Int. J. Oral Maxillofac. Surg. 2009; 38: 827–834
doi:10.1016/j.ijom.2009.03.715, available online at http://www.sciencedirect.com

International Journal of
Oral & Maxillofacial Surgery

Clinical Paper
TMJ Disorders

Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections

D. Manfredini[1], S. Bonnini[2], R. Arboretti[2], L. Guarda-Nardini[1]
[1]TMD Clinic, Department of Maxillofacial Surgery, University of Padova, Italy; [2]Department of Mathematics, University of Ferrara, Italy

D. Manfredini, S. Bonnini, R. Arboretti, L. Guarda-Nardini: Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections. Int. J. Oral Maxillofac. Surg. 2009; 38: 827–834. © 2009 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. This study is an open-label trial on a sample of 76 consecutive patients with temporomandibular joint (TMJ) osteoarthritis treated with a cycle of five weekly arthrocenteses plus hyaluronic acid injections. Patients had a diagnosis of osteoarthritis according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD Axis I Group IIIb). They underwent a cycle of five arthrocenteses with injections (1 per week) of 1 ml hyaluronic acid and four follow-up assessments after the end of the treatment (at 1 week, 1 month, 3 months, 6 months). At each appointment, several subjective and objective outcome variables were assessed to test the efficacy of the treatment protocol. Marked improvements were reported for all variables during the treatment phase. The improvements were maintained over the 6-month follow-up period. The *p*-value of the multivariate permutation test for the efficacy of the treatment over time (with Tippett's combination) was 0.001, and significant changes at the end of the follow-up period were detected for almost all the outcome variables. Data from this study lend further support to the usefulness of serial hyaluronic acid injections performed after arthrocentesis for the treatment of TMJ osteoarthritis and for the maintenance of improvements over a 6-month follow-up period.

Keywords: temporomandibular joint; osteoarthritis; RDC/TMD; hyaluronic acid; arthrocentesis; temporomandibular disorders.

Accepted for publication 30 March 2009
Available online 29 April 2009

Degenerative joint disease is a slowly progressive condition resulting in the destruction of joint structures over several years[16]. The signs and symptoms of degenerative joint disease of the temporomandibular joint (TMJ) are related to concurrent inflammatory processes and include unilateral pain, stiffness, joint clicking, crepitation and limitation of movement[9]. There are characteristic radiographic, histological and biochemical features of degenerative joint disease[10].

The complex of signs and symptoms characterizing inflammatory-degenerative disorders of the TMJ is commonly referred to as osteoarthritis[12].

Several conservative treatments, ranging from physiotherapy to occlusal splints, have been proposed over the years with the aim of reducing joint load and achieving pain relief[8,27]. Evidence

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suggesting that impaired joint lubrication may be involved in the pathogenesis of inflammatory-degenerative changes[24] has led to the introduction of viscosupplementation and hyaluronic acid injections as a promising treatment for these disorders[1,7,13,15].

Preliminary encouraging findings have been reported with a protocol providing a cycle of hyaluronic acid injections in combination with joint lavage[14], although large sample studies are needed to support their usefulness.

The present study is an open-label trial on a sample of consecutive patients with TMJ osteoarthritis treated with a cycle of five weekly arthrocenteses plus hyaluronic acid injections.

Materials and methods

Study design

76 consecutive patients with a diagnosis of osteoarthritis according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD Axis I Group IIIb) in the absence of RDC/TMD muscle disorders (Group I diagnoses) and rheumatic diseases underwent a cycle of five arthrocenteses with injections (1 per week) of 1 ml hyaluronic acid according to the technique described by Guarda-Nardini et al.[14] and four follow-up assessments after the end of the treatment (at 1 week, 1 month, 3 months and 6 months).

According to RDC/TMD guidelines[12], 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; and radiological signs of TMJ bone structure abnormalities, such as erosions, sclerosis, flattening and osteophytes.

The following five clinical parameters were assessed by the same operator at the time of diagnosis (baseline), at each appointment during the treatment and at each appointment during follow-up. Pain, at rest, at mastication and at phonation, was assessed using a visual analogue scale (VAS) from 0 to 10, with the extremes being 'no pain' and 'pain as bad as the patient ever experienced', respectively. Mastication efficiency was assessed by a VAS from 0 to 10, the extremes of which were 'eating only semi-liquid food' and 'eating solid hard food'. Maximum non-assisted and assisted mouth opening (in mm) was measured. The functional limitation during usual jaw movements was determined (0, absent; 1, slight; 2, moderate; 3, intense, 4, severe). The subjective efficacy of the treatment was assessed (0, poor; 1, slight, 2, moderate; 3, good; 4, excellent).

Hyaluronic acid

Hyaluronic acid is a polysaccharide of the glycosaminoglycans family, found in many extracellular tissues, including synovial fluid and cartilage[20]. Hyaluronic acid is produced by the chondrocytes and synoviocytes of the joints. In patients with osteoarthritis, it becomes depolymerized, resulting in decreased molecular weight and viscoelasticity[3], which increases the susceptibility of cartilage to injury. Exogenous hyaluronic acid can stimulate the synthesis of endogenous hyaluronic acid from the synoviocytes of osteoarthritic joints, reducing the joint friction coefficient and decreasing the risks of damages.

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

Injection technique

The injection technique used employs the same reference points as used in arthroscopic examination (lateral cantus-tragus). The skin surface is disinfected with povidone iodine. Local anaesthesia is achieved with mepivacaine 2% (Carbocaine, Sanofi Winthroph, NY, USA). The anaesthetic is injected into the joint cavity, relaxing this virtual space. The needle is withdrawn gently to the skin surface, anaesthetizing the soft tissues over the joint as well. Two 19 G 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 cc of Ringer lactate to eliminate the catabolytes present in the synovial fluid. Once arthrocentesis is completed, 1 cc of Hyalgan is injected into the joint in 3 s and the two needles are removed.

