

Predictive factors of hyaluronic acid injections short-term effectiveness for TMJ degenerative joint disease

L. GUARDA-NARDINI*, G. FERRONATO[†], L. FAVERO[‡] & D. MANFREDINI* *TMD Clinic,

[†]Section of Maxillofacial Surgery and [‡]School of Dentistry, University of Padova, Padova, Italy

SUMMARY This study attempted to identify baseline predictors of positive outcome of arthrocenteses plus hyaluronic acid injections in degenerative temporomandibular joint disease (TMJ DJD). Ninety ($n = 90$) consecutive patients with Research Diagnostic Criteria for Temporomandibular Disorders TMJ osteoarthritis (RDC/TMD 1.0 Axis I Group IIIb) underwent a cycle of five arthrocenteses with injections of 1 mL hyaluronic acid and were followed up for 3 months. Eight potential predictors of positive treatment outcome (sex, age, pain duration, baseline pain at chewing, presence of uni- or bilateral arthritis, presence of other concurrent RDC/TMD diagnoses, type of intervention and tolerability of treatment) were included in a logistic regression model to identify baseline predictors of treatment effectiveness. At follow-up, 85.6% of patients improved with respect to baseline VAS values, and 64.4% had a 50% or more decrease (positive outcomes). Correlation with positive outcomes existed

only for unilateral osteoarthritis, and the logistic regression identified the side of arthritis (unilateral/bilateral) as the only predictor of positive treatment outcome ($P = 0.032$). The achievement of any treatment improvement was predicted by high baseline pain levels ($P = 0.016$). The regression models explained only 7.7–15% of the variance in the outcome variable. The attempts to find predictors of positive treatment outcome with HA injections for TMJ degenerative joint disease have been successful only in part. The search for other outcome predictors is likely to benefit from the assessment of psychosocial features associated with TMJ disorders.

KEYWORDS: temporomandibular joint, temporomandibular disorders, osteoarthritis, degenerative joint disease, arthrocentesis, hyaluronic acid

Accepted for publication 7 September 2010

Introduction

Degenerative joint disease (DJD) is a slowly progressive condition resulting in the destruction of joint structures over a period of years (1). The signs and symptoms of degenerative joint disease of the temporomandibular joint (TMJ) are also related to concurrent inflammatory processes and include unilateral pain, stiffness, joint clicking, crepitation and limitation of movement (2–4).

The evolution and natural course of TMJ DJD is benign in the strong majority of cases (5, 6), thus justifying the adoption of conservative treatments, ranging from physiotherapy to occlusal splints, to reduce joint load and achieve pain relief (7, 8). Within the context of the search for new treatments, evidences

that impairment in joint lubrication may be involved in the pathogenesis (9) led to the introduction of viscosupplementation and hyaluronic acid injections as a treatment option for these disorders (10–16), but despite the encouraging and positive outcomes reported in most patients, literature findings did not provide conclusive findings as for the most effective protocol and did not allow identifying predictors for treatment efficacy.

Considering these premises, this study is an attempt to identify baseline predictors of positive outcome in a sample of consecutive patients with degenerative TMJ disease treated with a cycle of five weekly arthrocenteses plus hyaluronic acid injections.

Materials and methods

Study design

Participants to the study were 90 ($N = 90$) consecutive patients (80 women, 10 men; mean age 56.3 years, range 24–81) with a diagnosis of temporomandibular joint osteoarthritis according to the Research Diagnostic Criteria for Temporomandibular Disorders version 1.0 (RDC/TMD Axis I Group IIIb) in the absence of any systemic rheumatic disease seeking for the treatment at the TMD Clinic, University of Padova, Italy. All participants underwent a cycle of five arthrocenteses with injections (one per week) of 1 mL hyaluronic acid (Hyalgan*) according to the classical two-needle (13) or a newly introduced single-needle technique described by Guarda-Nardini *et al.* (17) and three follow-up assessments after the end of the treatment (at 1 week, at 1 month and at 3 months).

According to RDC/TMD 1.0 guidelines (18), a Group IIIb diagnosis of osteoarthritis was made when the following signs and symptoms were present:

- 1 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);
- 2 crepitus sounds;
- 3 radiological signs of TMJ bone structures abnormalities, such as erosions, sclerosis, flattening and osteophytes, showed by means of magnetic resonance imaging.

