Short-term therapeutic outcome of intra-articular high molecular weight hyaluronic acid injection for nonreducing disc displacement of the temporomandibular joint

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In a patient with temporomandibular disorder who does not respond to conservative treatment, treatment with intra-articular injection of high molecular weight sodium hyaluronate can be suggested. In our study, 27 patients with nonreduced disc displacement were diagnosed clinically and confirmed by magnetic resonance imaging. The age range was from 21 to 63 years old, with a mean of 39.3 years. Two cycles of injection of high molecular weight sodium hyaluronate was performed on alternative weeks. Pain intensity was measured by the visual analog scale. Maximal mouth opening, clicking joint noise, and lateral movement were measured before and after injection for more than 6 months. Reduction of pain intensity and improvement in the maximum mouth opening parameter was statistically significant. In conclusion, this intra-articular injection using high molecular weight sodium hyaluronate looks very positive for patients affected by nonreduced disc displacement and is encouraged to be used as a primary treatment of temporomandibular joint dysfunction. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102: 453-61)

The pathogenesis of internal derangement of the temporomandibular joint (TMJ) has shifted focus from a disc displacement theory1,2 to more emphasis on the biochemical causes.3-5 It has been suggested that TMJ internal derangement often progresses from a stage of clicking with normal maximal mouth opening (MMO) through one where clicking gradually ceases with varying degrees of restriction in mouth opening to a stage of closed lock.6 The latter stage is customarily attributed to a clinical state of nonreducible anteriorly displaced disc acting as an obstacle to the gliding condyle.7-9 In the past, treatment of TMJ dysfunction that did not respond to conservative treatment was surgical disc repair and repositioning to reestablish normal MMO.10-12 Arthroscopy,13 simple lysis and lavage, and the use of hydraulic pressure in the upper joint space were found to be highly effective in reestablishing normal MMO and relieving the symptoms14-16 despite the disc position not having been corrected.

Nitzan et al.17 proposed that closed lock was a result of reversible restriction in gliding movements of the disc caused by its adherence to the fossa. Such adherence may arise from a number of possible causes such as fibrous adhesions, severe friction between damaged rough surfaces, stickiness that may be a direct result of an increase in synovial fluid viscosity, or a vacuum effect. A vacuum effect or alteration in synovial fluid consistency may create the environment for a suction effect of the disc to the fossa, restricting gliding movements and therefore resulting in limited mouth opening.

The technique of TMJ arthrocentesis and lavage described by Nitzan et al.15 is a simple means of releasing the “stuck” disc from the fossa by simple irrigation of the superior joint space under local anesthesia on an outpatient basis. After arthrocentesis, pain and disturbance in jaw function decreased dramatically and in that study,15 13 of 17 patients did not have clicking following the arthrocentesis procedure.

The disc displacement theory has been well accepted in the past,1,2 however many researchers are currently focusing on the biochemistry of the synovial fluid in various stages of TMJ disease in trying to elucidate the pathogenesis of temporomandibular disorders (TMD).3,4,18 The role of inflammation has been investigated and proposed as an underlying mechanism of
pain and dysfunction of the TMJ because cellular and biochemical signs of inflammation were frequently observed in the TMJs of patients with longstanding pain and tenderness of this joint.\textsuperscript{19,20} Agus et al.,\textsuperscript{21} in 1983, simplified the therapeutic injection of steroids and reported a good response in 10 of 14 patients with unilateral TMJ synovitis.

Sodium hyaluronate had been identified and tested in animals with promising results.\textsuperscript{22,23} Clinical trials in patients who had severe knee arthritis not responding to conventional treatment showed considerable relief of symptoms.\textsuperscript{24-26} Kopp et al.\textsuperscript{27-29} reported that intra-articular injections of hyaluronate or corticosteroids combined with local anesthesia had short-term and long-term palliative effects on subjective symptoms and clinical signs of TMJ pain. Because of the unpredictable prognosis of intra-articular injections of corticosteroids for patients with TMJ osteoarthrosis and the uncertainty regarding local side effects of these drugs on joint tissues, corticosteroid injection remained unpopular.\textsuperscript{30,31}

In the use of sodium hyaluronate in TMJ, Kopp et al.\textsuperscript{27} investigated 33 patients with TMJ pain and tenderness to palpation of at least 6 months’ duration and who did not respond to previous conservative treatment. They used a volume of 0.5 mL of sodium hyaluronate or 0.5 mL corticosteroid injected twice into the superior joint compartment of the TMJ with a 2-week interval between injections. The results revealed that both drugs reduced symptoms and signs without a statistically significant difference, prompting a conclusion that sodium hyaluronate could be used as an alternative to corticosteroids in patients with signs of TMJ inflammation including symptomatic osteoarthrosis. This led to a new horizon of therapeutic options.