Statistical analysis

To test the hypothesis of efficacy of serial injections of hyaluronic acid to reduce symptoms over time, the authors implemented and performed a nonparametric multivariate statistical test based on the application of partial univariate permutation tests and on their combination according to the method proposed by Pesarin[26]. A nonparametric solution was used because the data do not follow a normal distribution and the treatment effects are presumed to act on more than one aspect, so the problem is multivariate and a parametric approach is not suitable because it needs to define and to describe explicitly the dependence structure of variables. The statistical analysis is too complex to be solved with a parametric method because there are 14 clinical responses, some patients abandoned the cure (missing values) and the data are repeated measures collected at 9 different times (5 during the treatment and 4 during follow-up).

The purpose of the analysis was to test the treatment effects over time. The null hypothesis is that the variables have the same joint distribution with respect to time (i.e. there is a null treatment effect). The alternative hypothesis is that the treatment has a significant improvement (increasing or decreasing) on the variables.

The application of the nonparametric multivariate statistical test involves the following five steps. First, all the possible bipartitions of the dataset obtained pooling the first m times and the other 9-m times (m=1,2,. . .,8) are considered. Second, for each variable and for each bipartition the mean values for the first m times and for the other 9-m times are calculated for every patient. Third, using data from step 2, for each variable and for each bipartition, a directional permutation test for paired data is performed to test the hypothesis of increase/decrease of means over time (the direction of the shift depends on the considered symptom). Fourth, a univariate test for each variable is obtained combining the results of the 8 partial tests. Fifth, the overall multivariate test is calculated combining the results of the 14 univariate tests.

The combinations at steps 4 and 5 follow the nonparametric combination of dependent permutation tests method proposed by Pesarin[26]. When a combined test was significant, according to the close testing procedure, the corrected partial p-values were considered to determine which of the partial tests caused the significance. All tests were performed using Matlab routines, the number of permutations is set to 1000 and to combine p-values with respect to the 8 bipartitions within each variable and with respect to the 14 variables, Tippett's combining function was used.

Descriptive results and expected sign of the shift (+ means increase; – means decrease) are reported in Table 1 (injection period) and Table 2 (follow-up) and represented in Figs. 1–10.

Table 1. Mean and standard deviation values of clinical responses during the treatment.

	Expected sign	1st injection	2nd injection	3rd injection	4th injection	5th injection
Masticatory efficiency	+	5.70 ± 2.05	5.80 ± 2.14	6.09 ± 2.11	6.40 ± 2.30	6.62 ± 2.15
Pain at mastication (max)	–	5.94 ± 2.95	5.66 ± 2.71	4.95 ± 2.78	4.68 ± 2.70	4.48 ± 2.49
Pain at mastication (min)	–	2.86 ± 2.71	2.80 ± 2.78	2.47 ± 2.62	2.12 ± 2.54	2.05 ± 2.36
Pain at phonation (max)	–	3.98 ± 3.31	3.49 ± 2.98	3.03 ± 3.08	2.64 ± 2.95	2.39 ± 2.74
Pain at phonation (min)	–	1.63 ± 2.47	1.43 ± 2.38	1.32 ± 2.22	1.07 ± 2.05	0.89 ± 1.92
Pain at rest (max)	–	3.91 ± 3.36	3.53 ± 3.28	2.99 ± 3.04	2.75 ± 2.87	2.24 ± 2.77
Pain at rest (min)	–	1.28 ± 2.19	1.25 ± 2.28	0.97 ± 2.01	0.83 ± 1.81	0.88 ± 1.91
Functional limitation	–	2.46 ± 0.88	2.31 ± 0.89	2.02 ± 0.97	1.83 ± 0.95	1.70 ± 0.86
Subjective efficacy	+	0.00 ± 0.00	1.36 ± 1.14	1.70 ± 1.15	2.05 ± 1.02	2.26 ± 1.11
MVMO before injection	+	37.9 ± 8.9	38.7 ± 9.3	40.1 ± 7.4	40.2 ± 7.9	40.9 ± 7.8
MVMO after injection	+	40.3 ± 9.3	40.7 ± 8.9	41.8 ± 7.7	41.3 ± 7.6	41.7 ± 7.2
MAMO before injection	+	41.9 ± 9.1	42.8 ± 9.1	43.7 ± 7.8	43.7 ± 8.2	44.3 ± 7.8
MAMO after injection	+	44.5 ± 8.7	44.9 ± 8.5	45.4 ± 7.9	45.0 ± 8.1	45.1 ± 7.7
Right laterality before injection	+	7.2 ± 3.2	7.8 ± 2.9	7.9 ± 3.1	7.7 ± 2.8	7.8 ± 2.9
Right laterality after injection	+	7.3 ± 3.0	7.9 ± 3.5	7.9 ± 3.3	7.7 ± 3.2	8.0 ± 2.9
Left laterality before injection	+	7.8 ± 3.0	8.1 ± 3.1	8.0 ± 3.2	8.3 ± 2.9	8.4 ± 2.9
Left laterality after injection	+	7.9 ± 3.1	8.4 ± 3.1	8.5 ± 3.5	8.3 ± 3.1	8.9 ± 2.9
Protrusion before injection	+	6.3 ± 2.1	6.4 ± 2.1	6.6 ± 1.9	6.9 ± 1.8	6.9 ± 2.1
Protrusion after injection	+	6.7 ± 2.0	6.8 ± 2.0	6.5 ± 2.0	7.1 ± 1.5	6.9 ± 2.0

Table 2. Mean and standard deviation values of clinical responses during the follow-up.