Outcome variable

Scores in the clinical parameter 'pain at chewing', assessed by means of 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, were assessed by the same operator at the time of the diagnosis (baseline), at each appointment during the treatment and at each appointment during the follow-up period. With the aim to create a dichotomic outcome variable, a 50% or more decrease in the 'pain at chewing' values at the end of the 3-month follow-up was taken as an indicator of clinical success (positive outcome), and all the other findings, viz.,

improvement of <50%, no change and negative changes, were taken as the indicators of unsuccessful results (non-positive outcome). The so-created variable was adopted as the dependent variable to be identified by the following predictors in a binary logistic regression model.

Predictors

Factors included in the logistic regression analysis as independent variables were:

- 1 sex: eighty women and 10 men;
- 2 age: the variable was dichotomised taking the mean age as the cut-off value. As a result, 39 patients were included in the <56 group and 51 in the ≥ 56 group;
- 3 pain duration: the study sample was split into two groups, made of patients with pain lasting from <12 months ($n = 38$) or equal or more than 12 months ($n = 52$);
- 4 baseline pain at chewing levels: a cut-off value of 7 points on the 10-point VAS was selected to split patients into a group with <7/10 VAS score ($n = 45$) and a group with 7 or more points ($n = 45$);
- 5 presence of uni- or bilateral arthritis: treatment was unilateral in 27 and bilateral in 63 patients;
- 6 presence of other concurrent RDC/TMD diagnoses: Fifty-two patients received multiple RDC/TMD axis I diagnoses, viz., any group I or II diagnoses alongside with group III diagnosis of osteoarthritis, while 38 received only a group III diagnosis;
- 7 type of intervention: the classical two-needle technique was performed in 82 patients, while eight underwent single-needle interventions [for detailed descriptions of the techniques, readers are referred to Guarda-Nardini *et al.* (13, 17)];
- 8 tolerability of treatment: a 4-point ordinal scale (0, poor; 1, slight; 2, moderate; 3, good and 4, excellent) was used to ask patients rating their subjective perception of treatment's tolerability. Tolerability was judged good if ranked 3 or 4 on the 4-point scale ($n = 52$ patients) and less than good if ranked 0, 1 or 2 ($n = 38$ patients).

All the clinical RDC/TMD assessments were performed using the standard, internationally accepted Italian version of the RDC/TMD instrument available since 2002 on the RDC/TMD consortium website. The assessments were performed by the two same trained examiners (D.M., L.G.N.), who took part in several previous researches adopting the RDC/TMD.

*Fidia, Abano Terme, Italy.

Statistical analysis

A correlation analysis with Spearman's rank test was performed to test the existence of a univariate relationship between the outcome variable and any of the predictors. Also, the accuracy of each of the single predictors to identify positive outcomes was assessed.

Furthermore, a stepwise multiple logistic regression model was used to identify the significant associations between the predictors (independent variables: sex, age, pain duration, baseline pain at chewing, presence of uni- or bilateral arthritis, presence of other concurrent RDC/TMD diagnoses, type of intervention and tolerability of treatment) and the outcome (dependent variable: 50% or more decrease in pain at chewing levels). Selection was made among the potential predictors of positive outcome using a backward stepwise selection method. Significance needed for removal was set at $P \geq 0.10$ and significance for re-entry at $P \leq 0.05$. Nagelkerke's R -square (R^2) was obtained as an estimation of the total log-likelihood explained by a summation of the significant clinical factors. The log-likelihood in a logistic regression model is the analogue of the variance in a linear regression model and represents the amount that the independent variables can differentiate the dependent variable. R^2 represents a numerical expression of the dependent variable's (positive/non-positive treatment outcome) variance accounted for by the model constituted of the significant predictors. If R^2 is >0.75 , the fitted model is considered capable of predicting the treatment outcome at a very good level. The model's ability to predict outcome is considered good if R^2 is comprised between 0.50 and 0.75, fair if R^2 is comprised between 0.25 and 0.50 and poor for a R^2 of 0.25 or less (19). Therefore, in the last case, the fitted model should predict treatment outcome at an unacceptable level. The accuracy of the final logistic regression model to correctly identify patients with positive outcomes was also assessed from the observed/predicted 2×2 classification table in the logistic output.

