

Conservative treatment of temporomandibular joint osteoarthritis: intra-articular injection of sodium hyaluronate

L. GUARDA-NARDINI*, S. MASIERO[†] & G. MARIONI[‡] **Department of Maxillofacial Surgery, University of Padua, Padua, Italy, [†]Department of Rehabilitation, University of Padua, Padua, Italy and [‡]Department of Otolaryngology, Head and Neck Surgery, University of Padua, Padua, Italy*

SUMMARY Promising short-term results in the treatment of temporomandibular joint osteoarthritis with intra-articular injections of sodium hyaluronate (SH) have been reported in preliminary studies. The present prospective study compared long-term outcomes of temporomandibular joint SH injections with those of a conventional non-surgical treatment (bite-plane). Data from three groups of 20 patients with degenerative temporomandibular joint disease were considered. Group A underwent one cycle of five injections of 1 mL SH. Group B underwent a bite-plane treatment for at least 6 months. We considered a control group of 20 patients who refused any treatments. The description of the outcomes was based on objective and subjective parameters after a 6-month follow-up. Sodium hyaluronate and bite-plane treatments significantly improved patients conditions in all considered parameters. No significant differences in outcomes

were confirmed by the statistical analysis. The tolerability of SH treatment resulted to be significantly higher. The analysis of results of serial controls in the SH treated group disclosed a significant worsening in pain at rest by comparing 1 and 6 months follow-up. Sodium hyaluronate infiltration resulted a valid non-surgical treatment for temporomandibular joint degenerative disease. Five well-tolerated intra-articular SH injections achieved equivalent results to those of a 6 months bite-plane treatment. We did not diagnose any complications of SH intra-articular injections. Longer time follow-up is necessary to determine the stability of SH properties.

KEYWORDS: sodium hyaluronate, injection, temporomandibular joint, osteoarthritis, bite-plane

Accepted for publication 26 January 2005

Introduction

Hyaluronic acid (HA) is a linear unbranched polysaccharide consisting of repeating disaccharide units. Proteoglycan monomers bind to HA to form large aggregates that are enmeshed in the collagen matrix of intact cartilage. HA is also a critical macromolecular component in normal synovial fluid (1) and seems to play a role in joint stabilization (2) and joint surfaces nutrition.

In osteoarthritis the concentration and molecular weight of HA in synovial fluid is diminished, because of dilution, fragmentation and production of lower

molecular weight HA by synoviocytes. These conclusions have led to the idea that restoring the concentration and molecular weight of HA by intra-articular HA injection (viscosupplementation) may have some therapeutic effect. In clinical trials, viscosupplementation has significantly modified osteoarthritic knee pain and functional disability (3, 4).

In 2002, we presented in a preliminary study the promising results of the treatment of temporomandibular joint (TMJ) degenerative disease with sodium hyaluronate (SH) infiltration (5).

The present prospective study compares in an academic tertiary referral centre setting the outcome of

intra-articular infiltration of SH with the outcomes of bite-plane treatment and with a third group of patients with diagnosis of degenerative TMJ disease who refused any treatments.

Material and methods

Clinically, inclusion criteria at the moment of diagnosis were painful TMJ, presence of unilateral or bilateral TMJ pain during palpation, joint sounds and impairment of jaw movements. Osteoarthrotic changes had to be diagnosed with magnetic resonance imaging. Magnetic resonance imaging diagnosis of TMJ osteoarthrosis was defined by the presence of flattening, subchondral sclerosis, surface irregularities, and erosion of the condyle or presence of condylar deformities associated with flattening, subchondral sclerosis, surface irregularities, erosion and osteophytes according to Emshoff and coworkers (6).

Data from three groups of 20 patients (55 females and five males) with diagnosis of TMJ osteoarthrosis were considered for this study. All patients gave informed consent to the study protocol.

The first group (group A) underwent one cycle of five injections (one per week) of 1 mL SH* according to the technique described by Guarda-Nardini *et al.* (5) The average age of patients (20 females) at the time of treatment was 49.8 years.

