

Treatment Effectiveness of Arthrocentesis Plus Hyaluronic Acid Injections in Different Age Groups of Patients With Temporomandibular Joint Osteoarthritis

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Purpose: To investigate for treatment effectiveness in different age groups of patients with temporomandibular joint osteoarthritis who underwent a cycle of 5 weekly arthrocenteses plus hyaluronic acid injections.

Materials and Methods: We implemented a retrospective study on 76 patients followed up for 1 year. Outcome variables were pain levels at rest and during chewing, subjective masticatory efficiency, functional limitation, perceived efficacy, and jaw range of motion. Three age groups of patients were identified, and treatment effectiveness was compared among groups by means of a multistrata permutation test.

Results: All the partial *P* values of the subtests related to the age groups, adjusted according to the close testing method for controlling multiplicity, were significant: *P* = .009 (aged <45 years), *P* = .001 (aged 45-65 years), and *P* = .001 (aged >65 years). For the younger age group, the treatment had a significant effect only on the pain at mastication and on the subjective efficacy. For the other age groups, the treatment effectiveness was evident with regard to almost all the considered symptoms.

Conclusions: Our findings suggested that the treatment protocol was more effective in patients older than 45 years, thus having important clinical implications regarding attempts to define tailored treatment protocols for patients with temporomandibular disorders.

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J Oral Maxillofac Surg 70:2048-2056, 2012

Hyaluronic acid (HA) is a fundamental component for normal joints' lubrication effect, so exogenous viscosupplementation was hypothesized to have a positive effect on temporomandibular joint (TMJ) disorders.¹ Some early studies supported the efficacy of HA injections to treat TMJ internal derangements,²⁻⁴ but more recent evidence suggested that it may be effective in inflammatory-degenerative disorders as well, especially if combined with a thorough joint lavage.⁵⁻⁸

Such findings allowed extending the indications for TMJ HA injections to a wider population of temporomandibular disorder (TMD) patients, especially in terms of age range, because a higher age of onset is recognized for inflammatory-degenerative disorders with respect to other forms of TMD.⁹⁻¹¹ Investigations of patients with TMJ osteoarthritis suggested that subjects aged up to 80 years may benefit from a treatment protocol providing arthrocentesis plus HA injection.

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Conflict of Interest Disclosures: None of the authors reported any disclosures.

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0278-2391/12/7009-0\$36.00/0

<http://dx.doi.org/10.1016/j.joms.2012.05.018>

tions,¹² even if several aspects related to specific treatment effects have yet to be understood.^{13,14} Among others, the effect of age on treatment effectiveness has never been assessed, so it might be interesting to gather data on this particular issue.

In consideration of these premises, the aim of this study was to test the effect of treatment over time in different age groups of patients with inflammatory-degenerative disorders who underwent a cycle of 5 weekly arthrocenteses plus HA injections, the null hypothesis being that treatment effectiveness does not change in relation with a patient's age.

Materials and Methods

STUDY DESIGN

This investigation had a retrospective design, and data are presented for 76 patients (86.8% of whom were women; age range, 28-81 years) with a diagnosis of osteoarthritis according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD axis I group IIIb) in the absence of both RDC/TMD muscle disorders (group I diagnoses) and rheumatic diseases who underwent a cycle of 5 two-needle arthrocenteses with injections (1 per week) of 1 mL of HA (Hyalgan; Fidia, Abano Terme, Italy) and follow-up assessments after the end of the treatment at 1 month, 3 months, 6 months, and 1 year. The need to undergo the treatment protocol was based on the clinicians' judgment that patients may benefit from such an approach. All patients had a common history of pain lasting for more than 6 months that did not improve or improved minimally with conservative physiotherapy or oral appliance therapy performed by their practitioners. All patients gave their consensus to undergo treatment, which was part of the clinical protocols already in use at the TMD Clinic (University of Padova, Padua, Italy) and was approved by the University of Padova's Medical Director.

According to the RDC/TMD guidelines,¹⁵ 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 anamnestic reporting of TMJ pain during maximum voluntary mouth opening and/or maximum assisted mouth opening and/or lateral excursions);
- crepitus sounds;
- radiologic signs of TMJ bone structure abnormalities, such as erosions, sclerosis, flattening, or osteophytes.

