Intra-articular injection of hyaluronic acid for temporomandibular joint osteoarthritis in elderly patients
Luca Guarda-Nardini, Daniele Manfredini, Marco Stifano, Alberto Staffieri, Gino Marioni

SUMMARY

Background. Preliminary findings gave encouraging results for the use of hyaluronic acid in temporomandibular joints with inflammatory/degenerative processes. This investigation aimed at evaluating retrospectively the efficacy of intra-articular injections of hyaluronic acid in elderly patients (aged >65 years) with osteoarthritis of the temporomandibular joint as compared with those of a group of adult non-elderly patients.

Materials and methods. Two groups of patients with Research Diagnostic Criteria for Temporomandibular Disorders axis I group IIIb diagnosis of osteoarthritis, aged over (N=17)/under (N=33) 65 years respectively (elderly/non-elderly groups), underwent a cycle of five injections (one per week) of 1 ml low molecular weight hyaluronic acid and four follow-up assessments after the end of the treatment (at one week, at one month, at three months, at six months).

Results. At the end of the treatment period, improvements in the elderly group were significant with respect to baseline values in the minimum and maximum masticatory pain, maximum pain at rest values, and functional limitation scores. In the non-elderly group, significant improvements at the end of treatment were showed in all treatment outcome variables, except than minimum pain at rest values. All improvements were maintained over the six-month span of the follow-up period, and no significant differences were showed between groups for any of the outcome variables, except than functional limitation scores, which improved more in the elderly group.

Conclusions. These findings are not supportive for a difference in efficacy between the elderly patients and the other subjects, even though further works on different age groups are needed before generalization of results.

Key words: temporomandibular joint; osteoarthritis; hyaluronic acid; injections; Research Diagnostic Criteria for Temporomandibular Disorders.

INTRODUCTION

Hyaluronic acid (HA) is a linear unbranched polysaccharide consisting of repeating disaccharide units. Proteoglycan monomers bind to HA to form large aggregates that are enmeshed in the collagen matrix of intact cartilage. HA is also a critical macromolecular component in normal synovial fluid and seems to play a role in joint stabilization and joint surfaces nutrition.

In joints affected by osteoarthritis the concentration and molecular weight of HA in the synovial fluid is diminished, due to dilution, fragmentation and production of lower molecular weight HA by synoviocytes. These conclusions have led to the idea that the attempt of restoring the concentration and molecular weight of HA by intra-articular HA injection (viscosupplementation) may have some therapeutic effect in joints with osteoarthritis [1]. Literature data suggest that patients with osteoarthritis of the knee reported a significant improvement in their symptoms with a cycle of five low molecular weight hyaluronic acid injections [2-4], thus allowing to hy-
It is hypothesized that similar benefits can be achieved in the treatment of other osteoarthritic joints. The literature on temporomandibular joint (TMJ) disorders supports the usefulness of hyaluronic acid injections to improve and restore normal lubrication in joints with disc position abnormalities [5-7], and preliminary findings have encouraged results in joints with inflammatory/degenerative processes as well [8-10].

The aim of the present study was to evaluate retrospectively the efficacy of intra-articular injections of hyaluronic acid in elderly patients (aged >65 years) with osteoarthritis of the temporomandibular joint. The results were compared with those of a group of adult non-elderly patients with osteoarthritis of TMJ treated consecutively with the same approach.

**MATERIALS AND METHODS**

*Study design*

All the available records of the 151 patients consecutively treated for TMJ osteoarthritis with intra-articular HA injection at the Department of Maxillofacial Surgery, University of Padova, Italy, a tertiary referral academic hospital, between March 2003 and September 2005 have been evaluated.

Criteria for the diagnosis of TMJ osteoarthritis were taken by the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD Axis I Group IIIb), [11], which provided that a Group IIIb diagnosis of osteoarthritis was made when the following signs and symptoms were present:

- arthralgia (TMJ pain with lateral and/or posterior palpation plus anamnestical reporting of TMJ pain during maximum voluntary mouth opening and/or maximum assisted mouth opening and/or lateral excursions);
- crepitus sounds;
- radiological signs of TMJ bone structures abnormalities, such as erosions, sclerosis, flattening, osteophytes.

Criteria for exclusion were the presence of RDC/TMD muscle disorders (Group I diagnoses) and/or systemic rheumatic diseases (i.e. rheumatoid arthritis, psoriatic arthritis, fibromyalgia), as diagnosed according to the American College of Rheumatology criteria [12].

The protocol adopted at the Department of Maxillofacial Surgery, University of Padova, Italy provided a cycle of five injections (one per week) of 1 ml hyaluronic acid (Hyalgan®; Fidia Farmaceutici SpA, Abano Terme, Italy) according to the technique described by Guarda-Nardini et al. [8] and five follow-up assessments after the end of the treatment (at one week, at one month, at three months, at six months, at one year). Patients with at least a 6-month follow-up and no missing data (n=50) were considered for statistical analysis.

