Comparison of 2 Hyaluronic Acid Drugs for the Treatment of Temporomandibular Joint Osteoarthritis

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Purpose: To compare the effectiveness of 2 treatment protocols providing 5 weekly temporomandibular joint (TMJ) arthrocenteses immediately followed by injections of 2 different molecular weight hyaluronic acid (HA) drugs to manage symptoms in patients with inflammatory-degenerative TMJ disease.

Materials and Methods: Patients with a Research Diagnostic Criteria for Temporomandibular Disorders diagnosis of osteoarthritis were randomly assigned to 1 of 2 study groups receiving either low- or medium-molecular weight HA after arthrocentesis. The level of maximum pain at chewing was the primary outcome variable, and maximum pain at rest, subjective chewing efficiency, functional limitation, treatment tolerability, perceived treatment effectiveness, and jaw range-of-motion function in millimeters were the secondary outcomes. All variables were assessed and compared between groups at baseline, at the end of treatment, and 3 months later.

Results: Forty subjects entered the study. At the end of the follow-up period, all the outcome variables improved in both groups of patients. A between-group comparison of changes over time showed that differences were not significant for any of the outcome variables, that is, pain at chewing (F = 0.056, P = .815), pain at rest (F = 0.383, P = .541), chewing efficiency (F = 0.050, P = .825), functional limitation (F = 0.268, P = .609), and mouth opening (F = 0.003, P = .954). In addition, no between-group differences were shown for perceived treatment effectiveness and treatment tolerability.

Conclusions: Similar positive effectiveness was shown for 2 treatment protocols for TMJ osteoarthritis (ie, 5-session single-needle arthrocentesis plus low- or medium-molecular weight HA).

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The first works on temporomandibular joint (TMJ) arthrocentesis focused on its application to increase jaw function and achieve relief from pain in patients with restricted mouth opening.1,2 Then, with the increase of knowledge on the role of joint lubrication impairment as a risk factor for TMJ internal derangements, viscosupplementation with sodium hyaluronate, that is, hyaluronic acid (HA), became an option for the management of symptoms in the clinical setting.3 This led to the progressive expansion of potential clinical indications for the use of arthrocentesis plus HA injections, with particular regard to joints with inflammatory-degenerative disorders.4,5 Protocols for symptom management in larger joints provided the adoption of a cycle of 5 weekly HA injections immediately after arthrocentesis,6,7 and encouraging findings also emerged from long-term case series on patients with TMJ disorders,8,9 as well as from a previous clinical trial from our research group supporting the superiority of multiple-injection protocols with respect to single-session joint lavage.10 Notwithstanding the previously mentioned findings, definitive information on the most suitable protocol as concerns the number of injections, the ideal HA molecular weight, and—more in general—the most effective approach (ie, arthrocentesis alone or combined with drugs) is still to be gathered.11 Among these aspects, comparative trials on the effectiveness of HA drugs of different molecular weight may be

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useful to add information to the existing amount of knowledge on TMJ injections.

In view of these considerations and in line with the need to perform exploratory trials on the issue, the aim of this investigation was to answer the following question: In patients with TMJ osteoarthritis who underwent a treatment protocol of 5 weekly arthrocenteses plus HA injection, does treatment effectiveness at 3 months depend on the use of different molecular weight HAs? The null hypothesis was that there are no differences between the protocols using the different molecular weight HAs. To test the hypothesis, we compared treatment-related changes in some clinical outcome variables between patients receiving low-molecular weight HA and patients receiving medium-molecular weight HA.

Materials and Methods

To address the research purpose, we designed an exploratory randomized clinical trial. The study population was composed of consecutive patients with a Research Diagnostic Criteria for Temporomandibular Disorders version 1.012 diagnosis of osteoarthritis (axis I group IIIb) with joint pain lasting for more than 6 months seeking treatment at the TMD Clinic, Department of Maxillofacial Surgery, University of Padova, Padua, Italy, who were randomly assigned to 1 of 2 study groups. Both groups of patients underwent 5 weekly single-needle arthrocenteses plus HA injection and a 3-month follow-up period. According to an alternate allocation of patients into the 2 groups, patients received 1 of 2 different types of HA, which was the same for all 5 sessions. Patients were instructed to undergo a 2-week washout period before starting the treatment protocol and to not use medications on a routine basis during the active treatment and follow-up periods (ie, only 500 mg of acetaminophen was allowed in the immediate post-intervention phases).

