

Systematic Review  
TMJ Disorders

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

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*M. C. Goiato, E. V. F. da Silva, R. A. de Medeiros, K. H. L. Túrcio, D. M. dos Santos: Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review. Int. J. Oral Maxillofac. Surg. 2016; xxx: xxx–xxx. © 2016 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.*

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

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

Accepted for publication 6 June 2016

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

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

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

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

## Materials and methods

A systematic literature review was performed following the PRISMA statement

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

## Search strategy and study selection

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

## Inclusion and exclusion criteria

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

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

## Quality analysis of studies

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

## Data analysis

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

## Results

### Study selection

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

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

### Study characteristics

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

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

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

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

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