificada conforme o nível de evidência do *Oxford Centre for Evidence Based Medicine*.

CONCLUSÃO: De acordo com a análise crítica dos estudos incluídos, pode-se afirmar que o uso do hialuronato de sódio é eficaz e seguro, sendo recomendado no tratamento das seguintes condições: deslocamento agudo e crônico do disco com redução e sem redução, osteoartrose, osteoartrite e doença articular degenerativa.

Descritores: Articulação temporomandibular, Deslocamento do disco sem redução, Deslocamento do disco com redução, Tratamento cirúrgico, Tratamento clínico, Osteoartrose, Osteoartrite, Hialuronato de sódio, Ácido hialurônico, Viscosuplementação.

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INTRODUCTION

Temporomandibular disorder (TMD) is a collective term involving clinical changes of masticatory muscles, temporomandibular joints (TMJ) and/or associated structures, which may be followed by pain, mouth opening limitation and joint noises^{1,2}. Individuals with such changes have major impact in their quality of life, with impairment of their functional activities and, very often, with mood and sleep changes³. TMD prevalence in general population varies from 10% to 70%, being more frequent among females between 20 and 40 years of age^{3,4}.

Among joint TMD, reducing and nonreducing disk displacements and osteoarthritis are more frequent changes in patients looking for treatment³⁻⁵.

Different approaches have been proposed to control such disorders, among them conservative treatments (drugs, physiotherapy, stabilizing and repositioning occlusal devices, guidelines), minimally invasive treatments (sodium hyaluronate or corticosteroid infiltrations and arthrocentesis), and invasive treatments (arthroscopy, arthroplasty, arthrotomy)⁶⁻⁸.

With regard to minimally invasive therapies, some studies have shown that sodium hyaluronate (SH) infiltrations in the superior joint space and, sometimes, in both spaces, are effective for the treatment of intra-articular TMJ changes^{9,10}.

Hyaluronic acid (HA) is a linear chain, hydrophilic, poly-ionic glycosaminoglycan of high molecular weight. It is found in the extracellular matrix of several connective tissues, including joint cartilage and synovial fluid¹¹⁻¹³. In such sites, HA molecules are predominantly synthesized by type B synovial cells¹²⁻¹⁵.

Metabolic HA activity in cell renewal helps the nutrition of avascular zones of the disk and joint cartilage through its combination with glycosaminoglycans coming from proteoglycans produced by chondrocytes. In pathological conditions, there is increased proteoglycan synthesis and metalloproteinase (MP) production. MPs act on collagen and proteoglycans, weakening joint cartilage matrix. Thus, there are collagen and proteoglycan fragments, in addition to leukotriens and cytokines in the capsular ligament, leading to joint movement limitation and followed or not by pain¹⁶⁻¹⁹.

TMJ viscosupplementation is a minimally invasive technique consisting in intra-articular injection of HA (sodium hyaluronate) aiming at eliminating or decreasing pain and providing joint functional gain, promoting qualitative and quantitative improvement of the synovial fluid²⁰⁻²².

The use of this product according to its molecular weight may increase the production of natural HA by synovial cells, improve or normalize jaw functions as from the release of adhesion zones between the mandibular fossa and the joint disk²³. HA properties are predominantly explored in the context of viscosupplementation, but it is worth stressing that very high molecular weight molecules (between 1 and 6 x 10⁶Da) are prevented from passing from the intra-articular to the intercellular medium, thus being unable to act on synoviocytes and chondrocytes, which would be needed to decrease syno-

vial inflammation and restore natural synovial fluid properties, which has been called "viscoinduction"^{14,15}. According to this theory¹³⁻¹⁵, products with molecular weight between 0.5 and 1 x 10⁶Da would provide better effects *in vivo*²³ and could promote endogenous HA synthesis by synoviocytes^{14,15}. In the same line, other researchers²⁴ have established an even narrower molecular weight range (500-730 kDa) as that able to act on synovial fibroblasts, restoring their ability to synthesize HA¹³.