The second group (group B) underwent a bite-plane treatment for at least 6 months. The bite-plane was adjusted in centric occlusion. The patients of group B underwent weekly adjustments during the first month, then monthly removing the pre-contacts in eccentric occlusion. The mean age in this group consisting of one male and 19 females was 51.4 years.

The patients were allocated in groups A or B at random. None of the patients of Groups A or B drop out from the study.

For ethic reasons, we considered in the control group of non-treated subjects, 20 consecutive patients with diagnosis of degenerative TMJ disease who refused for different reasons any treatments (four males, 16 females; average age 46.4 years).

The following parameters were assessed by the same blinded examiner (S.M.) at the time of diagnosis, at the end of the treatment and during the follow-up period for groups A and B (1, 3 and 6 months after the end of

the treatment) and at the time of diagnosis and after 6 months for group C:

- (i) maximum mouth opening (in mm);
- (ii) pain at rest and mastication [assessed by a Visual Analogue Scale (VAS) from 0 to 10, the extremes of which were 'no pain' and 'pain as bad as the patient ever experienced'] (5);
- (iii) mastication efficiency (assessed by a VAS from 0 to 10, the extremes of which were 'eating only semi-liquid food' and 'eating solid hard food') (5);
- (iv) functional limitation during usual jaw movements (0, absent; 1, slight; 2, moderate; 3, intense; 4, severe) (5).

The patients of groups A and B were also asked to subjectively evaluate:

- (i) tolerability of the treatment (0, poor; 1, slight; 2, moderate; 3, good; 4, excellent);
- (ii) efficacy of the treatment (0, poor; 1, slight; 2, moderate; 3, good; 4, excellent).

The statistical significance of the differences among means for parameters described by VAS values was determined by parametric statistics using the paired sample Student's *t*-test for results in the same set of cases and the pooled Student's *t*-test for comparing two means of different sets of cases. The significance of the changes in parameters described by a score was statistically analysed using non-parametric methods (Wilcoxon rank sum test). The statistical analysis was performed with a 11.0 version of a SPSS statistical software.[†] A significance level of 0.05 (two tailed) was assumed for all the calculations, to determine whether to reject the null hypothesis.

Injection technique

The technique used to perform arthrocentesis of the TMJ employs the same reference points as used in arthroscopic examination (lateral cantus-tragus). The skin surface is disinfected with povidone iodine. Local anaesthesia is then achieved with mepivacaine 2% (Carbocaine[‡]). The anaesthetic is first injected into the joint cavity, relaxing this virtual space. Subsequently, the needle is withdrawn gently to the skin surface, thus anaesthetizing the soft tissues over the joint, too. Two 19 G needles are then placed to make entry and exit points for the liquid to be injected that will wash out

*Hyalgan, Fidia, Abano Terme, Italy.

[†]SPSS Inc., Chicago, IL, USA.

[‡]Sanofi Winthrop, NY, USA.

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.

Results

There was no statistically significant difference in mean age between the patients considered in group A (SH treatment), the patients considered in groups B (bite-plane treatment) and C (untreated control group).

Maximum mouth opening

The pre-treatment mean maximum mouth opening values were 34.7 and 34.2 mm for groups A and B, respectively ($P = \text{non-significant}$). With both treatments (SH and bite-plane) a statistically significant increase in maximum mouth opening was observed ($P < 0.01$). The difference between 6-month SH versus bite-plane mean results (44.7 mm versus 40.6 mm) was not statistically significant. Paired sample Student's *t*-test did not disclose any significant differences by comparing the maximum mouth opening after 1, 3 and 6 months SH treatment.

