

Systematic Review TMJ Disorders

Effect of hyaluronic acid on the regulation of inflammatory mediators in osteoarthritis of the temporomandibular joint: a systematic review

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Abstract. Osteoarthritis is one of the most frequent pathologies affecting the temporomandibular joint (TMJ). There is evidence that the use of intra-articular hyaluronic acid (HA) for the treatment of this disorder achieves positive effects through a reduction in inflammatory mediators. A systematic review of the available evidence regarding the regulation of inflammatory mediators when applying HA in osteoarthritis of the TMJ in humans was performed. The Web of Science, Embase, ScienceDirect, MEDLINE, Scopus, EBSCOhost, and LILACS databases, SciELO library, and search engine Trip Database were searched systematically. Two thousand eight hundred and sixty-three related articles were found, of which only two met the selection criteria (both were clinical trials and evidence level 2b for treatment studies). These two articles represented a population of 87 patients. Both articles reported that the application of HA had a positive effect on the regulation of inflammatory mediators; the mediators studied were those of the plasminogen activator system and levels of nitric oxide. The limited evidence available suggests that the application of HA regulates various inflammatory mediators in osteoarthritic processes in the TMJ. Nevertheless, further evidence in this regard is required, through the study of specific pathologies of the TMJ, complementing the assessment of clinical parameters with molecular studies, and generating good quality clinical studies with larger sample sizes.

Key words: temporomandibular joint disorders; osteoarthritis; hyaluronic acid; inflammation; systematic review.

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One of the most frequent pathologies that can affect the temporomandibular joint (TMJ) is osteoarthritis (OA), a slow and progressive degenerative disease of the articular cartilage.^{1–3} It is characterized

by spontaneous pain at rest or in function, decreased range of motion, and articular noise.⁴ Furthermore, fibrillation and erosion of the articular surfaces, chondrocyte proliferation, articular cartilage eburna-

tion, synovitis, and the inhibition of articular component synthesis have been demonstrated.^{3,5}

There is evidence that the inflammatory reaction that occurs in OA of the TMJ is

partly responsible for the development and progression of the pathology,⁶ including high levels of inflammatory mediators in the synovial fluid, such as interleukin 1 beta (IL-1 β) and tumour necrosis factor alpha (TNF- α),⁷⁻⁹ among others. Furthermore, an increase in molecular weight, decomposition of hyaluronic acid (HA),¹⁰ and a decrease in proteoglycan 4 have been reported.¹¹ Secondary to this, there is a decrease in viscosity of the synovial fluid, which leads to a weakening in the protection of the joint proteoglycan matrix.¹⁰ In recent years, the pharmacological use of HA has been proposed for the treatment of this disorder and has achieved positive effects in reducing inflammatory mediators in animal model and humans studies.^{2,10,12}

The aim of this study was to perform a systematic review of the available evidence regarding the regulation of inflammatory mediators after the application of HA in OA of the TMJ in humans. The results of this review are presented in accordance with the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).¹³

Materials and methods

Primary articles reporting studies involving human populations, in which the effects of HA in regulating inflammatory mediators in OA of the TMJ were measured, were included. The following eligibility criteria were applied: clinical trials and observational studies; evaluation of the action of HA in regulating inflammatory mediators in OA of the TMJ in humans. There was no restriction on language or year of publication. Studies on patients with diagnoses other than OA were excluded.

Study variables

The response variable was the identification of the inflammatory mediators studied and the effect of HA on the regulation of these mediators in OA of the TMJ. Other variables of interest were the following: characteristics of the primary articles (language, publication year, characteristics of the study sample, design, and level of evidence); clinical variables (HA type used, substance used in the control group, application protocol, method of OA diagnosis, other outcome variables measured, monitoring time points, and process of synovial fluid sampling); and the methodological quality of the studies, as measured with the

MINCIR scale for articles on therapies or therapeutic procedures.¹⁴⁻¹⁷

Database search and search strategy

The following were searched: Web of Science, Embase, ScienceDirect, MEDLINE, Scopus, EBSCOhost, and LILACS databases, SciELO library, and the search engine Trip Database.

A broad search was initially performed, in which medical subject heading (MeSH) terms were used along with free words. Subsequently a specific search was performed in which Boolean operators (AND and OR) were added, as well as limits (type of study design (clinical trial and observational study), conducted in humans). The search was adapted to each database and its corresponding language. The search strategies used in the databases, library, and search engine consulted are listed in Table 1.

The titles and abstracts were first reviewed against the eligibility criteria; items fulfilling the exclusion criteria were removed sequentially. Moreover, a filter was applied to remove duplicate articles. Subsequently the full-text of each selected article was assessed carefully.

Study selection and data processing

Two independent researchers (VI and TB) performed the literature search, evaluating the items identified by title, abstract, and full-text reading. In situations where there was disagreement between the researchers, the dispute was resolved by consensus among researchers. Data were extracted manually and entered into a spreadsheet in Excel 2011 for Mac (version 14.5.5, 2010; Microsoft Corporation); these data were then subjected to further analysis.

Methodological quality

The MINCIR scale was used to evaluate the methodological quality of the studies.¹⁴⁻¹⁷ This scale is composed of three domains: (1) study type, (2) sample size, and (3) methodology used (objectives, design, eligibility criteria, and justification for the sample size). The scores obtained for each domain are added together to give a final total score, which can range from 6 to 36 points, with 6 corresponding to a study of low methodological quality and 36 corresponding to a study of good methodological quality (the cut-off point that defines the construct methodological quality is 18 points).¹⁴⁻¹⁷

Definitions

HA was defined as an unbranched linear polysaccharide formed of several units of glucuronic acid disaccharide and *N*-acetylglucosamine of natural or artificial origin that was injected into the TMJ as treatment; the terms 'hyaluronate' and 'viscosupplementation' were considered synonyms. OA of the TMJ was defined as a non-inflammatory degenerative chronic multifactorial disease that could affect all components of the TMJ and cause pathological changes in the articular surfaces. Finally, an inflammatory mediator was defined as any molecule having an action in the inflammatory process related to the TMJ, whether in the plasma or cellular.

Results

Search results

Two thousand eight hundred and sixty-three articles related to the review topic were found, of which 203 met the selection criteria on screening of the title. Following the application of the filter to remove duplicates, 111 articles remained, of which only 22 met the selection criteria on screening of the abstract. Details of the article selection according to the database, library, and search engine used are summarized in Table 2. Filters for the removal of duplicates were then applied, leaving seven items for full-text reading. Of these, only two met the selection criteria and were included in the analysis.^{18,19} A flow chart of the study selection process is given in Fig. 1.

Characteristics of the primary articles

One of the selected articles was written in Italian (published in 2004) and the other in English (published in 2010). The combined study sample comprised 87 patients (51 female and 36 male). One of the articles reported the average patient age for each of the study groups: HA group 43 years (range 28-57 years), saline solution group 44 years (range 25-63 years), and control group 41 years (range 27-55 years)¹⁸; the other study reported the overall average age of the study patients, which was 53.9 ± 14.6 years.¹⁹ Both studies were clinical trials and were classified as level of evidence 2b for studies on therapies or therapeutic procedures according to the Oxford classification.²⁰

Clinical characteristics

The clinical characteristics of the studies, including the type of HA used, substance

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