The single-needle technique refers to the approach first described by Guarda-Nardini et al,13 which adopted only 1 needle for both saline fluid injection and ejection. The technique was performed with the patient under local anesthesia, and on average, about 10 mL of saline fluid was used for joint lavage. After joint lavage, patients in group A received 1 mL of medium-molecular weight (ie, 1,200-kDa) HA (Sinovial; IBSA Farmaceutici, Lodi, Italy), and patients in group B

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Table 1. COMPARISON OF DEMOGRAPHIC FEATURES AND BASELINE VALUES IN OUTCOME VARIABLES BETWEEN STUDY GROUPS

<table>
<thead>
<tr>
<th>Study Variable</th>
<th>Group A (n = 17)</th>
<th>Group B (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>82</td>
<td>88</td>
<td>.357</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>47.7 ± 15.0</td>
<td>52.9 ± 16.1</td>
<td>.329</td>
</tr>
<tr>
<td>Pain at rest (0-10 on VAS)</td>
<td>1.9 ± 2.2</td>
<td>2.5 ± 3.1</td>
<td>.552</td>
</tr>
<tr>
<td>Pain at chewing (0-10 on VAS)</td>
<td>5.2 ± 2.5</td>
<td>5.1 ± 2.7</td>
<td>.889</td>
</tr>
<tr>
<td>Chewing efficiency (0-10 on VAS)</td>
<td>7.4 ± 1.6</td>
<td>6.4 ± 1.3</td>
<td>.062</td>
</tr>
<tr>
<td>Functional limitation (0-4 on Likert-type scale)</td>
<td>1.6 ± 1.0</td>
<td>1.8 ± 0.9</td>
<td>.304</td>
</tr>
<tr>
<td>Mouth opening (mm)</td>
<td>36.9 ± 8.4</td>
<td>36.7 ± 5.7</td>
<td>.946</td>
</tr>
</tbody>
</table>

received 1 mL of low–molecular weight (ie, 600-kDa) HA (Hyalgan; Fidia, Abano Terme, Italy).

To ascertain the needed sample size for the investigation, the primary outcome variable was treatment effectiveness based on the assessment of pain levels at chewing on a 10-point visual analog scale (VAS), with 0 being absence of pain and 10 being the worst pain ever. An a priori power analysis based on literature data\(^9\) and assuming a mean VAS value of 6/10 (out of 10) for the main outcome variable, that is, pain at chewing, showed that a 40-subject study design was needed to detect about a 40% between-group difference in mean VAS values for pain at chewing with a statistical power of 5% for type I error (ie, false-positive results) and 20% for type II error (ie, false-negative results).

For each patient, a number of secondary outcome parameters were assessed: maximum pain at rest on a 10-point VAS with the same extreme points as the pain-at-chewing scale; subjective chewing efficiency (0-10 VAS, with 0 being the worst efficiency ever and 10 the best efficiency ever); functional limitation; treatment tolerability and perceived treatment effectiveness on a 5-point scale, with 0 being the lowest and 4 the maximum value; and jaw range-of-motion function in millimeters. All variables were evaluated at baseline, at the end of treatment, and at a 3-month follow-up after the end of treatment. All interventions were performed by 1 of the 2 main investigators (D.M. and L.G.-N.) in accordance with the previously described random sequence of intervention, and the outcome parameters were recorded by the same clinician (C.C.) fully blinded to the type of HA injected in the patients. In an attempt to achieve a double-blind design, we did not tell the patients which of the