	Expected sign	1st follow-up	2nd follow-up	3rd follow-up	4th follow-up
Masticatory efficiency	+	7.17 ± 1.93	7.51 ± 1.88	7.60 ± 2.01	7.78 ± 2.10
Pain at mastication (max)	–	3.55 ± 2.68	2.76 ± 2.79	2.58 ± 2.72	2.33 ± 2.65
Pain at mastication (min)	–	1.64 ± 2.37	1.13 ± 1.93	1.04 ± 1.91	1.05 ± 1.93
Pain at phonation (max)	–	1.86 ± 2.44	1.57 ± 2.24	1.58 ± 2.22	1.95 ± 2.73
Pain at phonation (min)	–	0.82 ± 1.89	0.51 ± 1.37	0.63 ± 1.53	0.80 ± 1.78
Pain at rest (max)	–	1.84 ± 2.42	1.75 ± 2.36	1.88 ± 2.45	1.57 ± 2.34
Pain at rest (min)	–	0.72 ± 1.72	0.60 ± 1.48	0.60 ± 1.58	0.54 ± 1.61
Functional limitation	–	1.45 ± 0.94	1.38 ± 0.99	1.38 ± 0.99	1.22 ± 1.00
Subjective efficacy	+	2.47 ± 1.14	2.64 ± 0.98	2.64 ± 1.05	2.80 ± 1.08
MVMO	+	42.1 ± 6.8	42.6 ± 6.9	42.9 ± 6.9	42.1 ± 8.2
MAMO	+	45.3 ± 7.3	45.6 ± 7.2	45.9 ± 7.0	45.2 ± 8.4
Right laterality	+	7.8 ± 2.9	8.4 ± 2.9	8.4 ± 3.1	8.0 ± 3.1
Left laterality	+	8.8 ± 3.0	8.7 ± 3.3	8.9 ± 2.8	8.6 ± 3.0
Protrusion	+	7.3 ± 2.0	7.5 ± 2.1	7.6 ± 1.6	7.7 ± 1.9

Results

Masticatory efficiency

The mean masticatory efficiency VAS value at baseline was 5.70, and the sample standard deviation was 2.05 (Table 1). The mean value increased during therapy; it became 5.80 ± 2.14 at the second injection, 6.09 ± 2.11 at the third injection, 6.40 ± 2.30 at the fourth injection and 6.62 ± 2.15 at the end of the treatment. After 1 week the mean value was 7.17 ± 1.93 and during follow-up it continued to increase; it was 7.51 ± 1.88 after 1 month, 7.60 ± 2.01 after 3 months and 7.78 ± 2.10 after 6 months (Table 2). In general, from a descriptive point of view, it is evident that the masticatory efficiency mean value increased during the study (Fig. 1).

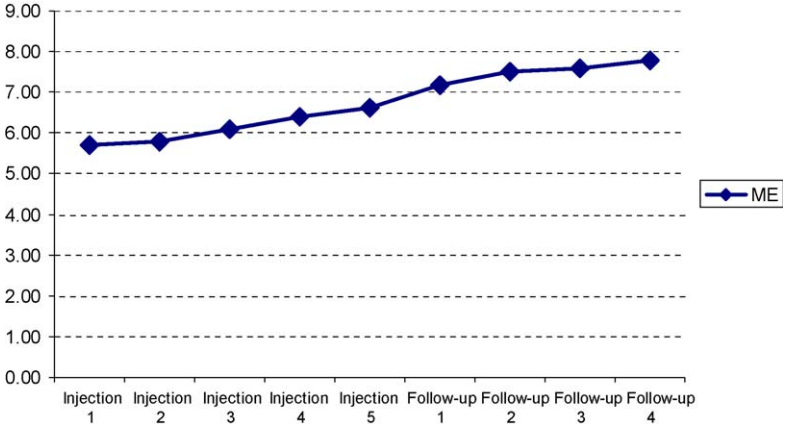

Fig. 1. Mean values of masticatory efficiency (ME).

Pain at mastication

The mean minimum pain during mastication, measured at the first appointment, was 2.86 ± 2.71 while the mean maximum pain declared by patients was 5.94 ± 2.95. The expected sign of the shift for these clinical responses is negative because efficacy of the treatment implies an expected reduction of pain at mastication. Observed sample means supported the theory because the mean values of pain at mastication decreased constantly in all the periods considered. For minimum pain, the mean value at the end of the treatment was 2.05 ± 2.36, at the beginning of the follow-up period it was 1.64 ± 2.37 and at the end of the follow-up it was 1.05 ± 1.93. For

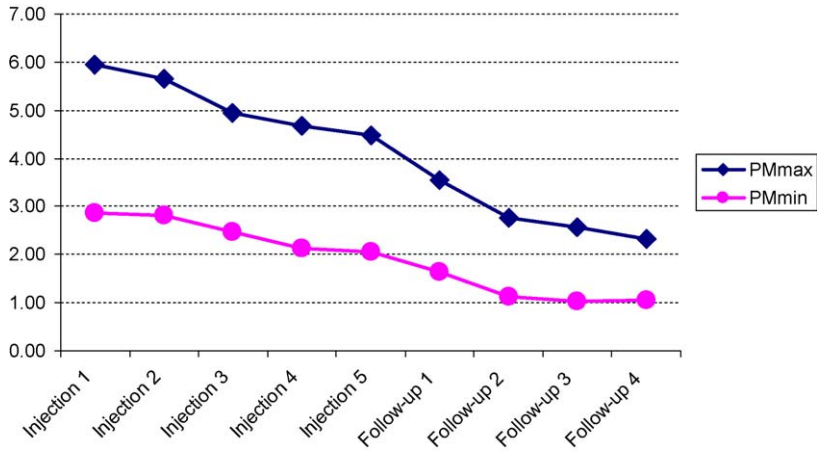

Fig. 2. Mean values of pain at mastication (PM).