**Injection technique**

The hyaluronic acid used in the present investigation, Hyalgan®, is a defined (500-730 kDa) molecular weight fraction of a highly purified avian sodium hyaluronate, buffered (pH 6.8-7.5) in physiologic saline.

The technique used to gain access to the temporomandibular joint and perform hyaluronic acid injection employs the same reference points as used in arthroscopic examination [13], that is to say the ones referred to the line lateral canthus-tragus according to the method proposed by Holmlund [14].

The injection technique provided that the skin surface is disinfected with povidone iodine before performing local anaesthesia. Mepivacaine 2% with adrenaline 1/100000 seeped in subcutaneous region with a pre-auricular approach is used to anaesthetise the soft tissues over the joint, then mepivacaine 3% without adrenaline is injected into the joint cavity, anaesthetising the joint capsule and relaxing this virtual space.

Two 18 G needles are placed to make entry and exit points for the Ringer lactate solution (25-50 cc)

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<th>Table 1. Age group &gt;65 years. Scores and values in the treatment outcome variables</th>
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P – values for comparisons vs. week 1 in parentheses. Legend: MVMO – maximum voluntary mouth opening; MAMO – maximum assisted mouth opening; * – p<0.05; ** – p<0.01; *** – p<0.001.
used to wash out the entire joint and eliminate the catabolites present in the synovial fluid [15]. The exit needle is then removed and 1 cc of HA is slowly injected into the joint.

**Treatment outcome**

The following parameters were assessed by the same examiner at the time of diagnosis (baseline), at each appointment during the treatment and at each appointment during the follow-up period (1 week, 1, 3, 6, months after the end of treatment):

- masticatory efficiency (assessed by a Visual Analog Scale from 0 to 10, the extremes of which were “eating only semi-liquid food” and “optimal masticatory efficiency of any kind of food”);
- pain at rest and mastication (assessed by a Visual Analog Scale from 0 to 10, the extremes of which were “no pain” and “pain as bad as the patient ever experienced”);
- functional limitation during usual jaw movements (0 absent; 1 slight; 2 moderate; 3 intense; 4 severe).
- subjective efficacy of the treatment (0 poor; 1 slight; 2 moderate; 3 good; 4 excellent).
- tolerability of the treatment (0 poor; 1 slight; 2 moderate; 3 good; 4 excellent);
- maximum non-assisted and assisted mouth opening (in mm).

**Data Analysis**

Patients were divided into two age groups (less than/more than 65 years). The statistical significance of the differences among means for parameters described by VAS values was determined by parametric statistics using the paired sample Student’s t test for results in the same set of cases and the pooled Student’s T-test for comparing two means of different sets of cases. The significance of the changes in parameters described by a score was statistically analysed using non parametric methods (Wilcoxon rank sum test). The statistical analysis was performed with a 11.0 version of a SPSS statistical software (SPSS Inc., Chicago, USA). A significance level of 0.05 (two tailed) was assumed for all the calculations, to determine whether to reject the null hypothesis.

**RESULTS**

Seventeen out of 50 patients (34%) were older than 65 years (elderly group), with a mean age of 72.7 years (Standard deviation, SD: 4.5 years; median age: 74 years; range: 66 to 80 years). All of them were female. The 33 patients (29 females and 4 males) (66%) with an age £ 65 years (adult non-elderly group of patients) had a mean age of 51.1 years (SD: 11.1 years; median age: 54 years, range: 24 to 64 years).

No significant differences were detected between groups for any of the treatment outcome variables at baseline.

At the end of the treatment period (one week follow-up), improvements in the elderly group were significant with respect to baseline values in the minimum and maximum masticatory pain, maximum pain at rest values, and functional limitation scores. No significant improvements were showed in the masticatory efficiency scores, minimum pain at rest and maximum assisted and unassisted mouth opening values (Table 1).

In the non-elderly group, significant improvements at the end of the treatment period were showed in all treatment outcome variables, except than minimum pain at rest values (Table 2).

All improvements were maintained over time. Moreover, at the six-month follow-up, masticatory efficiency scores and maximum assisted mouth opening value showed significant changes with respect to baseline in the elderly group.

Improvements in the non-elderly group were

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P – values for comparisons vs. week 1 in parentheses. Legend: MVMO – maximum voluntary mouth opening; MAMO – maximum assisted mouth opening; * – p<0.05; ** – p<0.01; *** – p<0.001.
Fig. 1. Mastication efficiency (VAS scores). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 2. Minimum pain at mastication (VAS scores). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 3. Maximum pain at mastication (VAS scores). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 4. Minimum pain at rest (VAS scores). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 5. Maximum pain at rest (VAS scores). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 6. Functional limitation (ordinal scale: 0 – absent; 1 – slight; 2 – moderate; 3 – intense; 4 – severe). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 7. Maximum unassisted mouth opening (mm). Comparison between age groups. Legends: week – W; follow-up – FU.