Due to HA mechanical and metabolic characteristics, viscosupplementation, alone or in combination with other interventions, has an excellent therapeutic property for inflammatory conditions and TMJ biomechanical changes, being the ideal conservative, minimally invasive and well recommended treatment^{22,23,25,26}.

Adverse reactions of HA combined with minimally invasive techniques or alone are mild and transient. Major complaints described by the literature are discomfort, edema or pain at injection site which spontaneously resolve in a short period of time^{11,20,27-30}.

A single case of TMJ joint tubercle necrosis has been reported after repeated SH injections in a TMD patient³¹.

In a meta-analysis study, some authors¹⁹ have concluded that there are not enough evidences to support or discard the use of SH to treat patients with TMD. However, short term results of intra-articular SH injections in preliminary studies have been very promising^{9,11}. These results were recently confirmed by other authors³².

This study aimed at analyzing through a literature search in major databases and further review of selected articles, the efficacy and safety of SH to treat TMD.

CONTENTS

Literature search strategies

Studies were obtained from the following databases: Medline, via Pubmed (1966-2013), Cochrane Central Registry of Controlled Trials (2012), Embase (1980-2013) and LILACS (1982-2013). The strategy was a broadly performed search adjusted for each database to identify the highest possible number of studies involving SH to treat joint TMD, aiming at evaluating its effectiveness and safety. Language was limited to articles published in English. The search was complemented by manual search of clinical trials references in indexed journals in the area of TMD and orofacial pain.

The following keywords were crossed: temporomandibular joint treatment versus SH versus chronic or acute reducing and nonreducing disk displacement, versus osteoarthritis versus viscosupplementation. Inclusion criteria were randomized, blind or double-blind studies, case series with 15 participants or more. Exclusion criteria were case reports, open-label studies, studies with animal models and articles related to arthrogenic disorders not using SH infiltration in the temporomandibular joint. The methodological quality of such studies was evaluated according to the level of evidence of the Oxford Centre for Evidence Based Medicine³³.

Description of selected literature

Some relevant studies have been published about the use of HA alone or compared to placebo (P) and corticosteroids (CS) or even combining its use with surgical interventions (arthrocentesis and arthroscopy) and with interocclusal device.

Considering HA properties, viscosupplementation with HA has been used in different joint TMDs, such as reducing and nonreducing disc displacement, osteoarthritis and degenerative joint disease^{16,17,20,21,23,34-38}.

A multicenter study¹⁶ involved a sample of 121 participants divided in two parallel groups, who were followed up for six months. Participants had documented diagnosis of TMJ intra-articular disease with severe dysfunction and with unfavorable results of conservative therapies to which they were submitted for at least six months. Group using HA was composed of 80 patients with mean age of 36 years. Thirty-five patients had reducing disk displacement (RDD); 8 had nonreducing disc displacement (NRDD) and 37 had degenerative joint disease (DJD). The group using saline solution (placebo) was composed of 41 patients with mean age of 40.7 years (15 with RDD; 6 with NRDD and 20 with DJD). Before the analysis, 14 patients were eliminated. Both interventions consisted in a single HA injection (10 mg/mL) in the first group and SS in the other, close to the superior TMJ compartment, being the volume dictated by the existing joint space. RDD results, total and intracapsular scores of dysfunction indices and clinical history, as well as more relevant variables, for example, joint noises and jaw shift, have shown consistent and significant improvement for the HA group as compared to the SS group. For DJD cases, scores related to history and total dysfunction have shown improvement in both groups without significant difference. NRDD results have shown improvement in at least one class of dysfunction in all HA group patients with significant difference between groups (level of evidence 2).