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Gender P Value</th>
<th>Age P Value</th>
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</thead>
<tbody>
<tr>
<td>Pain at rest (0-10 on VAS)</td>
<td>.415</td>
<td>.617</td>
</tr>
<tr>
<td>Pain at chewing (0-10 on VAS)</td>
<td>.333</td>
<td>.842</td>
</tr>
<tr>
<td>Chewing efficiency (0-10 on VAS)</td>
<td>.412</td>
<td>.527</td>
</tr>
<tr>
<td>Functional limitation (0-4 on Likert-type scale)</td>
<td>.659</td>
<td>.735</td>
</tr>
<tr>
<td>Mouth opening (mm)</td>
<td>.583</td>
<td>.612</td>
</tr>
</tbody>
</table>


**FIGURE 2.** Changes over time (x-axis) in pain-at-chewing VAS scores (y-axis) in the 2 study groups. Improvement over time was significant for both groups \((P < .001)\). Between-group differences in changes over time were not significant \((P = .815)\).

2 HA solutions was injected into the joint; they received a generic explanation of the potential benefit of administering arthrocentesis plus HA injections, as well as an explanation that the specific intervention that they were undergoing was indicated for their disease. All patients gave their written consent after being informed about the study’s aims and design. Official approval by the University Review Board and Medical Direction was received (authorization code 50361).

For statistical purposes, VAS pain levels and jaw range-of-motion values were managed as continuous variables, whereas data on subjective efficacy and tolerability levels were managed as ordinal variables. For all variables, analysis of variance for repeated measures was performed to assess the existence of significant within-group and between-group treatment effects. Adjustments for age and gender were performed to assess the influence of demographic features on treatment effectiveness. For all comparisons, statistical significance for differences was set at $P < .05$.

**Results**

A total of 40 consecutive patients entered the study protocol. The treatment protocol and follow-up period were completed by 17 patients (82% of whom were female patients; mean age, $47.7 \pm 15.0$ years) assigned to protocol A and 18 patients (88% of whom were female patients; mean age, $52.9 \pm 16.1$ years) assigned to protocol B. Between-group gender ($\chi^2 = 2.17, P = .337$) and age ($t = -0.990, P = .329$) differences were not significant. The remaining 5 patients (3 in group A and 2 in group B) did not complete the treatment protocol (1 subject) or strictly follow the weekly appointments (4 subjects) because of personal problems that prevented them from attending the clinic regularly (Fig 1). Baseline levels in the outcome parameters were not different between the 2 groups, with $P$ values ranging from .062 to .946 (Table 1).

At the end of the follow-up period, both groups of patients improved with regard to all the outcome variables. The effect of treatment was not different

![Figure 3](image-url)
with regard to age and gender, thus not being influenced by the demographic features of the sample (Table 2). Patients in group A reported significant improvement in pain at chewing \((P < .001)\), mouth opening \((P = .003)\), chewing efficiency \((P = .004)\), and functional limitation \((P = .041)\), whereas improvement in pain at rest was not significant \((P = .242)\). Patients in group B reported significant improvement in chewing efficiency \((P < .001)\), pain at chewing \((P < .001)\), and pain at rest \((P = .002)\), whereas improvement over time in mouth opening \((P = .106)\) and functional limitation \((P = .211)\) was not significant. No relevant adverse or side effects were observed in any patients, with the only minor exception of a transient anesthesia of the temporal and zygomatic branches of the facial nerve area after an intervention in 3 patients.

Between-group comparison of changes over time showed that differences were not significant either in the primary outcome variables, that is, pain at chewing \((F = 0.056, P = .815)\) (Fig 2), or in the other outcome variables, that is, pain at rest \((F = 0.383, P = .541)\) (Fig 3), chewing efficiency \((F = 0.050, P = .825)\) (Fig 4), functional limitation \((F = 0.268, P = .609)\) (Fig 5), and mouth opening \((F = 0.003, P = .954)\) (Fig 6). In addition, no between-group differences were shown for perceived treatment effectiveness and treatment tolerability (Table 3). The null hypothesis that there are no differences between the protocols using the different molecular weight HAs could not be rejected.