It must be pointed out that the original 1992 RDC/TMD publication allowed plain tomography

and panoramic radiographs to support the clinical diagnosis of osteoarthritis. In our investigation, as already discussed in some previous articles on TMD epidemiology in the Italian patients,¹¹ plain radiographs were already available for some patients at the time of the first assessment. In some other patients, cone-beam computed tomography was obtained to integrate the clinical diagnosis, despite the fact that this technique obviously was not available at the time when the early RDC/TMD guidelines were established.

The following clinical parameters were assessed by the same trained dental student at the time of diagnosis (baseline), at each appointment during the treatment, and at each appointment during the follow-up period:

- pain at rest and chewing, assessed by means of a visual analog scale from 0 to 10, with the extremes being "no pain" (0) and "pain as bad as the patient ever experienced" (10);
- mastication efficiency, assessed by a visual analog scale from 0 to 10, the extremes of which were "eating only semi-liquid" (0) and "eating solid hard food" (10);
- jaw range of motion, comprising maximum non-assisted and assisted mouth opening, left and right laterotrusion, and protrusion (in millimeters);
- functional limitation during usual jaw movements (0, absent; 1, slight; 2, moderate; 3, intense; or 4, severe);
- subjective efficacy of the treatment (0, poor; 1, slight; 2, moderate; 3, good; or 4, excellent).

INJECTION TECHNIQUE

The injection technique adopted in this study uses the same reference points as used in arthroscopic examination (lateral canthus-tragus).¹⁶ The skin surface is disinfected with povidone iodine. Local anesthesia is then achieved with 2% mepivacaine (Carbocaine; Sanofi Winthrop, New York, NY). The anesthetic is first injected into the joint cavity, relaxing this virtual space. Subsequently, the needle is withdrawn gently to the skin surface, thus also anesthetizing the soft tissues over the joint. Two 19-gauge needles are then placed to make entry and exit points for the liquid to be injected that will wash out the entire joint. The arthrocentesis is performed with 50 mL of Ringer lactate to eliminate the catabolites present in the synovial fluid. Once arthrocentesis is completed, the outflow needle is removed and 1 mL of HA is slowly injected into the joint through the other

Table 1. NUMBER, GENDER DISTRIBUTION, AND MEDICAL HISTORY OF PATIENTS BELONGING TO EACH AGE GROUP

Age Group	Patients (N)	Female Patients (%)	Diagnostic Computed Tomography (%)	Previous Oral Appliance (%)	Previous Physiotherapy (%)	Previous Frequent Use of Pain Killers	Concurrent Headache	Previous Surgery/Arthroscopy
<45 yr	23	86.9	52.1	65.2	100	100	26.0	0
45-65 yr	28	85.7	35.7	75	100	100	17.8	0
>65 yr	25	84	40	56	100	100	20	0

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needle. The HA used in this investigation is a defined (600-kDa) molecular weight fraction of a highly purified avian sodium hyaluronate, buffered (pH 6.8-7.5) in physiologic saline solution.

STATISTICAL ANALYSIS

Patients were divided into 3 age groups based on tertiles of the variable age: younger than 45 years (23 subjects, 86.9% of whom were women) (group 1); 46 to 65 years (28 subjects, 85.7% of whom were women) (group 2); and older than 65 years (25 subjects, 84% of whom were women) (group 3). The responses (clinical parameters) were measured for the patients in each age group. The demographic features and medical histories of patients belonging to the 3 age groups are described in Table 1.

The purpose of the statistical analysis consisted of proving the efficacy of serial injections of HA over time considering all the clinical parameters and taking into account the effect of age. All the outcome variables were managed as outcomes, whereas age was managed as a confounding factor based on the hypothesis that the real treatment effect could be affected by the age of patients if data were globally analyzed. Hence, a stratification of the sample with separate analyses was performed.

A multivariate and multistrata permutation test, based on the combination of dependent univariate tests, was applied. According to this testing procedure, for each univariate response and for each age stratum, a permutation test on ordering for repeated measures was performed; a first nonparametric combination of the results with respect to the responses was applied, obtaining 1 partial test for each of the 3 age groups; and finally, a second combination of the *P* values of these partial tests was performed, giving a final global *P* value for the overall test.^{17,18}

We also carried out the initial univariate tests using a combination-based test, considering all the 8 possible bipartitions of the dataset obtained pooling the first *t* times and the other 9 - *t* times (*t* = 1 . . . 8). Then, for each bipartition, that is, the mean values for the first *t* times and for the following 9 - *t* times, a 1-sided permutation test for dependent samples was performed to test the hypothesis of increasing or

decreasing mean (depending on the considered symptom) and the univariate test was obtained combining the 8 partial results related to the pooled samples.