Kopp et al.\textsuperscript{29} and Bertolami et al.\textsuperscript{32} injected hyaluronic acid of different molecular weights into the joint after arthrocentesis in patients with osteoarthritis. Later, Fader et al.\textsuperscript{33} reported the injection of combined local anesthesia and hyaluronic acid in patients with persistent, painful, nontranslatory closed lock of the TMJ and reported short-term beneficial effects. Yustin et al.\textsuperscript{34} reported the use of 1 mL of hylan GF-20 by intra-articular injection to manage osteoarthritis of the TMJ and their patient functioned well and felt comfortable for 4 months after 3 injections. Sato et al.\textsuperscript{35} injected 1 mL of sodium hyaluronate (Artz, Seikagaku Kyogo Co., Tokyo, Japan) into the superior joint space of patients with unilateral nonreducing disc displacement once a week for 5 consecutive weeks and reported resolution of TMJ symptoms. Hepguler et al.\textsuperscript{36} also reported the intra-articular injection of 0.5 mL of hyaluronic acid (15 mg mL$^{-1}$ orthovisc, Anika Therapeutics Inc., Woburn, MA) into the superior joint compartment of the TMJ in patients with reducible TMJ disc displacement and reported promising results.

Hence, with the experience of treating osteoarthritis (OA) of the knee, higher molecular weight sodium hyaluronate was found to be more effective than its low molecular weight equivalent in relieving OA knee pain,\textsuperscript{37} and has prompted us to consider it as a useful alternative in the treatment of TMD. Hylan G-F20 contains hylan A with average molecular weight of hylan G-F20 synvisc 6 000 000 and hylan B hydrated gel.\textsuperscript{38} The aim of this study is to report the short-term therapeutic outcome of intra-articular injection of high molecular weight hyaluronic acid in patients with a magnetic resonance imaging (MRI)-confirmed diagnosis of nonreducing displacement of the TMJ disc.

**MATERIALS AND METHODS**

From a large pool of patients attending the outpatient clinic at the department of Oral and Maxillofacial Surg-
gery, University of Hong Kong, those clinically diag-
nosed with TMD and who were unsuccessfully treated
by conservative therapy (soft diet, jaw exercises, splint
therapy) were considered for recruitment into this
study.

From the above large group, patients who still com-
plained of any one of the following: pain on mastica-
tion, joint clicking, joint noise, or limited MMO, were
approached to consent for inclusion in the study. After
informed consent was obtained, the following imaging
procedures for the TMJ were completed: panoramic
radiography, MRI in the sagittal and coronal planes,
and with the mouth open and closed. Those patients
with a firm diagnosis of nonreducing TMJ disc dis-
placement in one or both joints based on MRI findings
(Fig. 1) were included in this study.

The study protocol involved the administration of 2
intra-articular injections, 2 weeks apart, of 2 mL of
Hylan GF20 into the superior joint space of the affected
TMJ.

Prior to the first injection, and at 1 week, 2 weeks
(prior to second injection), 3 weeks, 4 weeks, 3 months,
and 6 months, the following parameters were recorded:
MMO, lateral jaw excursion, the presence of pain at
rest and on chewing, the presence of joint clicking, and
joint noise in the affected joint.

The pain level and location were determined by
patients’ self-assessment using a facial diagram and a
visual analog scale (VAS) by drawing a circle on the
diagram to indicate the site of pain and a pain score
from 0 to 10 (“0” is pain free and “10” is severe pain).
MMO was measured as the distance between the incisal
dege of the upper and lower central incisors.

The range of lateral movements of the mandible was
determined by measuring the distance between the up-
ner and lower incisor midlines on jaw movement to the
left and right respectively.