All statistical procedures were elaborated with the Statistical Package for the Social Sciences (SPSS 15.0[†]).

Results

At the end of the 3-month follow-up, 77/90 patients (85.6%) improved with respect to baseline VAS pain at

chewing values. Fifty-eight subjects (58/90, 64.4%) had a 50% or more decrease, thus being considered as 'positive outcomes' in the statistical analysis. No complications or side effects were observed in any patients.

Univariate analysis showed that correlation with positive outcomes existed only with unilateral osteoarthritis, because 22/27 subjects who received treatment only to a single joint had a positive outcome (81.4%) with respect to 36/63 subjects with bilateral osteoarthritis (57.1%) (Table 1).

As for logistic regression analysis, the best fitting model allowed confirming the identification of the side of arthritis (unilateral/bilateral) as the only predictor variable associated with positive treatment outcome ($P = 0.032$). Notwithstanding that, odds ratio for positive outcome is low and within the 95% confidence interval (OR 0.3; 95%CI 0.1–0.9), and the percentage of variance in the outcome variable explained by the significant predictor is poor (R^2 7.7%). Also, the accuracy of the model was 64.4%, only slightly higher than univariate analysis, thus suggesting that the clinical significance of the identified model is likely low.

In consideration of the poor predictability of the detected model, another logistic regression was performed by a dichotomisation of the outcome variable on the basis of the detection of any improvement (85.6%) vs. no improvement (14.4%) at the end of the follow-up period. The final model included the variable 'baseline pain levels' as the only significant predictor ($P = 0.016$; OR 6.95; 95%CI 1.44–33.51) and explained up to 15% of the variance in the outcome variable (Table 2).

Discussion

Techniques for temporomandibular joint lavage and injections have been the subject of several investigations over the past two decades, but despite the encouraging findings reported in the literature, it seems that available data are inconclusive as for the actual mechanism of action (20). The hydraulic distension provoked by the under pressure lavage of the upper joint compartment with a large volume of saline has been considered the reason for the positive clinical outcomes in patients with sudden-onset closed lock (21). Notwithstanding, once that a single-session arthrocentesis was proven effective also to improve pain and dysfunction also in subjects affected by TMJ osteoarthritis (22) and that the importance of

[†]SPSS Inc., Chicago, IL, USA.

Table 1. Potential predictors of treatment outcome. Results of univariate analysis

Predictors	Patients with positive outcome (%)	Correlation with positive outcome (<i>P</i> values)	Accuracy to predict positive outcome (%)
Sex			
Female	52/80 (65)	0.759	70
Male	6/10 (60)		
Age			
<56 years	25/39 (64.1)	0.953	52.2
≥56 years	33/51 (64.7)		
Pain duration			
<12 months	25/38 (65.7)	0.822	51.1
≥12 months	33/52 (63.4)		
Baseline pain			
VAS < 7	30/45 (66.6)	0.664	52.2
VAS ≥ 7	28/45 (62.2)		
Side of arthritis			
Unilateral	22/27 (81.4)	0.027	54.4
Bilateral	36/63 (57.1)		
Other diagnoses			
Multiple diagnoses	33/52 (63.4)	0.822	51.1
Group III diagnosis alone	25/38 (65.7)		
Type of intervention			
Two needles	53/82 (64.6)	0.906	62.2
Single needle	5/8 (62.5)		
Tolerability			
Good	35/52 (67.3)	0.512	55.5
Less than good	23/38 (60.5)		

lubrication impairment in the pathogenesis of degenerative joint disease was shown (9), viscosupplementation therapy with hyaluronic acid injections following arthrocentesis gained popularity as a treatment option, as happened for larger joints (23).

At present, the majority of data on TMJ DJD came from the use of the same protocol used for larger joints, viz., five weekly injections of low molecular weight HA (11–13, 16), but protocols providing two injections (14, 15) or even a single injection (10) of a higher molecular weight HA also gave positive outcomes. Such encour-

aging findings achieved with HA injections in the management of osteoarthritis symptoms described in almost all studies prevented researchers from identifying the best protocol to be routinely adopted in the clinical setting. Considering these premises, the identification of reliable outcome predictors may be a first step towards tailoring HA treatments and getting deeper into the description of specific indications and patients to be selected for viscosupplementation therapy.