The combinations of the partial tests, at each level of combination (initial univariate test, within-age group multivariate test, and overall test), consisted of the application of the Tippett combining function on the *P* values of the partial tests.

Adjusted *P* values of the partial tests (according to the close testing method) were considered, to attribute the significance of the overall test to 1 or more specific partial tests.

For all statistical procedures, the significance level was set at *P* < .05.

Results

MASTICATORY EFFICIENCY

Values of masticatory efficiency showed a slight but steady-over-time increase in values (Fig 1). This is evident for all 3 age groups and for both phases of the study: the treatment period and the follow-up phase. The middle-aged group had lower baseline values (5.10 ± 1.77), although the differences when compared with the other 2 groups were not significant (6.53 ± 2.10 for patients aged <45 years and 6.24 ± 2.24 for patients aged >65 years) (*P* > .05). Older-aged patients had higher masticatory efficiency values at the end of the follow-up period (8.32 ± 1.71), whereas the mean efficiencies of the 2 groups aged 65 years or younger were similar (7.50 ± 2.68 for patients aged <45 years and 7.53 ± 2.13 for patients aged 45-65 years). In general, it seems that improvement in masticatory efficiency was more evident for patients aged 45 years or older than for younger patients.

MAXIMUM PAIN AT CHEWING

In patients aged younger than 45 years, maximum pain at chewing presented a decreasing trend: the baseline value was 3.80 ± 3.80 , and the end-of-follow-up value was 2.82 ± 3.09 (Fig 2). Patients in the middle-aged group (aged 45-65 years) at the beginning of the therapy period had maximum pain

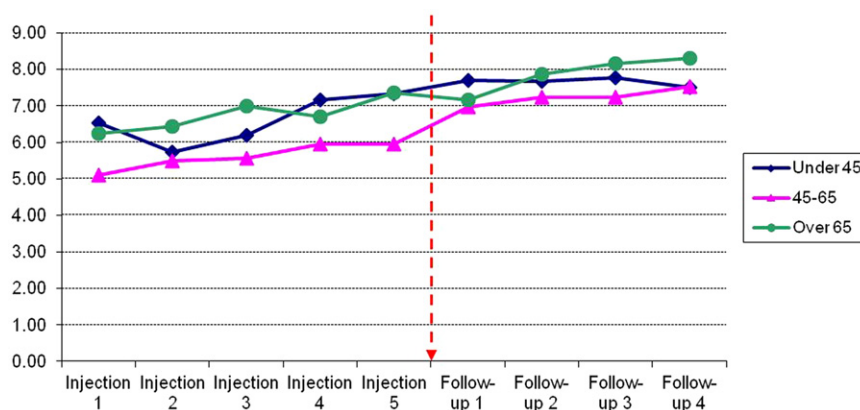


FIGURE 1. Mean values of masticatory efficiency for the 3 age groups.

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at mastication of 6.36 ± 2.53 ; at the end of the follow-up period, they presented a mean value of 2.69 ± 2.77 . A similar reduction of the values was observed in the older patients (aged >65 years): 6.67 ± 2.81 after the first injection versus 1.55 ± 2.14 at the end of the follow-up period. Hence, the decreasing trend for pain at mastication could be observed in all the age groups, but the shift for the younger patients was less than the shift for the older patients; however, it must be pointed out that baseline differences among the groups were significant ($P < .05$), with younger patients reporting less severe pain.

MAXIMUM PAIN AT REST

At baseline, values of maximum pain at rest for the youngest subjects (1.8 ± 2.83) were significantly different with respect to the other groups (4.48 ± 3.15 for patients aged 45-65 years and 4.33 ± 3.65 for patients aged >65 years) ($P < .05$). The mean values of maximum pain at rest seemed to be strongly decreasing with respect to time only for patients in the

group aged 46 to 65 years and the group aged older than 65 years (Fig 3), whereas for the patients aged younger than 45 years, the maximum pain at rest presented an almost constant or only slightly decreasing trend.