Pain at rest

The pre-treatment mean values that indicated pain at rest were 5.0 and 4.2 (VAS values) for groups A and B, respectively. With both treatments (SH and bite-plane) a statistically significant reduction in pain at rest was observed after 6 months ($P < 0.01$). Considering the SH treatment outcome, the most evident mean reduction of pain at rest was found after 1 month treatment with a value of 0.95 against 1.1 and 1.4 after 3 and 6 months, respectively. The difference between the reduction of mean pain at rest resulted statistically significant considering the 1-month treatment mean value against the 6-months treatment mean value ($P < 0.05$). The difference between 6-month SH versus bite-plane mean results (1.4 versus 1.4) was not statistically significant.

Pain on movement

The pre-treatment mean values related to pain on movement were 6.0 and 7.5 (VAS values) for SH treatment group and bite-plane treatment group,

respectively. With both treatments a statistically significant reduction in pain at rest was found after 6-months ($P < 0.01$). Not significant difference was found between the two treatments after 6 months.

Mastication efficiency

Both treatments (SH and bite-plane) determined a statistically significant improvement after 6 months ($P < 0.01$). A significant difference was found between the results of SH and bite-plane treatments after 6 months (7.8 versus 6.1) ($P < 0.05$). Nevertheless the pre-treatment determination of mastication efficiency disclosed a less serious limitation in the SH group ($P < 0.01$). The change in mastication efficiency after treatment was determined by the difference between the post-treatment value and the pre-treatment value. There was no statistically significant difference in mean change of efficiency between SH injection group and bite-plane group.

Functional limitation level

The SH and bite-plane treatments achieved a statistically significant reduction of functional limitation level (Wilcoxon rank sum test $P < 0.01$). No significant difference was observed between the two treatments after 6 months.

Tolerability of the treatment

Thirteen of the 20 patients (65%) considered the SH treatment tolerability at least 'good' (score 3 or 4), only one patient (5%) considered the bite-plane treatment tolerability 'good' and none 'excellent'. The higher tolerability of the SH treatment compared with bite-plane treatment was confirmed by statistical analysis (Wilcoxon rank sum test $P < 0.01$).

Subjective efficacy of the treatment

Thirteen of the 20 patients (65%) and 14 of the 20 patients (70%) considered at least 'good' the subjective efficacy of SH and bite-plane treatments, respectively. No significant differences in subjective efficiency of the treatments were found by the patient considered.

No significant modifications were found in the untreated control group (group C) for any of the considered parameters after 6-month control.

Table 1 SH treatment (group A) and bite-plane treatment (group B) outcomes. Group C (no treatments) was the control group

Parameters	Groups	Pre-treatment (mean)	Follow-up (mean)		
			1 month	3 months	6 months
Maximal mouth opening (mm)	Group A (SH)	37.7	41.8	41.9	44.7
	Group B (bite-plane)	34.2	40.5	40.0	40.6
	Group C (no treatments)	40.3	–	–	38.6
Pain at rest (VAS)	Group A (SH)	5.0	0.9	1.1	1.4
	Group B (bite-plane)	4.2	1.6	1.6	1.4
	Group C (no treatments)	1.6	–	–	1.5
Pain on movement (VAS)	Group A (SH)	6.0	1.7	2.0	1.8
	Group B (bite-plane)	7.5	5.1	2.2	2.3
	Group C (no treatments)	2.4	–	–	2.2
Mastication efficiency (VAS)	Group A (SH)	5.3	7.7	7.9	7.8
	Group B (bite-plane)	3.1	5.3	6.2	6.1
	Group C (no treatments)	6.0	–	–	4.7

Pre- and post-treatments results for group A and B were summarized in Table 1.

Complications

We did not describe any complications of SH intra-articular injections in group A.

Discussion

The present study compared long-term results in the treatment of TMJ osteoarthritis with SH injection with those of a conventional non-surgical treatment as bite-plane. This prospective study demonstrated that five well-tolerated intra-articular SH injections achieved equivalent results to those of a 6 months conventional bite-plane treatment considering as parameters maximum mouth opening, pain at rest and mastication, mastication efficiency, functional limitation during usual jaw movements.