**Discussion**

The available literature has not been conclusive so far in terms of indicating which is the most suitable viscosupplementation protocol to achieve pain relief and restore jaw function in patients with TMJ osteoarthritis.\(^{11}\) So, there is a need to gather as much data as possible to explore the effectiveness of the different protocols’ features (eg, number and sites of injections, HA molecular weight, and combination with arthrocentesis) for the different conditions (eg, physical and psychosocial diagnoses). Considering these drawbacks, as part of an ongoing attempt to gain deeper knowledge on the effectiveness of arthrocen-
theses and injections in the management of inflammatory-degenerative disorders of the TMJ, investigations were performed by our research group to identify predictors of treatment effectiveness and to compare different protocols. With these premises, the aim of the present investigation was to assess whether, in patients with TMJ osteoarthritis who underwent a treatment protocol of 5 weekly arthrocenteses plus HA injection, treatment effectiveness at 3 months depends on the use of different molecular weight HA. To address the research question, we designed a clinical trial to compare the treatment-related changes in some clinical outcome variables in patients receiving low- versus medium-molecular weight HA.

Findings suggested that both protocols were effective in improving symptoms at the 3-month follow-up, and no between-protocol differences in effectiveness were shown. These findings are open to several suggestions with regard to the magnitude of the treatment effectiveness and to the comparison of the 2 protocols providing HA of different molecular weight. Both study groups improved significantly with regard to most outcome variables, with a 57.8% reduction in pain-at-chewing levels for group A and a 59.3% reduction for group B. These findings are in line with literature data supporting the effectiveness of 5-sesion single-needle arthrocentesis plus HA injection for TMJ osteoarthritis. Importantly, the fact that between-group differences were not significant suggests that medium-molecular weight HA is equally as effective as low-molecular weight HA. This finding assumes importance in light of previous reports on the adoption of low-molecular weight HA in patients with TMJ disorders and may be worthy of further exploration with future trials.

The adoption of the 5-injection protocol for viscosupplementation of the TMJ was based on similar approaches adopted for larger joints, and a recent randomized controlled trial by our group suggested that it may be viewed as the most effective approach for viscosupplementation of the TMJ. The same study also concluded that high-molecular weight HA is not suitable for injecting the TMJ because of its high viscosity and large steric interaction that prevents one from achieving a quick diffusion within the small

**FIGURE 5.** Changes over time (x-axis) in 5-point Likert-type scores for functional limitation (y-axis) in the 2 study groups. Improvement over time was significant for group A \( (P = .041) \), whereas it was not significant for group B \( (P = .211) \). Between-group differences in changes over time were not significant \( (P = .609) \).

TMJ intra-articular space. Notwithstanding that, no information is available on the effectiveness of using HA of medium molecular weight, which is the rationale underlying this investigation. Another comparative trial suggested that no differences existed in protocols adopting the classical 2-needle technique or the newly introduced single-needle technique for administering arthrocentesis. For that reason, our investigation adopted the single-needle technique to reduce the number of needles inserted into the joint during the 5-session protocol, to avoid the outflow of the HA from the second skin hole and, possibly, reduce the patient’s discomfort.

Indeed, the risk for overtreating the TMJ, especially if one is performing the 2-needle arthrocentesis with a total of 10 needles inserted into the small joint cavity within a 5-week span, cannot be denied. As a further step on the way to reduce joint trauma, a reduction of the number of serial injections seems to be a promising strategy, and the use of HA with potentially longer-lasting activity is an option worthy to be explored to pursue that goal. The medium-molecular weight HA adopted in this investigation was shown to be equally as effective and tolerable as the commonly used low-molecular weight preparation, showing an absence of side effects that chara-

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**Figure 6.** Changes over time [x-axis] in millimeters of mouth opening [y-axis] in the 2 study groups. Improvement over time was significant for group A (P = .003), whereas it was not significant for group B (P = .106). Between-group differences in changes over time were not significant (P = .954).