FUNCTIONAL LIMITATION

From a descriptive point of view, the functional limitation also progressively decreased, starting from baseline values that were not different among the 3 groups (aged <45 years, 2.17 ± 1.16 ; aged 45-65 years, 2.58 ± 0.74 ; and aged >65 years, 2.45 ± 0.89) ($P > .05$) (Fig 4). This was evident for all the age groups. Both the values at each time and the decreasing rate were similar for the 3 age groups. The mean values were around 2.25 at the beginning of the study and 1.25 at the end of the follow-up period.

SUBJECTIVE EFFICACY

The subjective efficacy tended to increase over time regardless of age (Fig 5). For each age group, the

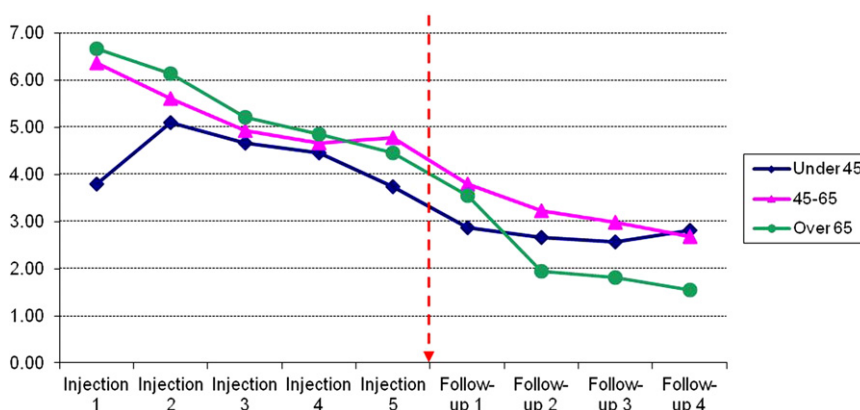


FIGURE 2. Mean values of maximum pain at mastication for the 3 age groups.

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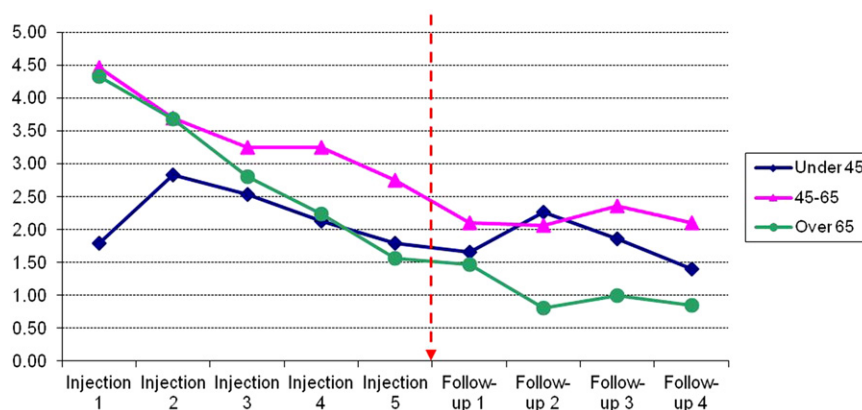


FIGURE 3. Mean values of maximum pain at rest for the 3 age groups.

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difference in effectiveness between 2 consecutive periods decreased over time. The subjective efficacy of patients in the group aged 46 to 65 years and the group aged older than 65 years was almost the same at each stage of the study: it showed a value around 1.50 after the second injection and near 3.00 at the fourth follow-up visit. The trend of subjective efficacy for the patients aged younger than 45 years was very similar to the other 2 groups over time, but it was slightly lower at each point in time (from 0.80 after the second infiltration to 2.50 at the end of the study).

MAXIMUM NON-ASSISTED (VOLUNTARY) MOUTH OPENING

Baseline values for maximum non-assisted (voluntary) mouth opening were within the range of normality (aged <45 years, 39.87 ± 9.28 mm; aged 45-65 years, 36.55 ± 8.68 mm; and aged >65 years, 39.14 ± 9.07 mm) ($P > .05$), so treatment effectiveness on these parameters was less evident than for the other clinical parameters (Fig 6). Different response behav-

iors over time were found with respect to age. For the groups of patients aged 45 years or older, the trend was slightly increasing, whereas for patients aged younger than 45 years, the tendency was neither uniformly increasing nor decreasing and the final value at the end of the follow-up (41.0 ± 9.2) was equivalent to the baseline value (41.07 ± 12.2). The response curve tended to be constant during the treatment period, to increase reaching the maximum (44.00 ± 6.0) at the second follow-up assessment and then to decrease until the end of the follow-up span.