The technique used to perform the intraarticular in-
jection (Fig. 2) employed the same landmarks as used
in arthroscopic examination.39

After each injection, patients were asked to rest the
joint totally for 3 days. Soft diet was prescribed. During
the study period, no physiotherapy or splint therapy
was used.

The pain intensity, degree of mouth opening, and
lateral excursion at different postoperative follow-up
times were compared and analyzed using Statistical
Package for Social Sciences Version 11.0 (SPSS Inc.,
Chicago, IL). The mean scores were calculated and the
differences were compared and tested with the paired-
samples t-test (2 tailed). The proportional changes in
clicking and crepitus were tested with the McNemar
test. All the tests were carried out at the confidence
level of 95% and significance level at 5%.

The protocol was approved by the human ethics
committees of the Faculty of Dentistry, The University of Hong Kong.

RESULTS

Preinjection findings

A total of 27 patients, 7 males and 20 females, male-to-female ratio 1:2.9, received intra-articular injection in 34 temporomandibular joints. The age range was 21 to 63 years (mean age 39.3 years) and the majority (mean 48.1%) of patients were from the age group of 40 to 49 years (Fig. 3). All patients did not have diabetes and none of them was on steroid therapy. Five patients were smokers.

The diagnoses of the joint condition based on the MRI in these 27 patients are shown in Table I.

Preoperatively, 14 patients (41.1%) presented with unilateral clicking; 2 patients (5.9%) with bilateral clicking. Bilateral crepitus was found only in 2 patients before the intra-articular injection and 1 patient presented with unilateral crepitus.

Regarding pain symptoms, 4 patients (14.8%) com-

Table I. Diagnoses of the joint condition in the 27 subjects

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Side of injection</th>
<th>Dx of injected side</th>
<th>Dx of non-injected side</th>
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<td>M</td>
<td>R</td>
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<td>DDWR</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>R</td>
<td>DDWR</td>
<td>DDWR</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>R</td>
<td>DDWR</td>
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<tr>
<td>4</td>
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<tr>
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<tr>
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<td>27</td>
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<td>Bilateral</td>
<td>DDWR</td>
<td>DDWR</td>
</tr>
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</table>

Table II. The mean pain intensity (VAS score) at different postoperative periods in comparison to preoperative pain (n = 34)

<table>
<thead>
<tr>
<th>Period</th>
<th>Mean pain intensity (VAS score)</th>
<th>P value</th>
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<tr>
<td>Preoperative</td>
<td>4.2</td>
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<tr>
<td>Postop 1 week</td>
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<td>&lt;.01*</td>
</tr>
<tr>
<td>Postop 2 weeks</td>
<td>1.9</td>
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<tr>
<td>Postop 3 weeks</td>
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<td>&lt;.01*</td>
</tr>
<tr>
<td>Postop 2 months</td>
<td>2.4</td>
<td>.06</td>
</tr>
<tr>
<td>Postop 3 months</td>
<td>2.5</td>
<td>.05*</td>
</tr>
<tr>
<td>Postop 6 months</td>
<td>2.6</td>
<td>.01*</td>
</tr>
</tbody>
</table>

*Statistically significant (paired-samples t test).

Table III. Comparison of difference in mean pain intensity (VAS score) after first injection with after second injection (n = 34)

<table>
<thead>
<tr>
<th>Period</th>
<th>Mean pain intensity (VAS score)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First injection</td>
<td>1.6</td>
<td>—</td>
</tr>
<tr>
<td>(Postop 1 week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second injection</td>
<td>1.9</td>
<td>2*</td>
</tr>
<tr>
<td>(Postop 3 weeks)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No statistical significance (paired-samples t test).
plained of bilateral TMJ pain and 17 patients (63%) had unilateral pain over the joint. Preinjection mean pain intensity was 4.2, mean mouth opening was 38 mm, and the mean right and left lateral excursions were 7.5 mm and 7.3 mm, respectively.

Among the 27 patients, 20 patients had intra-articular injection of one TMJ only; while the remaining 7 patients had both joints injected with hyaluronate. All of these 34 joints have been followed up for more than 6 months and 16 of them were followed up for 1 year.

**Pain outcome**

The mean pain intensity decreased with time. There was less pain over the TMJ after the intra-articular injections and this difference was statistically significant (Table II). However, when comparing the pain reduction between the first and third postoperative weeks (1 week after the first injection and 1 week after the second injection) there was no significant difference (Table III).