In a different study¹⁷, RDD patients aged above 21 years who have not responded to conservative therapy for more than two months were divided in two parallel groups and followed up for six months. Each group was composed of 19 patients with mean age of 31.9 years for HA group and 31.1 years for SS group. The first group received 0.5 mL of HA (15 mg/mL) and the other received the same volume of SS, in the superior TMJ compartment. This procedure was repeated one week later. Results for noise and pain intensity in the infiltrated joint have shown significantly higher improvements in the first and sixth month for patients using HA as compared to patients using SS (level of evidence 3).

A different study²² has involved 41 patients with TMJ rheumatoid arthritis who were followed up for four weeks. From these, two were males with mean age of 65 years, and 39 were females with mean age of 56 years. Patients were divided in three groups. The first (n = 14) received two injections of 0.7 mL (10 mg/mL) HA in the superior TMJ space, every two weeks; the second received 0.7 mL of SS (n = 13), using the same approach and frequency of HA, and the last group (n = 14) received 0.7 mL (40 mg/mL) of methylprednisolone

(ME). Both HA and ME groups had significantly positive effects on joint signs and symptoms according to patients' subjective evaluation. Maximum voluntary mouth opening has significantly improved only for HA and ME groups (level of evidence 2).

In case of TMJ intra-articular disorders, three double-blind, randomized, placebo-controlled studies have positively evaluated HA in such patients in the long term^{16,17,22}.

Another study¹⁸ has investigated jaw function and the presence of pain in 22 TMJ with NRDD and in 30 TMJ without pathological changes. In this double-blind, randomized study, five injections of 1 mL HA were administered with one week interval between doses. When compared to healthy joints in a mean period of 17 months, it has been observed that structural deformity and disc displacement have persisted after treatment, but clinical signs and symptoms have improved (level of evidence 2).

With regard to surgical treatments, two studies were carried out using arthroscopy, arthrocentesis and HA and comparing such surgical techniques to lactated Ringer's solution (LR) and placebo (P)^{27,34} with similar protocols. Thirty-three patients²⁷, 55 TMJ with clinical evaluation, were randomly selected for TMJ arthroscopy. From these, four were males (12%) and 29 were females (88%). Mean age was 34 years. Twenty-two patients (67%) were submitted to bilateral procedure. From total sample, 33 TMJ were submitted to arthroscopy with HA and 22 joints have received LR solution. During the procedure, the control of synovial fluid debris, intra-articular hemorrhage and tissue debridement were evaluated. After two months of follow-up, it was observed that the administration of HA during arthroscopy has significantly improved as compared to control group, in addition to not having presented short or long term complications as a consequence of the use of this viscoelastic substance (level of evidence 2).

TMJ arthrocentesis³⁴ was evaluated with and without SH injection to treat reducing and closed lock disc displacement. Sample was made up of 31 individuals with clinical presentation of mouth opening limitation, pain and TMJ sensitivity and joint noises during function. Patients were randomly divided in two groups. The first was submitted to arthrocentesis and the second to arthrocentesis associated to 1 mL of HA injection in the superior TMJ compartment. Clinical evaluation was performed before and soon after procedure and in the 1st until the 24th month of evolution. Joint pain intensity, jaw function and joint noises were evaluated by the visual analog scale (VAS). Maximum mouth opening and lateral jaw movements were measured every control visit. Both techniques have produced mouth opening gain, lateral jaw movements improvement and have decreased pain and joint noises; however the combination of arthrocentesis and HS injection was superior to arthrocentesis alone (level of evidence 2).

These studies positively point to the association of HA with arthroscopy and arthrocentesis, showing better results both in the evaluation of intra-articular bone changes and the evaluation of subjective clinical symptoms.

Some studies^{35,36} have compared HA to the use of corticosteroids (CS).

Short term effect (1 month) of intra-articular infiltration of SH or corticosteroids (betamethasone) was compared to a sample³⁵ of 33 patients with TMJ pain and sensitivity to palpation for at least six months and who had not responded to conservative treatment. Both drugs were randomly allocated to patients. Two infiltrations of 0.5 mL HS or betamethasone were performed in the superior joint compartment, depending on the group, with a two-week interval. The effect on subjective symptoms, clinical signs and bite strength was evaluated. Both groups have improved with symptoms remission in 13 out of 18 patients treated with SH and in 9 out of 15 patients treated with corticosteroids, without statistically significant difference between groups. Results indicate that SH may be used as alternative to corticosteroids for patients with signs of TMJ inflammation, especially those with symptomatic osteoarthritis (level of evidence 3).