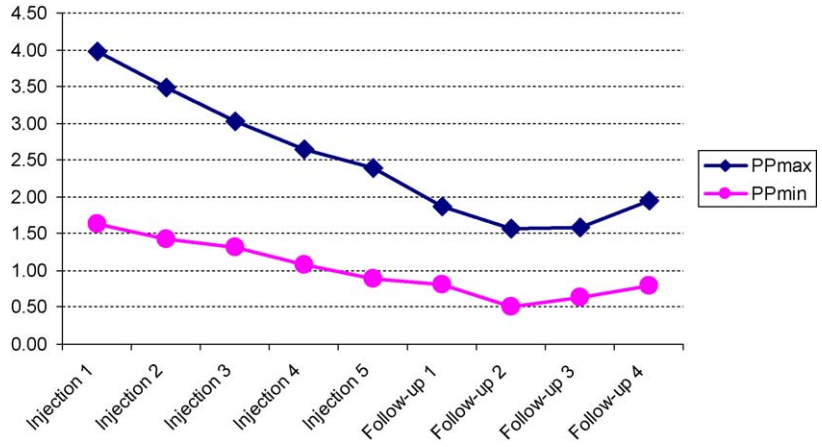

Fig. 3. Mean values of pain at phonation (PP).

maximum pain, the mean value at the end of the treatment was 4.48 ± 2.49, after 1 week it was 3.55 ± 2.68 and after 6 months it decreased to 2.33 ± 2.65. Fig. 2 shows the decreasing trend of the mean values from the beginning of therapy to the end of follow-up.

Pain at phonation

The reported baseline mean minimum and maximum pain values during phonation were 1.63 ± 2.47 and 3.98 ± 3.31, respectively. Both values decreased after every injection and at the end of the therapy they were 0.89 ± 1.92 and 2.39 ± 2.74, respectively. During follow-up, the mean values continued to diminish until the second follow-up, when the minimum value of minimum and maximum pain at phonation was 0.51 ± 1.37 and 1.57 ± 2.24, respectively. After this, the patients' pain during phonation started to increase (Fig. 3). After 6 months, the mean minimum pain was 0.80 ± 1.78 and the mean maximum pain was 1.95 ± 2.73. This reversal of the direction for these clinical symptoms may be attributable to 17 patients withdrawing from the study, possibly because those who felt better decided to stop the clinical monitoring.

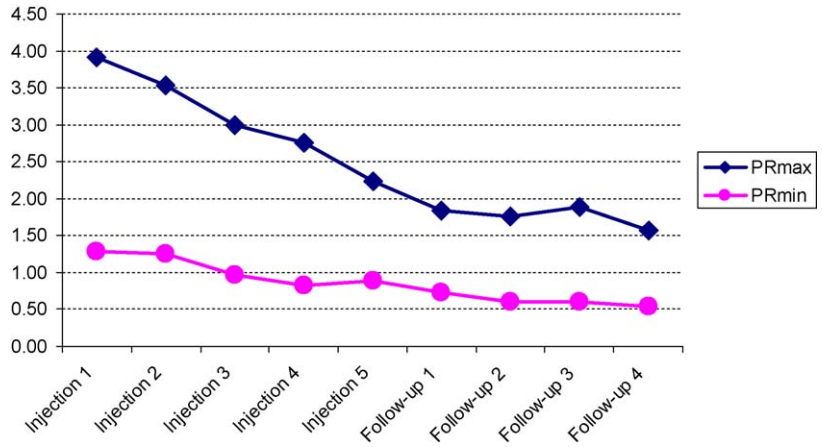

Fig. 4. Mean values of pain at rest (PR).

Pain at rest

The pretreatment mean minimum and maximum pain levels at rest were 1.28 ± 2.19 and 3.91 ± 3.36, respectively. A reduction in the mean maximum pain at rest emerged at the time of the fifth injection (mean value 2.24 ± 2.77). The mean minimum pain at rest values decreased more slowly, and at the end of the treatment the mean value was 0.88 ± 1.91. The improvement of symptoms after therapy was less evident but quite constant (Fig. 4) and the last observed mean values of mean pain at rest were 0.54 ± 1.61 (minimum) and 1.57 ± 2.34 (maximum).

Functional limitation

The mean score of functional limitation at the beginning of the treatment was 2.46 ± 0.88. This symptom showed a tendency over time that corroborated the expected trend. The mean moved to progressively lower values: after the fifth injection the mean value was 1.70 ± 0.86, 1 week later the mean value was 1.45 ± 0.94 and after 6 months the value reached its minimum (1.22 ± 1.00). The decreasing trend is shown in Fig. 5.

Subjective efficacy

At the second injection, the mean subjective efficacy increased from 0 (starting value before the treatment) to 1.36 ± 1.14 (second injection). The value continued to increase during therapy (2.26 ± 1.11 at fifth injection) and after therapy (2.80 ± 1.08 after 6 months). Fig. 6 shows the growth of the curve of means, characterized by decreasing increments over time.

