

Effects of the hyaluronic acid infiltration in the treatment of internal temporomandibular joint disorders

Efeitos da infiltração de ácido hialurônico no tratamento das desordens internas da articulação temporomandibular

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ABSTRACT

BACKGROUND AND OBJECTIVES: The primary protocol for the control of temporomandibular disorders prioritizes reversible and less invasive measures. However, conservative treatment is sometimes ineffective. Therefore, the use of hyaluronic acid has been suggested as a therapeutic alternative to verify the effectiveness of the hyaluronic acid in patients who are not responsive to the most conservative treatments, helping them in the control of pain. This article aims to perform a literature review on the efficacy of this substance in the treatment of internal changes of the temporomandibular joint.

CONTENTS: The search strategy used the Pubmed portal and the Web of Science database for the last 10 years. We included articles in English that evaluated the efficacy of the hyaluronic acid in the intra-articular disorders of temporomandibular joint, and excluded articles from literature review, clinical case reports, theses, and dissertations. Fifteen studies, classified as randomized clinical trials, prospective and retrospective studies, case-control, pilot study, and systematic reviews were selected. The hyaluronic acid is of fundamental importance in the function and lubrication of joint tissues due to its high molecular weight. When degenerative and inflammatory changes are present, their concentration and molecular weight are diminished, and the injection of this acid raises these levels, which can generate pain relief.

CONCLUSION: Intra-articular therapy with hyaluronic acid is effective in the reduction of symptomatologic levels and the functional restoration of the temporomandibular joint.

Keywords: Hyaluronic acid, Intra-articular injections, Viscosupplementation, Temporomandibular joint disorder.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O protocolo primário de controle das disfunções temporomandibulares prioriza as medidas reversíveis e menos invasivas. Entretanto, o tratamento conservador mostra-se, algumas vezes, ineficaz, e como alternativa terapêutica, tem sido sugerido o uso de ácido hialurônico para com isso, verificar a sua efetividade em pacientes não responsivos aos tratamentos mais conservadores e poder ajudá-los no controle da dor. O objetivo deste estudo foi rever na literatura a eficácia dessa substância no tratamento das alterações internas da articulação temporomandibular.

CONTEÚDO: A estratégia de busca utilizou o portal eletrônico Pubmed e a base de dados *Web of Science*, nos últimos 10 anos. Foram incluídos artigos em inglês que avaliaram a eficácia do ácido hialurônico nas desordens intra-articulares da articulação temporomandibular, e excluídos artigos de revisão de literatura, relatos de casos clínicos, teses e dissertações. Foram selecionados 15 estudos, classificados como ensaios clínicos randomizados, estudos prospectivos e retrospectivos, caso-controle, estudo piloto e revisões sistemáticas. O ácido hialurônico tem importância fundamental na função e lubrificação dos tecidos articulares, devido ao seu alto peso molecular. Quando alterações degenerativas e inflamatórias estão presentes, sua concentração e peso molecular estão diminuídos, e a injeção desse ácido eleva esses níveis, o que pode gerar alívio da dor.

CONCLUSÃO: A terapia intra-articular com ácido hialurônico é efetiva na diminuição dos níveis sintomatológicos e no restabelecimento funcional da articulação temporomandibular.

Descritores: Ácido hialurônico, Injeções intra-articulares, Viscosuplementação, Transtornos da articulação temporomandibular.

INTRODUCTION

The temporomandibular joint (TMJ) consists of a ginglymoarthral joint that allows hinging movements on one axle and sliding movements on another axle¹. The synovial fluid nourishes and lubricates the joint tissues, and its quality and quantity are directly related to the joint normal function and health^{1,2}.

Temporomandibular dysfunction (TMD) is a collective term that encompasses clinical disorders in the TMJ, chewing muscles and associated structures. Among the signs and symptoms, the individuals may have pain, limitation of the mandibular movements and clicking^{1,3}. The possible etiological factors are trauma in the facial structures; occlusal factors; increased emotional

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stress; source of deep pain; muscle hyperactivity; parafunctional activities and orthopedic instability^{1,4}. TMDs of articular origin include dislocation of the disc with and without reduction, arthralgia, osteoarthritis, and TMJ osteoarthritis³.