MAXIMUM ASSISTED MOUTH OPENING

The shifts of maximum assisted mouth opening values over time were similar to the maximum voluntary mouth opening values (Fig 7). Baseline values were normal for all 3 age groups and were not different among them (aged <45 years, 43.8 ± 9.24 mm; aged 45-65 years, 41.03 ± 8.69 mm; and aged >65 years, 42.33 ± 9.5 mm) ($P > .05$). Hence, the effect

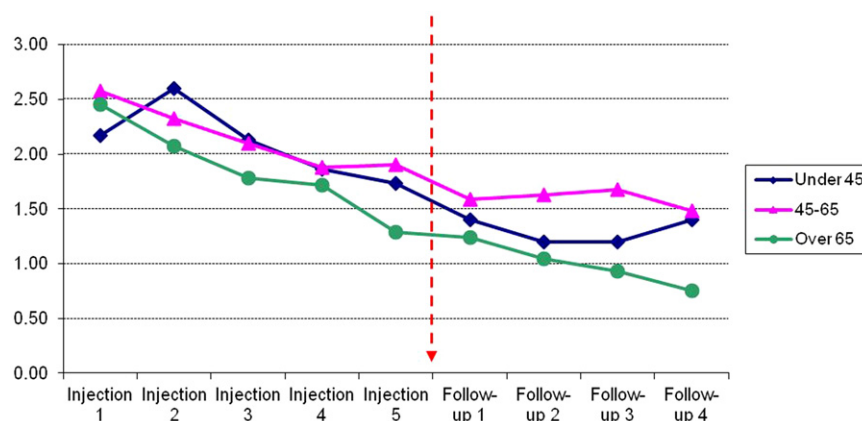


FIGURE 4. Mean values of functional limitation for the 3 age groups.

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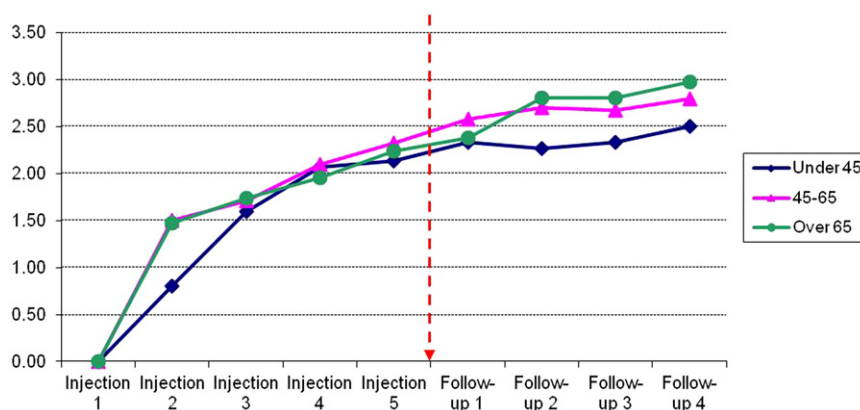


FIGURE 5. Mean values of subjective efficacy for the 3 age groups.

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of the therapy on the maximum assisted mouth opening was less evident than for the other parameters.

PERMUTATION TEST ON ORDERING

The global P value of the combined permutation test on ordering (with Tippett combination) is equal to .002, and at significance level $\alpha = .05$, it leads to the rejection of the null hypothesis of equality in distribution of the multivariate response for every age group over time in favor of the alternative, that is, the symptoms improve over time. All the partial P values of the subtests related to the age groups, adjusted according to the close testing method for controlling multiplicity, were significant: .009 (aged <45 years), .001 (aged 45-65 years), and .001 (aged >65 years), that is, at significance level $\alpha = .05$, there was a significant effect of the treatment on the symptoms within each age group, and this was slightly stronger for patients aged 45 years or older.

The adjusted P values of the partial tests for the single responses within each age group are shown in Table 2. It is evident that for the younger age group,

the treatment had a significant effect only on the pain at mastication and on the subjective efficacy. For the other age groups, the treatment effectiveness was evident with regard to almost all the considered symptoms.

SIDE EFFECTS

No relevant 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 5 patients.