Maximum non-assisted mouth opening

At baseline, the mean maximum voluntary opening (in mm) before injection was

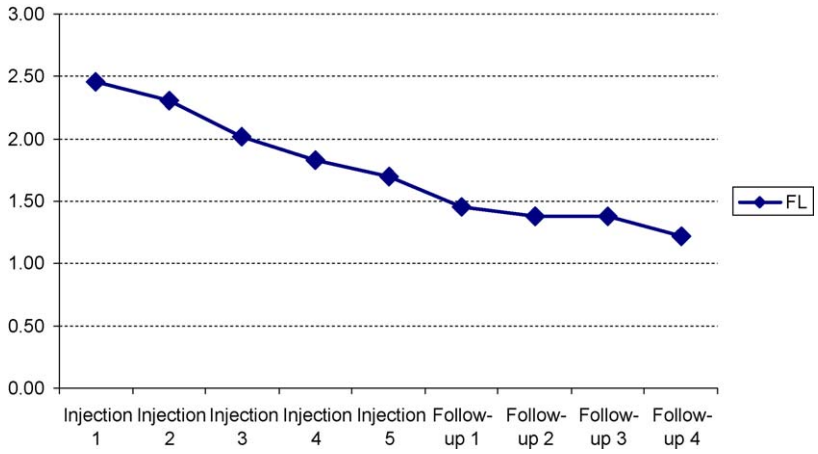

Fig. 5. Mean values of functional limitation (FL).

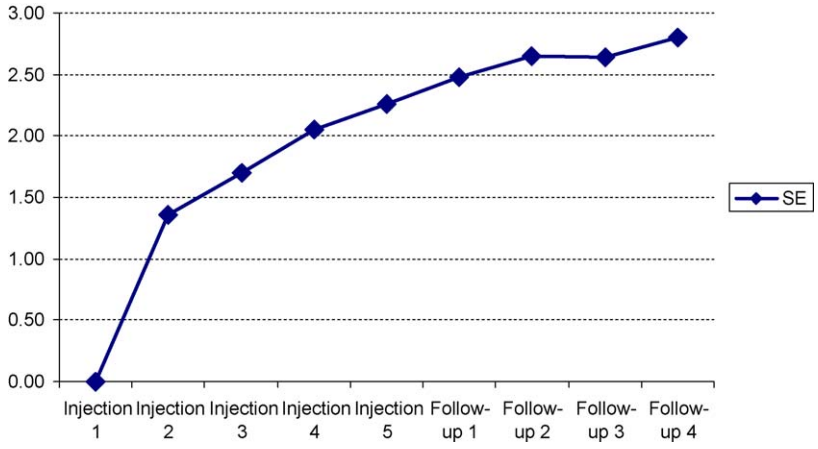

Fig. 6. Mean values of subjective efficacy (SE).

37.9 ± 8.9 mm and after injection it was 40.3 ± 9.3 mm. During the therapy, the mean value before injection increased progressively up to 40.9 ± 7.8 mm while the mean value after injection reached its maximum (41.8 ± 7.7 mm) after the third injection and was 41.7 ± 7.2 mm at the end of the cure. The difference between the non-assisted mouth opening levels before and after the injection reduced over time (Fig. 7). The improvement is evident considering that 1 week after the cure the mean level was 42.1 ± 6.8 mm, even if 6 months later the mean level was more or less the same (42.1 ± 8.2 mm).

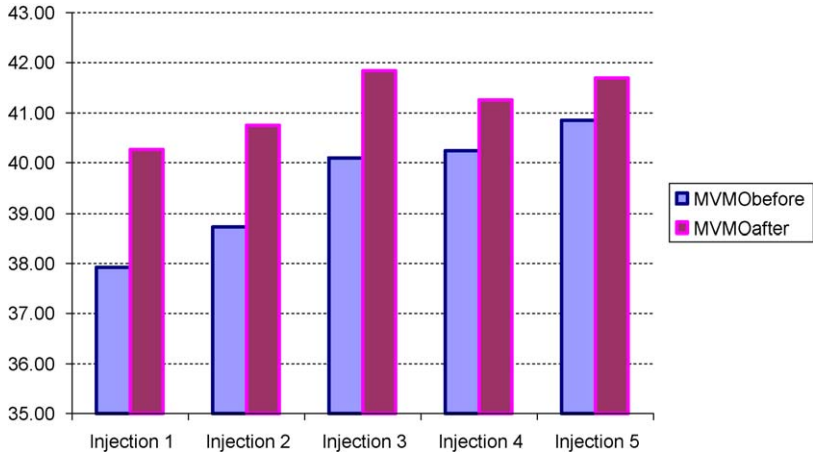

Fig. 7. Mean values of maximum non-assisted mouth opening (MVMO) before and after injection during the therapy.

Maximum assisted mouth opening

Maximum assisted mouth opening presented a trend similar to that of maximum non-assisted mouth opening (Fig. 8). The mean value before the first injection, 41.9 ± 9.1 mm, increased to 44.3 ± 7.8 mm (before the fifth injection) and the mean value after the first injection increased from 44.5 ± 8.7 to 45.4 ± 7.9 mm (after the third injection) and fell to 45.1 ± 7.7 mm after the fifth injection. The difference between the symptom before and after the injection reduced over time (Fig. 9). The mean value increased slightly after the cure and decreased from the third to the sixth month after the therapy: the final value was 45.2 ± 8.4 mm.

Right laterotrusion, left laterotrusion and protrusion

During treatment and follow-up, the variations of the mean values of right laterotrusion, left laterotrusion and protrusion did not follow a monotonic trend (Table 1 and 2). During the study, the mean value of right laterotrusion increased from 7.3 ± 3.1 to 8.0 ± 3.1 mm, the mean value of left laterotrusion increased from 7.9 ± 3.1 to 8.6 ± 3.0 mm and the mean value of protrusion increased from 6.7 ± 2.0 to 7.7 ± 1.9 mm. All the clinical parameters indicated an improvement in the health status of patients. The time series of the means of the three variables showed similar patterns (Fig. 10).

Nonparametric test

The *p*-value of the multivariate permutation test for the efficacy of the treatment over time (with Tippett's combination) was 0.001, thus allowing the rejection of the hypothesis of null treatment effect in favour of the alternative hypothesis of positive effect (i.e. improvement of the symptoms). Table 3 shows the *p*-values of the partial univariate tests, adjusted with the close testing method.