In the present study, attempts to identify outcome predictors were focused on those factors that may be easily recorded in the clinical records of any healthcare centre (sex, age, pain levels and duration, type of intervention, side of the disorders, concurrent disorders and treatment tolerability) and a protocol combining TMJ arthrocentesis plus HA injection performed once a week for 5 weeks was adopted because long-term positive effects in the management of TMJ degenerative joint disease have been already described over a 1-year span (13).

At 3 months, up to 85% of the patients showed an improvement with respect to their baseline pain at chewing levels, thus confirming the positive outcome achieved with this protocol and its effectiveness in the management of clinical symptoms related to TMJ disorders. About two-thirds of patients did exhibit a 50% or more decrease in their pain levels; such finding, which is without any doubt a clinically relevant outcome, was taken as the indicator of positive outcome, and its predictability was tested by means of both univariate analysis and logistic regression.

Unfortunately, the search for strongly significant predictors failed, and few clinically useful information may be drawn. The presence of unilateral disease was identified as the only significant predictor, because more than 80% of subjects treated for unilateral disease reported the above-defined positive outcome with respect to 57% of subjects with bilateral disease. Moreover, up to 92.5% (25/27) patients with unilateral disease showed at least a partial improvement at the end of 3-month observation period. Also, when a

Table 2. Significant predictors in the final logit models

Outcome variable	Significant predictor(s)	<i>P</i> value	Odds ratio (95%CI)	Model's <i>R</i> ² (%)
50% or more improvement in VAS pain levels	Side of arthritis	0.032	0.3 (0.1–0.9)	7.7
Any improvement	Baseline pain	0.016	6.95 (1.44–33.51)	15

model predicting the achievement of any improvement was identified, the only significant predictor was baseline pain level, viz., the higher the baseline pain the higher the probability to improve. Both these findings are not unexpected, because in the clinical setting it may be plausible that patients with localised disease, viz., unilateral, and with high pain levels are more likely to benefit from treatment. Apart from these suggestions, the present investigation seems to suggest that the effectiveness of a cycle of five arthrocenteses plus hyaluronic acid injections in patients with DJD is not specific and only in part dependent upon structural and biomedical factors.

The present investigation did not gather data on the use of other protocols providing the adoption of joint lavage alone or in combination with HA injections in a single session, which have been also suggested to be useful approaches for the management of TMJ disorders' symptoms (10, 14, 21). The reason for the adoption of a five-session combined arthrocentesis plus HA protocol lies in the fact that a multi-session HA protocol is the standard of reference in larger joints (24) and in the strong experience achieved by the authors over the years with this technique. The two main authors performed all the injections and each of them attended the intervention performed by the colleague, and despite there are no data on their calibration in the treatment phases, the operator's influence on treatment outcomes is likely to be low, as both operators were skilled TMD practitioners with years of experience and training in TMJ arthrocentesis and injections. Besides, to avoid potential influences of the examiners on data recording, before each injection, patients were asked to rate their pain levels by a dental student blind with respect to the study's aim.

Notwithstanding that, the need for a better understanding of the most suitable protocol for the management of symptoms in smaller joints cannot be underestimated, and a compelling aim for future studies is the design of randomised and controlled trials comparing different treatment protocols.

In the search towards the identification of other predictors of treatment effectiveness, it is likely that useful information may be drawn by the assessment of psychosocial features related with the presence of TMJ disorders. Also, the assessment of predictors at the individual level is likely to benefit from a detailed investigation of several other quantitative and qualitative features of the subjective pain experience, viz.,

timing of the pain, factors inducing the pain (yawning, chewing, talking), location of the pain, and, more in general, from a thorough recording of information regarding the clinical examination and the individual imaging. Moreover, it should be kept in mind that the present investigation involved patients treated by few researchers in a single tertiary clinic and followed up for a short post-treatment period. Thus, the external validity of these findings has to be tested with future studies on larger sample sizes, with the involvement of more researchers and performed over a longer follow-up. In any case, in consideration of the strong need to define better the epidemiology, natural course and prognosis of temporomandibular disorders, the above-mentioned data may represent a first step towards the definition of specific and tailored treatment protocols.