The disc displacement of the TMJ is described as an abnormal relationship of the mandibular condyle with the joint disc, fossa and articular eminence, which can occur with and without disc reduction⁵. TMJ arthralgia is a localized pain (of moderate to severe intensity) located in the TMJ and adjacent tissues⁴. In osteoarthritis, there is a chronic and non-inflammatory degeneration that affects the cartilaginous tissue of the synovial joints and is associated with the remodeling processes of the subchondral bone and the involvement of the synovial tissue^{2,3}. TMJ osteoarthritis occurs when there is a compromise of the dynamic balance between the collapse and repair of the joint tissues^{5,6}.

One of the minimally invasive therapies for the control of the TMJ internal disorders is known as viscosupplementation (infiltration of hyaluronic acid in the TMJ). The hyaluronic acid (HA) is an acidic mucopolysaccharide that is present in the primary substance of animal tissues, being the major component of the synovial fluid and has vital importance in the lubrication of the articular tissues^{2,3,7}. In the degenerative and inflammatory disorders, its concentration and weight are reduced, and the HA injection elevates these levels, which may be related to pain relief since it contains anti-inflammatory effects, such as inhibition of phagocytosis, chemotaxis, prostaglandin synthesis, metalloproteinases activity, and removal of oxygen radicals from the synovial tissue^{5,8}.

The primary protocol to control TMD prioritizes simple, reversible and less invasive approaches. However, the conservative treatment is sometimes ineffective, and as a therapeutic alternative, the use of HA has been suggested. Thus, checking the effectiveness of the HA in patients who are not responsive to more conservative treatments can help to control their pain. Therefore, the objective of the present study was to review the literature on the efficacy of this substance in the treatment of internal changes of the TMJ.

CONTENTS

A literature review was conducted using the Pubmed electronic portal and the *Web of Science* database, using the MeSH keywords: “Temporomandibular Joint Disorder”, “Hyaluronic Acid”, “Viscosupplementation” and “Injections”, “Intra-articular”. The articles were selected according to the pre-established eligibility criteria. The inclusion criteria were studies related to the effects of the HA on intra-articular changes of the TMJ; studies that reported

the applicability of the HA; articles in English published in the last ten years. The exclusion criteria were literature reviews; clinical case reports; theses and dissertations; articles not available in full. After searching the database and the electronic portal, the duplicates were removed, and the titles and abstracts were read to identify potentially eligible articles that met the inclusion criteria. The articles that met the exclusion criteria were removed from the study. It is worth mentioning that the full text of each selected article was carefully evaluated. The initial selection generated a total of 415 articles, of which 107 duplicates were removed. After being adapted to the inclusion criteria, 288 articles remained, and 15 articles were selected in full after an exploratory reading and critical analysis of titles and abstracts. The detailed selection method of the articles, according to the search mechanisms, is summarized in table 1.

The articles selected were randomized clinical trials, prospective and retrospective studies, case-control, pilot study, and systematic reviews that evaluated, primarily, the efficacy of the HA infiltration for the treatment of internal temporomandibular joint disorders. Of the 15 articles selected, 4 are systematic reviews, 2 of these were published in 2017, 2 in 2016 and 2010, respectively. The publication period ranged from 2009 to 2017. Study samples varied from 25 to 141 patients. The age of the groups of patients ranged from 17 to 65 years. In most the analyzed cases, the follow-up of the results was of short and medium term, between three and six months. Table 2 shows the selection of the studies included with their main characteristics.