Almost all the *p*-values are less then 0.05. The improvement in symptoms can be attributable to almost all the considered aspects with the exception of maximum assisted mouth opening (*p*-value = 0.074) and right laterality (*p*-value = 0.062). The increasing of means of left laterality over time is significant but close to the significance level (*p*-value = 0.048) and the

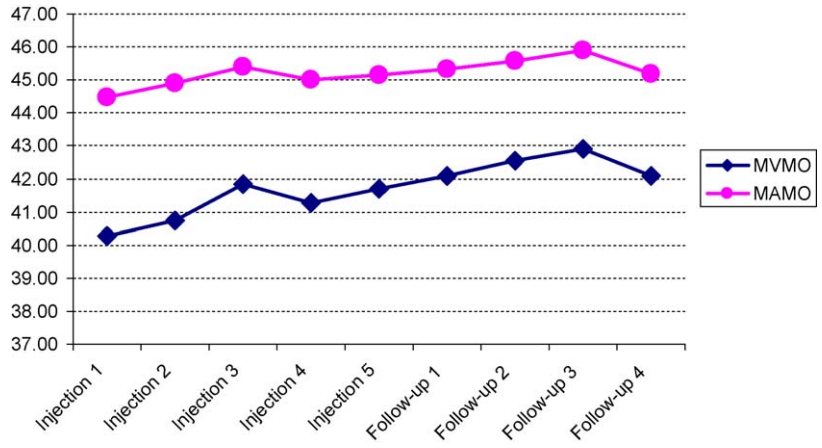

Fig. 8. Mean values of maximum non-assisted mouth opening (MVMO) and maximum assisted mouth opening (MAMO).

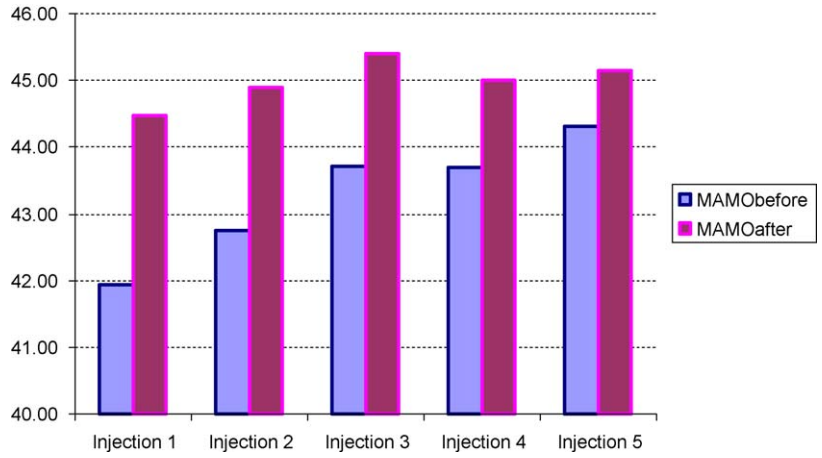

Fig. 9. Mean values of maximum assisted mouth opening (MAMO) before and after injection during the therapy.

significance is due to the difference between the means of the first four times and the means of the subsequent five (bipartition 4, p-value = 0.046), i.e. to the shift after the fourth injection. For maximum pain at rest and protrusion (p-value = 0.025) the improvement in symptoms is fairly significant and for both it is due to variations from the third injection to 1 week after the end of the therapy. In general, it can be suggested that masticatory efficiency, subjective efficacy, functional limitation and pain at mastication presented the best improvement over time thanks to the therapy.

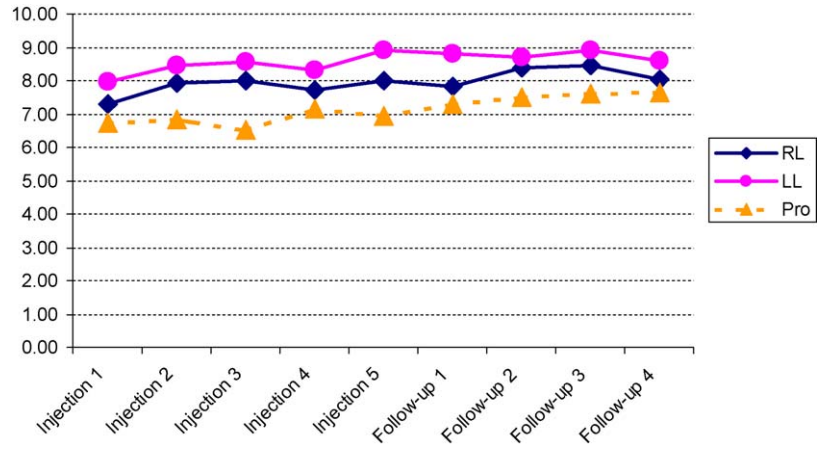

Fig. 10. Mean values of right laterality (RL), left laterality (LL) and protrusion (Pro).

Discussion

Techniques providing joint lavage have found increasing application in the clinical setting for TMJ disorders[23,25]. Research supports the usefulness of arthrocentesis to treat TMJ internal derangements. The potential of such a technique to break adherences is helpful to increase joint mobility in patients with a reduced range of jaw movements[30]. Several authors have described the efficacy of a single-session arthrocentesis, and follow-up studies support the maintenance of improvements in patients with TMJ disk displacements over a long term[6,11,18].