Neo *et al.* (7) developed an animal-model to determine the results of HA treatment in experimentally induced temporomandibular osteoarthritis. They concluded that the effect of HA might be either mechanical or metabolic. The mechanical concept is based on HA joint lubrication while HA had a metabolic role in nutrition of avascular parts of the disc and the condylar cartilage. These authors also pointed out the structural role of HA in cartilage formation. Hirota (8) demonstrated that SH injections in patients with TMJ dysfunction reduced the presence of catabolites of arachidonic acid and cytokines in the synovial fluid.

Considering an intensive meta-analysis Shi and coworkers (9) recently concluded that there is insufficient evidence to either support or refuse the use of hyaluronate for treating patients with TMJ disorders. Nevertheless, short-term results of TMJ intra-articular injections of SH investigated in preliminary studies were very promising (10, 11). These results were recently confirmed by Guarda Nardini *et al.* (5).

There is a dearth of studies regarding the stability of the effects achieved with SH injection in cases of TMJ osteoarthritis. In 1993, Bertolami *et al.* (12) designed the first randomized, double blind, placebo-controlled study to test the efficacy of high-molecular-weight SH in treating TMJ disorders. Alpaslan and Alpaslan (13) investigated the long-term efficiency of arthrocentesis with injection of SH but only in patients with TMJ dysfunction. The parameters considered were limited to maximal mouth opening and lateral movements.

In our comparative study, the description of the outcome was based on a wide range of objective (maximum mouth opening) and subjective parameters (pain at rest and mastication, mastication efficiency, functional limitation level during usual jaw movements). SH and bite-plane treatments significantly improved patients conditions in all considered parameters. No significant differences in outcomes between SH and bite-plane treatments were confirmed by the statistical analysis. Post-treatment data were evaluated and compared at long-term, i.e. after 6 months. Subjective efficacy of the treatments described by the considered patients resulted equivalent. The tolerability of SH treatment resulted to be significantly higher for the patients than that of bite-plane treatment. It is

necessary to point out that the SH treatment is based on five well-tolerated intra-articular injections and the bite-plane treatment on a time-spending long-term rehabilitation program that may last for many months.

An exhaustive review of the literature disclosed a limited number of reports describing complications of SH intra-articular injections. An isolated case of bone necrosis of the articular tubercle of the TMJ was described by Lida *et al.* (14). Laquerre and coworkers (15) reported one case of septic arthritis due to *Actinomyces Naeslundii* after intra-articular (knee) injection of hyaluronate. Acute arthritis after hyaluronate intra-articular viscosupplementation was reported in one case (knee) by Evanich *et al.* (16) and in two cases by Bernardeu *et al.* (17) Granulomatous inflammation of the knee articulation after hyaluronate-derived viscosupplementation was described in five patients by Chen *et al.* (18).

The analysis of results of serial controls in the SH treated group disclosed a significant worsening in pain at rest by comparing 1 and 6 months follow-up. This may suggest to reconsider the hypothesis about the long lasting persistence of hyaluronate properties. Alpaslan and Alpaslan (13) pointed out the problem of stability of therapeutic SH properties stating that the lubricant effect was highly effective in the first 3 months.

Conclusion

SH infiltration is a valid non-surgical treatment for TMJ degenerative disease. The present prospective study demonstrated that five well-tolerated intra-articular SH injections achieved results statistically equivalent to those of a 6 months conventional bite-plane treatment. The tolerability for the patients of the SH treatment resulted significantly higher than that of the bite-plane treatment. We did not diagnose any complications of SH intra-articular injections.

Evaluation of a longer time follow-up is necessary to determine the stability of SH properties in the treatment of temporomandibular osteoarthritis and to confirm the need of serial SH treatments for the maintenance of the achieved results.