Table 1. Article selection flowchart

Articles selection	Search strategy
Pubmed	Hyaluronic acid and temporomandibular joint disorder: 104 Temporomandibular joint disorder and viscosupplementation: 4 Injections, intra-articular and temporomandibular joint disorder: 216
Web of Science	Hyaluronic acid and temporomandibular joint disorder: 54 Temporomandibular joint disorder and viscosupplementation: 8 Injections, intra-articular and temporomandibular joint disorder: 29
Articles removed	Duplicates: 107
15 selected articles	Inclusion and exclusion criteria: 33 articles excluded Reading of titles and abstracts: 260 articles excluded

Table 2. Description of the studies included in the review

Authors	Type of study	Objective	n	Diagnosis	Main findings	Conclusion
Long et al. ⁵	Randomized clinical trial	To compare HA infiltration in the lower and upper joint space	120	DDSR	Pain improvement in both groups	The intra-articular infiltration of HA in the upper and lower joint space was effective
Korkmaz et al. ⁹	Prospective clinical study	Compare the HA therapy and the treatment with the occlusal splint	-	DDCR	Better results with the HA therapy	The injection of HA and the occlusal splint therapy were effective in relieving the signs and symptoms of DDCR

Continue...

Table 2. Description of the studies included in the review – continuation

Authors	Type of study	Objective	n	Diagnosis	Main findings	Conclusion
Guarda-Nardini et al. ¹⁰	Retrospective clinical trial	To compare the efficacy of the HA infiltration therapy in different age groups	76	Osteoarthritis of the TMJ	The HA was effective in most of the evaluated symptoms	The treatment protocol was more effective in people over 45 years of age
Li et al. ¹¹	Randomized clinical trial	To compare the effects of HA infiltration in the lower and upper joint space	141	Osteoarthritis of the TMJ and DDSR	Improvement of TMJ function in both groups	The HA infiltration is an effective method for the treatment of DDSR associated with osteoarthritis
Bonotto et al. ¹²	Retrospective clinical study	Discuss the viscosupplementation in the treatment of internal alterations of the TMJ	55	DDSR and osteoarthritis of the TMJ	There was an increase in mouth opening in patients with DDSR and osteoarthritis	The viscosupplementation with HA is considered a good alternative to improve the function of the TMJ in the short term
Goiato et al. ¹³	Systematic review	Compare the HA injections and other drugs used in the arthrocentesis of the TMJ	–	Internal TMJ disorders	Intra-articular injections of HA are beneficial to improve the functional symptoms of TMD	Positive results were observed with the HA therapy, but other therapies may be used
Iturriaga et al. ¹⁴	Systematic review	Analyze the evidence of the efficacy of the HA	–	Osteoarthritis of the TMJ	The application of HA had positive results	Further research is needed.
Guarda-Nardini, Manfredini and Ferronato ¹⁵	Pilot study	Provide data about the effect of a cycle of five arthrocentesis plus HA infiltration	31	DDCR and arthralgia	Improvement regarding all variables of the study	Five infiltrations of HA after arthrocentesis was effective to ameliorate the DDR symptoms
Aktas, Yalcin and Sencer ¹⁶	Retrospective clinical study	Analyze the prognosis of arthrocentesis with and without HA	25	DDSR	It is sufficient to use only arthrocentesis in patients without degenerative alterations	Having a standardized study group for future studies is necessary
Guarda-Nardini et al. ¹⁷	Case-control study	Determine the effectiveness of viscosupplementation with the HA	25	Osteoarthritis of the TMJ	Improvement in all outcome parameters	Effective therapy for pain improvement and the TMJ function
Guarda-Nardini et al. ¹⁸	Retrospective clinical study	Evaluate the effect of viscosupplementation with HA	49	Osteoarthritis	Significant reduction of pain over time	Further studies are required
Guarda-Nardini et al. ¹⁹	Retrospective clinical study	Evaluate the efficacy of the HA in elderly patients	50	Osteoarthritis of the TMJ	Significant improvement of signs and symptoms	There was no significant difference between the groups
Guarda-Nardini et al. ²⁰	Randomized clinical trial	Compare the efficacy of a single session protocol with a five-session protocol of HA infiltration in the TMJ	30	Osteoarthritis of the TMJ	There was greater reduction of pain in the group treated with the 5-session protocol of HA infiltration	The five-session protocol showed better results in 6 months
Manfredini, Piccotti and Guarda-Nardini ²¹	Systematic review	Evaluate the clinical studies on HA infiltration in the TMJ	–	TMJ disorders	All studies reported a decrease in pain levels	The results are similar to those obtained with corticosteroid injection and the use of occlusal splints
Manfredini et al. ²²	Prospective randomized clinical trial	Evaluate the efficacy of platelet-rich plasma with growth factors injection versus HA	100	Internal TMJ disorder and osteoarthritis	The group treated with platelet-rich plasma with growth factors injection had better results	The injection of platelet-rich plasma with growth factors after arthroscopy has shown to be more effective than the HA injection in patients with internal TMJ disorders