Another study³⁶ has compared efficacy and complications of intra-articular TMJ infiltrations in 40 patients with osteoarthritis. Individuals were randomly divided in two groups: patients have received two intra-articular SH injections or two intra-articular SS injections with 14-day interval between them. Treatment effect was evaluated within 14 days and six months after first infiltration, considering pain intensity, its location, joint noises, jaw function and complications. In both groups, pain has decreased within six months of follow-up. Pain in the SH group was significantly milder as compared to SS group. The whole sample has shown decreased clicking. In 20 individuals receiving SH, both vertical jaw opening and protrusion have significantly improved. Lateral movement of affected side has improved for both groups. This study confirms that TMJ infiltration with SH or SS may decrease pain and improve function in patients with osteoarthritis and that SH infiltrations were significantly more effective to decrease pain intensity as compared to SS. In addition, regardless of injecting SH or SS, one may emphasize that there will be no bone structure changes, as shown by other authors³⁷ in a study with 36 patients with bilateral TMJ osteoarthritis (level of evidence 2).

Two well-designed clinical trials^{35,36} show better results for intra-articular TMJ infiltration with SH as compared to corticosteroids for joint TMD signs and symptoms. Both are effective at the short and long term, however HA has not the undesirable effects which may be induced by corticosteroids^{35,36}, that is structural bone changes.

Another study²⁸ has compared long term results of TMJ SH infiltrations to the use of interocclusal device (IOD) in patients with degenerative joint disease (DJD). Sample was divided in three groups of 20 patients. Group A was submitted to a cycle of five injections of 1 mL of HS. Group B used IOD for at least six months; and the third group was made up of 20 patients who have refused all proposed therapies (control). Description of results was based on objective and subjective parameters after six months of follow up. Both SH and IOD have significantly improved clinical presentation of patients

(maximum mouth opening, pain at rest and during chewing, masticatory efficiency and functional limitation during normal jaw movements). There has been no significant difference between groups. The analysis of control group results has shown significant worsening of pain at rest, when evaluated at one and six months of follow up. SH infiltrations are an effective non-surgical treatment for TMJ DJD. Five SH infiltrations are well tolerated and have results equivalent to six months of treatment with IOD, without any complications with the use of such substance in TMJ (level of evidence 2). Some authors³² have compared the efficacy of two treatment protocols using, during five weeks, TMJ arthrocentesis followed by injections of HA with two different molecular weights aiming at minimizing symptoms of patients with TMJ degenerative inflammatory processes. RDC/TMD (diagnostic criteria for temporomandibular disorder research) was used as evaluation tool. Sample was made up of 40 subjects randomly distributed in two groups. The first has received low molecular weight HA and the second a product with medium weight molecule, in both cases soon after single needle arthrocentesis. Maximum pain at chewing was the primary result variable, maximum pain at rest, chewing efficacy, functional limitation, tolerability to treatment, perceived efficacy and jaw movement amplitude in millimeters were secondary outcomes. All variables were evaluated and compared between groups at treatment completion and three months after. At the end of this period, all parameters had improved for both groups. A comparison of changes along time between groups has shown that differences were not significant for any variable, that is, pain at chewing and at rest, chewing efficacy, functional limitation and mouth opening. In addition, there has been no difference between groups in perceived treatment efficacy and tolerability. Authors have concluded that the therapeutic response was similar for both protocols for TMJ osteoarthritis, regardless of HA molecular weight (level of evidence 2).