Discussion

In the field of TMD practice, several approaches have been proposed over the years to manage symptoms, and the encouraging findings reported for many treatments suggested that several unspecific factors related, for example, to placebo effects and natural fluctuation of symptoms may be called into cause to explain treatment effectiveness.¹⁹ On the other hand,

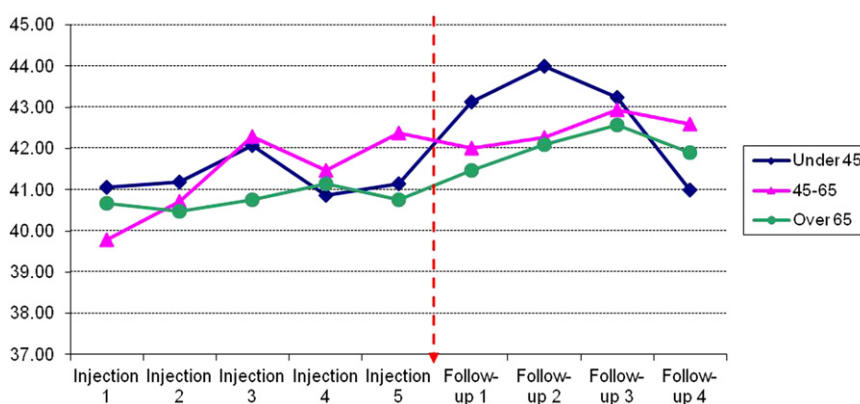


FIGURE 6. Mean values of maximum non-assisted mouth opening for the 3 age groups.

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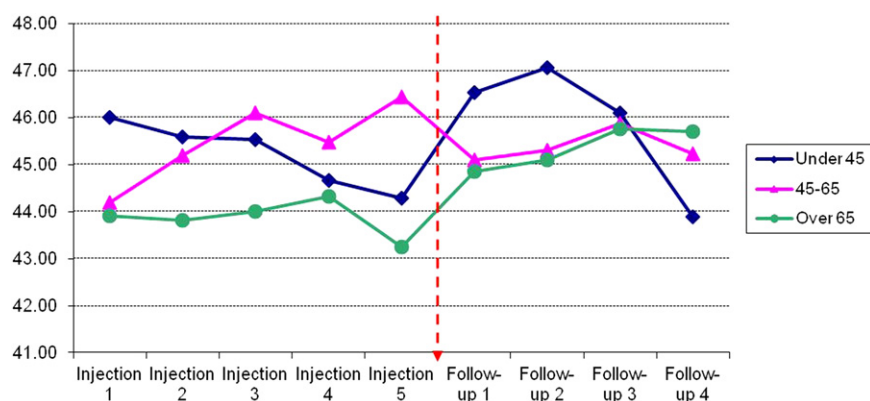


FIGURE 7. Mean values of maximum assisted mouth opening for the 3 age groups.

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it must be pointed out that the TMD literature is characterized by some shortcomings regarding the level of knowledge on treatment effectiveness at the individual level, given that studies are often performed on unspecific populations identified by the umbrella term “TMD” or, on the contrary, on unrepresentative samples of selected patients, thus limiting the external validity of findings.²⁰ One possible strategy to improve the validity of the available information at the individual level is trying to assess the therapeutic outcomes with respect to the different patients’ features. Among these, age-related patterns of disease have emerged as important aspects to define the epidemiology of the different TMD diagnoses.¹¹ Thus our investigation attempted to assess the existence of different patterns of treatment response in relation to the patients’ age.

Since the time of introduction of viscosupplementation with HA in the armamentarium of pain clinicians, a series of 5 weekly injections has been assumed as the injection protocol of reference for

managing osteoarthritis of larger joints, such as the hip and the knee.²¹ For that reason, investigations focused on the same series of injections to test its applicability in the TMJ. A protocol providing 5 weekly arthrocenteses plus HA injections has been suggested as effective to manage symptoms of TMJ inflammatory-degenerative disease, and positive findings have been reported in case series of patients followed up for 1 year.⁷ In this investigation previously unpublished findings on a sample of the first 76 patients who have reached the 1-year follow-up appointment were appraised to assess for age-related differences in treatment effectiveness, with the aim to provide useful data for increasing treatment customization.

At the 1-year follow-up, marked improvement with respect to baseline values was reported in all the subjective parameters of evaluation, that is, masticatory efficiency, functional limitation, and pain levels; in addition, the perceived subjective efficacy increased over the 1-year span. On the contrary, mouth opening values were not significantly improved over time, given that baseline values were already within the range of normality, that is, over 40 mm. Such information on the overall study sample is in line with previous studies on lower sample size⁷ and on shorter follow-up periods.¹² Notwithstanding that, interesting findings emerged from the analysis of treatment effects in relation to the patients’ age.