Theories supporting a role for viscosupplementation with hyaluronic acid in the treatment of TMJ disorders has led to the introduction of hyaluronic acid injections, alone or combined with arthrocentesis, as a valuable therapeutic option[1,7,17,24]. Studies on larger joints have suggested that viscosupplementation has positive effects on inflammatory-degenerative disorders[2,4,5], thus providing a rationale for the adoption of hyaluronic acid injections in TMJ osteoarthritis. Treatment protocols for larger joints, such as the hip, the shoulder and the knee, suggest that a cycle of five weekly injections represents the most effective treatment regimen for low molecular weight hyaluronic acid. Fewer injections are needed in the case of medium or high molecular weight hyaluronic acid.

Recent findings suggest that arthrocentesis combined with hyaluronic acid injections is superior to arthrocentesis alone in reducing impairment in patients with TMJ internal derangements[1]. Such findings seem to be supported by animal model studies[22,28]. In rabbits with artificially induced osteoarthritis, a combination of arthrocentesis followed by hyaluronic acid injection was more effective in inhibiting the development of osteoarthritis than hyaluronic acid or arthrocentesis alone[28]. Hyaluronic acid injections alone led to a decrease in the development of pathologic changes within the joint, but arthrocentesis alone was ineffective at slowing the degeneration of joint surfaces. These findings support suggestions from an earlier study, which reported that the recrudescence ratio of knee rheumatism treated with arthrocentesis and hyaluronic acid

Table 3. Adjusted *p*-values of partial permutation directional tests (*p*-values > 0.05 in bold).

	Univariate Test	Bipartition							
		1	2	3	4	5	6	7	8
Masticatory efficiency	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Pain at mastication (max)	0.001	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Pain at mastication (min)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Pain at phonation (max)	0.006	0.003	0.003	0.003	0.003	0.003	0.010	0.095	**0.315**
Pain at phonation (min)	0.004	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.008
Pain at rest (max)	0.025	0.014	0.014	0.004	0.004	0.018	0.017	0.048	**0.076**
Pain at rest (min)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Functional limitation	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
Subjective efficacy	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
MVMO	0.006	0.036	0.004	0.007	0.007	0.007	0.007	0.036	**0.216**
MAMO	**0.074**	–	–	–	–	–	–	–	–
Right laterality	**0.062**	–	–	–	–	–	–	–	–
Left laterality	0.048	**0.091**	**0.120**	**0.081**	0.046	**0.073**	**0.116**	**0.091**	**0.120**
Protrusion	0.025	**0.073**	**0.073**	0.006	0.006	0.013	0.006	0.016	**0.073**

injections was less than hyaluronic acid alone[5].

The synergistic effect when arthrocentesis is followed by hyaluronic acid injections seems to justify their combined use in TMJ osteoarthritis, providing a rationale for washing the joint before each hyaluronic acid infiltration.

The cycle used in this study of five weekly hyaluronic acid injections performed after arthrocentesis gave interesting preliminary data in a small sample of patients with TMJ osteoarthritis[14]. The present investigation supported the results of its short-to-medium term efficacy in providing symptom relief for those patients.

Several objective (maximum non-assisted and assisted mouth opening, protrusive and laterotrusive movements) and subjective (pain at rest; pain at mastication; pain at phonation; mastication efficiency; functional limitation; subjective efficacy of the treatment) outcome variables were assessed to evaluate treatment efficacy, and significant improvements were reported for all variables during the treatment phase. The improvements achieved during the treatment period were maintained over the follow-up period, in line with preliminary data provided on a smaller sample[14].

The improvement in the range of motion of the jaw, even though statistically significant, might have little importance clinically, since baseline values were almost normal for most patients, but the reduction in pain and functional limitations are noteworthy results. Pain and reduced masticatory efficiency are the main complaints of patients with inflammatory-degenerative disorders.

The present investigation provided further data for comparison with similarly designed investigations. The use of the RDC/TMD classification system allows standardization of the TMD diagnosis and cross-study comparisons, as in the case of works on TMD epidemiology[19,21,29].

The main limitation of the present investigation is the absence of control groups receiving only one of the two treatments (hyaluronic acid or arthrocentesis), thus it is impossible to determine which is the effective part of the protocol. Research on the efficacy of arthrocentesis alone is impressive, and a randomized clinical trial should be undertaken to compare the different treatments. A double-blind trial cannot be designed to address the specific issue of the superiority of arthrocentesis plus hyaluronic acid injections over the two treatments alone, because different treatment regimens and protocols characterize arthrocentesis (single session) and hyaluronic acid injections (five injections once a week). Experimental and animal models suggest that joint lavage and viscosupplementation have a synergistic effect[1,28].

The introduction of medium and high molecular weight hyaluronic acid solutions might reduce the number of sessions needed, simplifying the design phase of research trials. Most parameters improved markedly within the first two injections, and improvements became slower during the rest of the treatment period. These findings may suggest that a smaller number of injections may be effective to alleviate the symptoms of osteoarthritis. It would be interesting to assess radiologically the effects of this and other similar treatment protocols on joint degeneration. This could verify if arthrocentesis and hyaluronic acid multiple injections have a positive or stabilizing effect on the objective signs of joint degeneration, or if multiple violations of the joint space may have negative effects in the long term.

In conclusion, despite some limitations, data from this open-label study on 76 patients lend further support to the usefulness of serial hyaluronic acid injections performed after arthrocentesis for the treatment of TMJ osteoarthritis and for the maintenance of improvements over a 6-month follow-up period.