References

1. Marshall KW. Intra-articular hyaluronan therapy. *Curr Opin Rheumatol.* 2000;12:468–474.

2. Cascone P, Fonzi Dagger L, Aboh IV. Hyaluronic acid's biomechanical stabilisation function in the temporomandibular joint. *J Craniofac Surg.* 2002;13:751–754.
3. Wobig M, Bach G, Beks P, Dickhut A, Runzheimer J et al. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther.* 1999;21:1549–1562.
4. Huskisson EC, Donnelly S. Hyaluronic acid in the treatment of osteoarthritis of the knee. *Rheumatology* 1999;38:602–607.
5. Guarda-Nardini L, Tito R, Staffieri A, Beltrame A. Treatment of patients with arthrosis of the temporomandibular joint by infiltration of sodium hyaluronate: a preliminary study. *Eur Arch Otorhinolaryngol.* 2002;259:279–284.
6. Emshoff R, Innerhofer K, Rudisch A, Bertram S. The biological concept of "internal derangement and osteoarthritis": a diagnostic approach in patients with temporomandibular joint pain? *Oral Surg Oral Med oral Pathol Oral Radiol Endod.* 2002;93:39–44.
7. Neo H, Ishimaru JI, Kurita K, Goss AN. The effect of hyaluronic acid on experimental temporomandibular joint osteoarthritis in the sheep. *J Oral Maxillofacial Surg.* 1997;55:1114–1149.
8. Hirota W. Intra-articular injection of hyaluronic acid reduces total amounts of leukotriene C4, 6-keto-prostaglandin F1 alpha, prostaglandin F2 alpha and interleukin-1 beta in synovial fluid of patients with internal derangement in disorders of temporomandibular joint. *Br J Oral Maxillofac Surg.* 1998;36:35–38.
9. Shi Z, Guo C, Awad M. Hyaluronate for temporomandibular joint disorders. *Cochrane Database Syst Rev.* 2003;1:CD002970.
10. Kopp S, Wenneberg B, Haraldson T, Carlsson GE. The short-term effect of intra-articular injections of sodium hyaluronate and corticosteroid on temporomandibular joint and dysfunction. *J Oral Maxillofac Surg.* 1985;43:429–435.
11. Fader WW, Grummons DC, Maijer R, Christensen LV. Pressurized infusion of sodium hyaluronate for closed-lock of the temporomandibular joint. Part I. A case study. *J Craniofac Surg.* 1993;11:68–72.
12. Bertolami CN, Gay T, Clark GT, Rendell J, Shetty V, Liu C, Swann DA. Use of sodium hyaluronate in treating temporomandibular joint disorders: a randomized, double blind, placebo controlled clinical trial. *J Oral Maxillofacial Surg.* 1993;51:232–242.
13. Alpaslan GH, Alpaslan C. Efficacy of temporomandibular joint arthrocentesis with and without injection of sodium hyaluronate in treatment of internal derangement. *J Oral Maxillofacial Surg.* 2001;59:613–618.
14. Lida K, Kurita K, Tange K, Yoshida K. Necrosis of the articular tubercle after repeated injections of sodium hyaluronate in temporomandibular joint. A case report. *Int J Maxillofac Surg.* 1998;27:278–279.
15. Laquerre T, Nouvellon M, Kraznowska K, Bruno MC, Vittecoq O et al. Septic arthritis due to *Actinomyces naeslundii*: report of a case. *Joint Bone Spine.* 2002;69:499–501.
16. Evanich JD, Evanich CJ, Wright MB, Rydlewicz JA. Efficacy of intraarticular hyaluronic acid injections in knee osteoarthritis. *Clin Orthop.* 2001;390:173–181.

17. Bernardeau C, Bucki B, Liote F. Acute arthritis after intra-articular hyaluronate injection: onset of effusion without crystal. *Ann Rheum Dis.* 2001;60:518-520.
18. Chen AL, Desai P, Adler EM, Di Cesare PE. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee: a report of six cases. *J Bone Joint Surg Am.* 2002;84:1142-1147.

Correspondence: Luca Guarda-Nardini, MD, Department of Maxillo-facial Surgery, University of Padua, Via Giustiniani n.2 Padua, Italy.
E-mail: luca.guarda@unipd.it