n = number of patients; TMJ = temporomandibular joint; HA = hyaluronic acid; DDSR = anterior disc displacement without reduction; DDCR = anterior disc displacement with reduction.

DISCUSSION

In its first reports, the HA was used to treat racehorses diagnosed with traumatic arthritis. It was later used in humans to treat osteoarthritis involving larger joints such as knees, hips, and shoulder²¹. In 1979, it was first used in intracapsular changes of the TMJ^{16,19,22}, and since then some studies have tried to evaluate the efficacy of the technique as well as to establish a protocol for its use²⁰. Its metabolic activity contributes to cell renewal and facilitates the nutrition of the avascular areas of the disc and the articular cartilage due to its combination with the glycosaminoglycans originated by proteoglycans^{5,19}.

Viscosupplementation consists of intra-articular infiltration of HA in the TMJ¹⁷ to eliminate or reduce the symptomatic levels and restoring the masticatory function by qualitative and quantitative enhancement of the synovial fluid^{16,17}, mainly because of the metabolic and mechanical properties of the HA⁵. Viscosupplementation alone or in combination with other modalities such as arthrocentesis is being considered a treatment option for inflammatory or biomechanical changes of the TMJ^{18,20}.

It is believed that the decrease of painful symptoms with viscosupplementation may occur by the blockade of endogenous receptors and pain substances in the synovial tissues^{16,18}. The infiltration of HA can improve or normalize the functionality of the TMJ by disrupting the adhesions or adherences between the mandibular fossa and the articular disc^{16,17}. Moreover, it may decrease the secondary wear allowing better perfusion of nutrients and metabolites of the synovial fluid to the vascular tissues¹⁷. Although the HA is kept in the joint only for a few days, the results last for months^{18,21}. The low molecular weight of the HA molecules showed the best in vivo results and are more likely to induce the synthesis of the endogenous HA^{19,20}. However, products that have a high molecular weight are less able to pass into the intracellular environment^{17,20,21} and ends up precluding their action on the synoviocytes and chondrocytes, which is necessary for the reduction of the synovial inflammation and the restoration of the properties of the synovial fluid¹⁹.

A systematic review conducted by Iturriaga et al.¹⁴ evaluated the regulation of inflammatory mediators when applying HA in patients with TMJ osteoarthritis (OA). The results showed that the application of HA had a positive effect on the regulation of the inflammatory mediators. The mediators studied were plasminogen, activating system, and nitric oxide levels. The evidence available suggested that the application of HA regulates several inflammatory mediators in osteoarthritic processes in the TMJ. However, the authors stated that further evidence is needed in this regard, through the study of specific TMJ diseases, complementing the evaluation of clinical parameters with quality experimental studies with larger sample sizes.