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**Table 3. BETWEEN-GROUP COMPARISON (T TEST) FOR PERCEIVED TREATMENT EFFECTIVENESS AND TREATMENT TOLERABILITY AT END OF FOLLOW-UP PERIOD**

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Group A (n = 17)</th>
<th>Group B (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived treatment effectiveness</td>
<td>2.6 ± 1.1</td>
<td>2.5 ± 0.8</td>
<td>.879</td>
</tr>
<tr>
<td>Treatment tolerability</td>
<td>3.0 ± 0.9</td>
<td>2.4 ± 0.9</td>
<td>.116</td>
</tr>
</tbody>
</table>

terized previous experimental use of higher-molecular weight HA for TMJ disorders. In view of these considerations, data gathered in this investigation may be viewed as a starting point to explore the possibility to identify less invasive protocols, with a reduced number of serial injections by the use of medium-molecular weight HA.

Longer follow-up periods are strongly needed to support these findings, even though it must be borne in mind that the technique used in our study as a comparison reference (ie, 5-session single-needle arthrocentesis plus low-molecular weight HA injections) was already shown to be effective for longer post-treatment spans than that adopted in this study.

Generally, despite the need to define potentially less invasive protocols and to better identify, the indications for performing joint lavage and injections, it should also be stressed that no side effects have been reported with the adoption of the described protocol. The worst, and only, discomfort noted by the patient is the unpleasant feeling associated with the transient effects of the local anesthesia in the TMJ area, as shown by the good tolerability level. So, safety in use for the technique described in this study has been supported, and future studies might help to define the needed learning curve for approaching TMJ arthrocentesis and injection with a good risk management strategy.

From a methodologic viewpoint, it should be borne in mind that, because of the paucity of available data on these treatment protocols, it was difficult to adhere strictly to the criteria for conducting randomized controlled trials. In particular, along with comparisons with placebo, injection techniques must withstand comparison with other conservative approaches, such as oral appliances, physiotherapy, and cognitive-behavioral treatments. With this premise, specific study designs for comparison with other treatments must be adopted on the basis of the CONSORT (Consolidated Standards of Reporting Trials) guidelines for reporting clinical trials, with additional strategies for measuring pain in a multidimensional conceptualization and for controlling for symptoms’ fluctuation over time. Notwithstanding that, it should be kept in mind that the peculiar nature of the treatments under investigation prevents one from achieving a full double-blind design, because the operators were blind with respect to the patients’ outcome parameters but the operators could not obviously be blind with respect to the technique they were performing. Actually, the expertise of the investigators performing the interventions and the expertise of the blinded single examiner recording the patients’ outcome parameters seem to be key factors to warrant the validity of the results and should be taken into account also in future investigations. As a further suggestion for the design of future studies, it can be pointed out that, on the basis of data gathered in this study and in our previous publication, much larger sample sizes are necessary to detect lower threshold differences; for instance, up to 43 patients per group and 97 patients per group are needed to detect 30% and 20% between-group differences, respectively. Thus, considering the clinical and logistic difficulties in performing large-sample clinical trials on this issue, studies attempting to identify the clinically significant VAS change threshold in patients with chronic TMJ pain have to be designed in the near future to avoid type II errors in the field of research on TMJ disorder treatment. Keeping this in mind, the design of multicenter studies has to be taken into account as a possible strategy to increase the external validity of these findings.

Within the limits of this investigation, similar positive effectiveness was shown for 2 treatment protocols for TMJ osteoarthritis (ie, 5-session single-needle arthrocentesis plus low- or medium-molecular weight HA). The null hypothesis that no differences existed between the protocols using the different molecular weight HAs could not be rejected. Future investigations with longer follow-up periods and possibly including other comparison protocols (eg, saline fluid injections) have to be planned to increase knowledge on the strategies to perform TMJ arthrocentesis and injections in patients with TMJ inflammatory-degenerative disorders.

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References