Conclusions

The positive effects of a cycle of five weekly arthrocenteses followed by hyaluronic acid injections in the management of symptoms of degenerative temporomandibular joint disease, which at the 3-month follow-up were observed in up to 85% of patients and seem to be mainly unspecific. The only variables that appear to be associated with a successful outcome were high baseline pain levels, which are predictors of symptoms improvement, and the presence of unilateral disease, which is associated with clinically relevant, viz., more than 50% symptoms improvement. In the next future, the search for other predictors of positive treatment outcome is likely to benefit from the assessment of psychosocial features associated with TMJ disorders.

References

1. 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.
2. De Bont LGM, Stegenga B. Pathology of temporomandibular joint internal derangement and osteoarthritis. *Int J Oral Maxillofac Surg.* 1993;22:71–74.
3. Tanaka E, Detamore MS, Mercuri LG. Degenerative disorders of the temporomandibular joint: etiology, diagnosis and treatment. *J Dent Res.* 2008;87:296–307.
4. Milam SB. Perspectives and epidemiology of TMJ. *J Musculoskelet Neuronal Interact.* 2003;3:382–390.
5. De Leeuw R, Boering G, Stegenga B. Clinical signs of TMJ osteoarthritis and internal derangement 30 years after non-surgical treatment. *J Orofac Pain.* 1994;8:18–24.

6. Milam SB. TMJ osteoarthritis. In: Laskin DM, Greene CS, Hylander WL, eds. *TMDs An evidence-based approach to diagnosis and treatment*. Chicago: Quintessence Publishing; 2006: 105–123.
7. Dao TT, Lavigne GJ. Oral splints: the crutches for temporomandibular disorders and bruxism? *Crit Rev Oral Biol Med*. 1998;9:345–361.
8. Stohler CS, Zarb GA. On the management of temporomandibular disorders: A plea for a low-tech, high-prudence therapeutic approach. *J Orofac Pain*. 1999;13:255–261.
9. Nitzan DW, Kreiner B, Zeltser B. TMJ lubrication system: its effect on the joint function, dysfunction, and treatment approach. *Compend Contin Educ Dent*. 2004;25:437–444.
10. 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.
11. 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.
12. 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.
13. 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.
14. Bjørnland T, Gjørnum AA, Møystad A. Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injection compared with injection with sodium hyaluronate. *J Oral Rehabil*. 2007;34: 583–589.
15. Møystad A, Mork-Knutsen BB, Bjørnland T. Injection of sodium hyaluronate compared to a corticosteroid in the treatment of patients with temporomandibular joint osteoarthritis: a CT evaluation. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;105:e53–e60.
16. Manfredini D, Bonnini S, Arboretti R, Guarda-Nardini L. 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.
17. Guarda-Nardini L, Manfredini D, Ferronato G. Arthrocentesis of the temporomandibular joint: a proposal for a single-needle technique. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2008;106:483–486.
18. Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomand Disord Fac Oral Pain*. 1992;6:301–355.
19. Cox DR, Snell EJ. *Analysis of binary data*, 2nd edn. London: Chapman and Hall, 1989, p. 209.
20. Brennan PA, Ilankovan V. Arthrocentesis for temporomandibular joint pain dysfunction syndrome. *J Oral Maxillofac Surg*. 2006;64:949–951.
21. Nitzan DW, Samson B, Better H. Long-term outcome of arthrocentesis for sudden-onset, persistent, severe closed lock of the temporomandibular joint. *J Oral Maxillofac Surg*. 1997;55:151–157.
22. Nitzan DW, Price A. The use of arthrocentesis for the treatment of osteoarthritic temporomandibular joints. *J Oral Maxillofac Surg*. 2001;59:1154–1159.
23. Axe MJ, Shields CL. Potential applications of hyaluronans in orthopaedics. *Sports Med*. 2005;35:853–864.
24. Gerwin N, Hops C, Lucke A. Intra-articular drug delivery in osteoarthritis. *Adv Drug Deliv Rev*. 2006;58:226–242.

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