In this context, the efficacy of the HA treatment was also evaluated by Guarda-Nardini, Ferronato and Manfredini², but in patients with different age groups diagnosed with OA. From this study, it was suggested that the protocol of treatment applied until then was more effective in older patients. In the study conducted by Long et al.⁵, 120 patients diagnosed with disc displacement without reduction (DDSR) received an HA infiltra-

tion. One group of patients received injections in the upper joint space, and the other group was treated with injections in the lower joint space. The clinical symptoms were evaluated at the follow-up visits of 3 and 6 months. The parameters evaluated were maximum mouth opening (MMO), pain intensity on a visual analog scale (VAS) and the Helkimo's clinical dysfunction index. The MMO, VAS, and Helkimo index of the two groups improved significantly, with no difference between the groups.

In agreement with the study by Long et al.⁵, Bonotto et al.¹² discussed the viscosupplementation technique in the treatment of internal TMJ alterations in 55 patients with disc displacement with reduction (DDCR) and DDSR. The results showed a significant increase in mouth opening in all groups. These results remained constant over four months of follow-up, and the authors stated that the viscosupplementation with HA could be a good alternative, in the short-term, to the functional restoration of the TMJ in patients with internal TMJ alteration that did not respond to conservative treatments.

With the study by Li et al.,¹¹ it was possible to compare the effect of the HA injections in the upper and lower joint space in patients diagnosed with DDSR in association with OA by cone beam computed tomography. It showed that the HA injections in the upper and lower joint space are effective methods to treat DDSR in association with OA, corroborating previous studies using the HA in the treatment of degenerative alterations and DDSR and DDCR of the TMJ^{5,12}.

Korkmaz et al.⁹ compared the effectiveness of single and double infiltrations of HA and the therapy with an occlusal splint to treat DDCR. The patients were divided into four groups: control (group 1), single HA injection (group 2), double HA injection (group 3) and therapy with an occlusal splint (group 4). The results showed functional improvement and a decrease in the pain symptoms in all groups, but the patients who underwent the HA therapy had better results. Thus, they concluded that the HA is more effective in improving the clinical signs and symptoms of DDCR than the occlusal splint therapy.

Accordingly, Guarda-Nardini, Manfredini and Ferronato¹⁵ evaluated the short-term effect of a weekly cycle of five arthrocentesis associated with HA injections to control the signs and symptoms of 31 patients with DDCR. At the end of the treatment, there was a significant improvement over baseline in all variables analyzed and maintained for three months of follow-up. Thus, they concluded that a cycle of five weekly injections of HA performed immediately after arthrocentesis, is effective in improving the signs and symptoms of DDCR.

Goiato et al.¹³ conducted a systematic review to investigate whether intra-articular injections of HA are more effective than other drugs used in TMJ arthrocentesis and showed that intra-articular injections of HA are beneficial in the control of pain and the functional symptoms of TMD. However, corticosteroids and nonsteroidal anti-inflammatory drugs can be used with satisfactory results.

Manfredini et al.²² evaluated the efficacy of platelet-rich plasma in growth factor (PRGF) versus HA injection after arthroscopic surgery in patients with OA. Group A (n=50) received a PRGF injection, and Group B (n=50) an HA injection. The mean age

was 35.5 years (ranging from 18 to 77 years), and 88% of the patients were women. The pain intensity (VAS) and maximum mouth opening before and after the procedure were analyzed statistically. The best results were observed in the PRGF treated group, with a significant reduction in pain at 18 months compared to patients treated with HA. Regarding mouth opening, there was an increase in both groups, with no significant difference, besides an improvement in the functional capacity of the group treated with PRGF.

Some early studies supported the efficacy of HA injections to treat internal TMJ disorders. However, recent evidence suggests that it may also be effective in inflammatory and degenerative disorders²¹, especially if it is associated with arthrocentesis⁹. These considerations allowed widening the indications for HA injections to a broader range of TMDs^{3,8}.

CONCLUSION

Most of the studies analyzed showed that the intra-articular infiltration of HA is an effective treatment, both in short and medium terms, for the internal alterations of the TMJ provided that a correct diagnosis is made, and the patient has not responded successfully to the more conservative therapies. HA infiltration can eliminate or diminish the levels of the symptoms and restore the function through the qualitative and quantitative improvement of the synovial fluid. -

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