The effectiveness of the treatment protocol was higher in those subjects aged 45 years or older, as shown by the significantly higher improvement reported by the middle-aged (45-65 years) and the older-aged (>65 years) patient groups with respect to the younger patients. These findings are open to several interpretations, based on the observation that younger patients seemed to report less severe pain levels at baseline. First, it should be borne in mind that subjects with lower baseline pain levels were less

Table 2. ADJUSTED P VALUES OF WITHIN-STRATUM PARTIAL COMBINED TESTS FOR SINGLE RESPONSES

Age Group	Outcome Variables						
	ME	PC	PR	FL	SE	MVMO	MAMO
<45 yr	.141	.030*	.399	.064	.009†	.144	.374
45-65 yr	.004†	.001†	.010*	.004†	.004†	.010*	.010*
>65 yr	.016*	.001†	.001†	.001†	.001†	.011*	.006†

Abbreviations: FL, functional limitation; MAMO, maximum assisted mouth opening; ME, masticatory efficiency; MVMO, maximum non-assisted (voluntary) mouth opening; PC, maximum pain at chewing; PR, maximum pain at rest; SE, subjective efficacy.

* $P < .05$.

† $P < .01$.

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prone to report significant improvement with respect to patients belonging to the other 2 age groups, who reported higher baseline pain levels. Regression to the mean phenomena may easily explain this symptoms' course and cannot be excluded. On the other hand, some peculiar features of the symptoms course's pattern—such as the observation that the group aged younger than 45 years showed a deterioration in symptoms of pain at chewing, pain at rest, and functional limitation after the first injection, to go into line with the values of the other 2 groups—are worthy of exploration in future studies. A possible explanation for those findings is that pain symptoms in the younger patients were less related to osteoarthritis, and an interpretation of those findings may become easier with further data collection on enlarged samples.

Second, even if patients belonging to the younger age group were all diagnosed with TMJ osteoarthritis and the need to perform a 5-session arthrocentesis-plus-HA protocol was based on patients' unresponsiveness to more conservative therapies, the risk for overtreatment and mismanagement of those patients has to be considered. Indeed, according to these findings, the combination of 5 joint lavages and HA injections was likely shown to be a quite invasive protocol to provide pain relief in subjects aged younger than 45 years with moderate pain levels associated with TMJ osteoarthritis, as confirmed by the moderate improvement in pain levels perceived by patients in such an age group. Anyway, the patients' history suggested that the effectiveness of less invasive protocols was not enough to stop the patients from seeking care. In the near future, information on the best protocol to adopt under the different clinical conditions hopefully will be available, to be able to provide targeted therapies at the individual level. On the other hand, the issue of treatment benefit-to-cost ratio should also be addressed in future studies, because protocols providing HA injections need to withstand comparison with conservative approaches, such as occlusal splints, physiotherapy, and pain medication, before being definitively introduced within the daily armamentarium of the TMD specialist as a second-stage option for younger subjects.

Third, it must be pointed out that, on the counterpart of the above, patients aged 45 years or older reported significant improvements over the 1-year follow-up, thus suggesting that in those age groups, symptoms were more likely to be related to TMJ osteoarthritis and to benefit more from the treatment protocol described in this investigation. This finding may be interpreted as a further support for the need to gather further data on the epidemiology of TMDs. For instance, TMJ osteoarthritis has shown an age-related peak of onset that is markedly

different from that of the other TMD diagnoses,¹¹ and this investigation supports the need for delving deeper into each specific diagnostic group in treatment studies as well.

In general, this investigation provided data that may be useful in the treatment decision planning at the individual level, suggesting that a cycle of TMJ arthrocenteses plus HA injections to manage symptoms of TMJ osteoarthritis is less indicated for subjects aged younger than 45 years than for older patients. These findings add to the ongoing increasing efforts aiming to design clinical research that may be useful for clinicians to tailor TMD treatment.

A series of 76 patients with TMJ osteoarthritis who underwent a cycle of 5 weekly arthrocenteses plus HA injections were followed up for 1 year, and treatment effectiveness was evaluated with respect to patient age. Findings suggested that the treatment protocol was more effective in patients aged 45 years or older, thus having important clinical implications regarding attempts to define tailored treatment protocols for patients with TMDs.

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