Funding

None

Competing Interests

None

Ethical Approval

Not required

References

1. Alpaslan GH, Alpaslan C. Efficacy of temporomandibular joint arthrocentesis with and without injection of hyaluronic acid in treatment of internal derangements. J Oral Maxillofac Surg 2001: **59**: 613–618.
2. Altman RD. Intra-articular sodium hyaluronate in osteoarthritis of the knee. Semin Arthritis Rheum 2000: **30**: 11–18.
3. Balazs EA, Watson D, Duff IF, Roseman S. Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritic human fluids. Arthritis Rheum 1967: **10**: 357–376.
4. Barbucci R, Lamponi S, Borzacchiello A, Ambrosio L, Fini M, Torricelli P, Giardino R. Hyaluronic acid hydrogel in the treatment of osteoarthritis. Biomaterials 2002: **23**: 4503–4513.
5. Brandt KD, Smith GNJ, Simon LS. Intra-articular injection of hyaluronan as treatment for knee osteoarthritis: what

is the evidence? Arthritis Rheum 2000: **43**: 1192–1203.
6. Brennan PA, Ilankovan V. Arthrocentesis for temporomandibular joint pain dysfunction sindrome. J Oral Maxillofac Surg 2006: **64**: 949–951.
7. Cascone P, Fonzi Dagger L, Aboh IV. Hyaluronic acid's biomechanical stabilization function in the temporomandibular joint. J Craniofac Surg 2002: **13**: 751–754.
8. Dao TT, Lavigne GJ. Oral splints: the crutches for temporomandibular disorders and bruxism? Crit Rev Oral Biol Med 1998: **9**: 345–361.
9. De Bont LGM, Dijkgraaf LC, Stegenga B. Epidemiology and natural progression of articular temporomandibular disorders. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997: **83**: 72–76.
10. De Bont LGM, Stegenga B. Pathology of temporomandibular joint internal derangement and osteoarthrosis. Int J Oral Maxillofac Surg 1993: **22**: 71–74.
11. Dimitroulis G, Dolwick MF, Martinez A. Temporomandibular joint arthrocentesis and lavage for the treatment of closed lock: A follow-up study. Br J Oral Maxillofac Surg 1995: **33**: 23–26.
12. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomand Disord 1992: **6**: 301–355.
13. Guarda-Nardini L, Masiero S, Marioni G. Conservative treatment of temporomandibular joint osteoarthrosis: intra-articular injection of hyaluronic acid. J Oral Rehabil 2005: **32**: 729–734.
14. Guarda-Nardini L, Stifano M, Brombin C, Salmaso L, Manfredini D. A one-year case series of arthrocentesis with hyaluronic acid injections for temporomandibular joint osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007: **103**: e14–e22.
15. Guarda-Nardini L, Tito R, Staffieri A, Beltrame A. Treatment of patients with arthrosis of the temporomandibular joint by infiltration of hyaluronic acid: a preliminary study. Eur Arch Otorhinolaryngol 2002: **259**: 279–284.
16. Haskin CL, Milam SB, Cameron IL. Pathogenesis of degenerative joint disease in the human temporomandibular joint. Crit Rev Oral Biol Med 1995: **6**: 248–277.
17. Hepguler S, Akkoc YS, Pehlivan M, Ozturk C, Celebi G, Saracoglu A, Opzinar B. The efficacy of intra-articular hyaluronic acid in patients with reducing displaced disc of the temporomandibular joint. J Oral Rehabil 2002: **29**: 80–86.
18. Hosaka H, Murakami K, Goto K, Iizuka T. Outcome of arthrocentesis for temporomandibular joint with closed lock at 3 years follow-up. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996: **82**: 501–504.
19. List T, Dworkin SF. Comparing TMD diagnoses and clinical findings at Swedish and US TMD center using Research Diagnostic Criteria for Temporomandibular Disorders. J Orofac Pain 1996: **10**: 240–253.
20. Magnani A, Rappuoli R, Lamponi S, Barbucci R. Novel polysaccharides hydrogels: characterization and properties. Polym Adv Tech 2000: **11**: 488–493.
21. Manfredini D, Chiappe G, Bosco M. Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) axis I diagnoses in an Italian patients population. J Oral Rehabil 2006: **33**: 551–558.
22. Neo H, Ishimaru JI, Kurita K, Goss AN. The effect of hyaluronic acid on experimental temporomandibular joint osteoarthrosis in the sheep. J Oral Maxillofac Surg 1997: **56**: 1114–1119.
23. Nitzan DW, Dolwick FM, Martinez GA. Temporomandibular joint arthrocentesis: a simplified method for severe limited mouth opening. J Oral Maxillofac Surg 1991: **49**: 1163–1167.
24. Nitzan DW, Kreiner B, Zeltser B. TMJ lubrification system: its effect on the joint function, dysfunction, and treatment approach. Compen Contin Educ Dent 2004: **25**: 437–444.
25. Nitzan DW, Samson B, Better H. Long term outcome of arthrocentesis for sudden-onset, persistent, severe closed lock of the TMJ. J Oral Maxillofac Surg 1997: **55**: 151–157.
26. Pesarin F. Multivariate permutation tests with application in biostatistics. Chichester, NY: John Wiley & Sons 2001.
27. Reisner-Keller LA. Pharmacotherapeutics in the management of orofacial pain. Dent Clin North Am 1997: **41**: 259–278.
28. Xinmin Y, Hu J. Treatment of temporomandibular joint osteoarthritis with viscosuplementation and arthrocentesis on rabbit model. Oral Surg Oral Med Oral Pathol Oral Radiol Endo 2005: **100**: e35–e38.
29. Yap AJU, Dworkin SF, Chua EK, List T, Tan KBC, Tan HH. Prevalence of temporomandibular disorders subtypes, psycologic distress and psychosocial dysfunction in Asian patients. J Orofac Pain 2003: **17**: 21–28.
30. Yura S, Totsuka Y, Inoue N. Can arthrocentesis release intracapsular adhesions? Arthoscopic findings before and after irrigation under sufficient hydraulic pressure. J Oral Maxillofac Surg 2003: **61**: 1253–1256.

Address:
Daniele Manfredini
Viale XX Settembre 298
54033 Marina di Carrara (MS) Italy
E-mail: daniele.manfredini@tin.it