A different study²⁹ has evaluated 76 patients with TMJ osteoarthritis, who were divided by age groups (less than 45 years, between 45 and 65 years and above 65 years of age), who were submitted to weekly arthrocentesis associated to 1 mL HA (SH) after flushing. The procedure was repeated for five weeks and patients were followed up for 12 months. Individuals above 45 years of age have shown better response to treatment with regard to chewing efficacy, mouth opening amplitude and pain severity (level of evidence 3).

A pilot study³⁸ was carried out to compare the efficacy of six treatment protocols in 72 patients with TMJ osteoarthritis with pain for more than six months. Patients were randomly allocated to one group receiving the following arthrocentesis protocols: single double-needle arthrocentesis (A), single double-needle arthrocentesis and steroids (B), single double-needle arthrocentesis and low molecular weight HA (C), single double-needle arthrocentesis and high molecular weight HA (D), five weekly double-needle arthrocenteses and low molecular weight HA (E), and five weekly single-needle arthrocentesis and low molecular weight HA (F). All five groups

who completed the protocol have improved during the three months of follow up, except for group D where patients had edema and very severe pain soon after infiltration. There have been no significant differences among groups. The protocol with five double-needle arthrocenteses and low molecular weight HA has produced better results with regard to pain, mouth opening and joint noises. Study findings suggest that there are no statistically significant differences among treatment groups. The clinical significance of these findings needs further studies with a larger sample and follow up for a longer period of time (level of evidence 2).

Another study³⁹ has used double-needle arthrocentesis (DNA), with a volume of 200 mL followed by intra-articular infiltration of 1 mL of SH and jaw manipulation. Sample was made up of 33 patients with NRDD with unilateral TMJ involvement. These patients were clinically evaluated and by means of TMJ magnetic resonance imaging (MRI) before and after the procedure. Clinical presentation varied from one week to two years. After DNA and HS infiltrations, mild diet, physiotherapy and IOD were prescribed. MRI images were taken one month after the procedure. Clinical evaluation, with maximum mouth opening evaluation, VAS and a self-administered questionnaire were used to evaluate pain, jaw dysfunction and daily life activities. Patients were followed up for one year. Results after this period have shown significant improvement in maximum mouth opening, with significant pain decrease. Global therapeutic response was 72.7%; higher in acute patients (87.5%) as compared to chronic patients (68.0%). Disc was recaptured (it was interposed between condylar head and joint tubercle in MRI images with open and closed mouth) in three cases where displacement lasted less than one month, that is, acute patients (level of evidence 4). Several protocols with HA to treat joint TMD have been proposed; however, the most recommended protocols establish a weekly intra-articular 1 to 2 mL infiltration (TMJ) repeated for three to five consecutive weeks^{9,18,24,40} (level of evidence 1, 3, 3 and 3, respectively).

The efficacy and safety of HA (SH) infiltration in the superior joint space have been compared, in a systematic review, to the infiltration of superior and inferior joint spaces to control joint TMD signs and symptoms (pain relief, increased mouth opening). Results of this review, with moderate bias risk, have shown satisfactory results for both techniques, however with better results when infiltration was performed in both joint spaces, notwithstanding the higher difficulty of this type of procedure. In both techniques there have been no major adverse effects, showing the safety of such interventions¹⁰ (level of evidence 2).

In addition to all described benefits, sodium hyaluronate infiltration, alone or associated to surgical procedures, is a simple, fast and minimally invasive treatment, does not leave scars, does not need sophisticated tools, materials and equipment, does not require hospitalization and may be performed under local anesthesia in outpatient settings or in the dental office itself. These aspects, together with its safety and efficacy profile, in addition to few adverse and transient effects, have

motivated professionals to elect SH infiltration directly in the TMJ for several joint disorders^{10,16,18,25} (level of evidence 2, 2, 3 and 3, respectively).

CONCLUSION

According to the analysis of studies included in this review, one may state that SH is effective and safe, being recommended to treat the following conditions: acute and chronic reducing and nonreducing disc displacement, osteoarthritis and degenerative joint disease.

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