Fig. 8. Maximum assisted mouth opening (mm). Comparison between age groups. Legends: week – W; follow-up – FU.
trophic joints [21].

As for the comparison between the two age groups (Figures 1-8), the elderly group showed a slightly higher rate of improvement with respect to some treatment outcome parameters, but no significant differences at the end of the treatment period (one week follow up) were detected for any of the outcome variables.

The functional limitation score seems to be the only parameter for which a significantly higher improvement in the elderly group is detectable and maintained over time (significant differences with the non-elderly group were showed at the fourth injection appointment and at one month and three months follow-up, and differences close to significance were detected at the other follow-up appointments).

**DISCUSSION**

The present investigation reported data about the relative efficacy at six months of a cycle of five hyaluronic acid injections for the treatment of temporomandibular joint osteoarthritis in two different age groups of patients.

The rationale for the use of hyaluronic acid infiltrations in the management of temporomandibular joint pathologies is based upon recent suggestions that an increase in joint friction coefficient is a main risk factor for degenerative joint pathologies [16,17] and that hyaluronic acid, being an essential component for joints lubrication, may help reducing joint friction [18,19].

The first investigation on the use of hyaluronic acid for TMJ disorders was a double-blind, placebo-controlled clinical trial reporting that HA injections may be effective to reduce symptoms at six-months in subjects with reducing disk displacement but not in patients with degenerative joint diseases [20].

On the basis on that first report and successive investigations, the main indication for intrarticular injections of hyaluronic acid seemed to be the need for restoring normal lubrication and improving function in joints with disc position abnormalities [5-7]. More recently, a protocol of five infiltrations performed immediately after joint lavage has been shown effective to improve function and reduce symptoms in inflammatory-degenerative conditions as well [8-10]. Moreover, a recent investigation reported that injections with a high molecular weight hyaluronic acid were significantly more effective in decreasing pain intensity than injections of corticosteroids in osteoarthritic joints [21].

The present investigation provided the adoption of the above described five-injection protocol, due to the use of a low molecular weight hyaluronic acid.

A number of parameters has been assessed as objective (maximum assisted and unassisted mouth opening) and subjective (masticatory efficiency, functional limitation, pain at rest and at mastication) treatment outcome variables.

The aim of the study was twofold: to confirm previous preliminary positive reports with the same protocol, and to investigate for differences in the treatment efficacy between two age groups of patients.

Findings from this study showed that all parameters of treatment efficacy markedly improved in both age groups since the time of the first injection, kept on improving during the five weeks treatment period and were maintained over the six months follow up period.

As for this study’s findings in the two age groups, improvements seemed to be slightly more marked in the elderly patients group, but no significant differences between groups were clearly detected, except than in the functional limitation scores.

These results confirmed findings obtained over a one year follow up span in a smaller sample and extended the positive effects to a group of elderly patients as well [10], lending further support to the usefulness of hyaluronic acid injections combined with joint lavage, to reduce symptoms and improve function in patients with temporomandibular joint osteoarthritis.

In particular, as already described in previous studies [8-10], positive effects on pain, both at rest and at mastication, have been shown after the first injection in both age groups, thus suggesting that the combined adoption of joint lavage and HA injection may have indications in pain management as well as joint lubrication.

These data have to be compared with future studies adopting a higher molecular weight hyaluronic acid which, according to the existing literature, gave better results in terms of pain reduction and analgesic effects in larger joints [2-4, 22-24].

Indeed, the good and immediate analgesic effect achieved with a low molecular weight HA is a quite unexpected finding, and future studies should be directed toward the comprehension of the mechanisms leading to pain relief in osteoarthritic temporomandibular joints treated with HA injections.

In the case of the present investigation, it is also possible that the joint lavage that was performed before HA injection contributed to eliminate the most part of catabolites and inflammatory mediators within the synovial fluid, thus being the main responsible for
pain relief. Otherwise, the efficacy of hyaluronic acid infiltration within an arthritic joint should be strongly limited by the presence of inflammatory substances. Thus, researches with an active control group have to be performed to assess which is the effective part of the protocol (i.e., if hyaluronic acid injections are the main responsible for symptoms’ improvement).

Also, the efficacy of different molecular weight HA have to be compared in order to assess the most effective protocol in terms of cost-benefit ratio. Indeed, higher molecular weight HA should allow performing a reduced number of injection, thus avoiding the serial injections described in this protocol.

REFERENCES


CONCLUSIONS

In general, these findings are not supportive for a difference in efficacy between the elderly patients and the other subjects, even though further works on different age groups are needed before generalization of results. Nonetheless, if confirmed, these results might support the usefulness of intraarticular hyaluronic acid injections as an effective treatment option for a large percentage of elderly patients with temporomandibular joint inflammatory-degenerative disorders, thus representing a concrete therapeutic alternative to manage these disorders.