**Mouth opening and lateral excursion**

The change in degree of mouth opening is shown in Table IV. Mouth opening was noted to decrease when compared to preinjection measurement in a statistically significant manner up to 1 month after injection. Later review did not show any further decrease in MMO. Furthermore, there was no statistically significant difference in the mean lateral excursion at different postoperative periods (Table V).

**Clicking and crepitus**

The longitudinal changes of joint clicking and crepitus on the injected side are shown in (Fig. 4 and Fig. 5). Prevalence of joint clicking was found to have a statistically significant decrease from preinjection to 1 year after injection; however, there was no significant change in the joint crepitus.

**DISCUSSION**

The use of sodium hyaluronate was first described in the 1970s by Rydell and Balázs and by Helfet in the treatment of osteoarthrosis of the knee. Many studies conducted since then on osteoarthrosis of the knee demonstrated that sodium hyaluronate helps to alleviate pain, improve knee function, and reduce knee joint crepitus. In the treatment of TMJ disorders, this substance presents a therapeutic opportunity either as an adjunct medication after arthrocentesis or as a therapeutic intra-articular injection.

Sodium hyaluronate, the sodium salt of hyaluronic acid, is a high molecular weight polysaccharide and a major natural component of synovial fluid. The importance of hyaluronate to the lubrication of synovial tissue has been established but its function in relation to the occurrence of joint disease is not precisely known. In 1939 Mayer et al. first identified it in synovial fluid. Hyaluronic acid is a glycosaminoglycan made of the periodic repeat of d-glucuronic acid and N-acetylglucosamine disaccharides units. It plays a role in the regulation of synovial fluid.

Hyaluronate is largely responsible for the viscosity and rheologic properties of normal synovial fluid. Its capacity to function as a molecular sieve is thought to be important both in regulating the nutrition of articular cartilage and in physical interactions with the macromolecules of the articular surfaces. Hyaluronate is a good soft tissue lubricant under low loads and may exert important interactions with the synovial lining to preserve the latter’s physical properties, especially its characteristic smoothness and low friction surfaces. Hyaluronate is not known to induce damage or to elicit tissue reactions when used as an intra-articular injection. Hyaluronate had been reported to prevent intra-articular adhesions and elicit little if any immune response when injected into humans or animals. Even repeated injections of hyaluronate into the joints of experimental animals have not shown any deleterious effects resulting only in transient infiltration of polymorphonuclear macrophagelike cells into the synovial membrane. No clinical signs of inflammation can be demonstrated after the use of hyaluronate.

Chen et al. reported 6 cases of granulomatous inflammation after Hylan GF20 viscosupplementation of the knee but overall incidence of adverse reactions has been reported at just 1% per injection with the majority consisting of localized inflammation at the site of injection. In our study, no patient had an acute local reaction or persistent symptoms.

Kopp et al. first reported in 1985 and 1987 the short-term and long-term therapeutic outcome of hyaluronic acid given after arthrocentesis and compared its effect with that of a corticosteroid (betamethasone).
injection in patients who had signs of TMJ inflammation. Both drugs were able to demonstrate a reduction of pain and improvement in mouth opening and mastication especially for those who had symptomatic osteoarthrosis. They concluded that sodium hyaluronate should be the better alternative because of its lesser side effects. In 1991, Kopp et al.44 again reported the short-term effect of intra-articular injection of sodium hyaluronate by comparing it with glucocorticoids and saline solution in the TMJ of rheumatoid arthritis (RA) patients. In all these RA patients, significantly positive results were reported in patients treated with either sodium hyaluronate or glucocorticoids. In 1993, Bertolami et al.32 assessed the efficacy of high molecular weight sodium hyaluronate as a treatment of various intracapsular TMJ disorders including degenerative joint disease, reducing disc displacement and nonreducing disc displacement. They injected 1% sodium hyaluronate in physiologic saline or pure physiologic saline into the upper joint space unilaterally. At the second- and third-month examination interval, patients treated with hyaluronate showed improvement compared to those receiving placebo. Sato et al.35 proposed the use of sodium hyaluronate in nonreducing TMJ disc displacement obtaining overall improvement in clinical signs and symptoms, however the disc displacement remained uncorrected. The main indication for the use of this substance had thus progressively extended from degenerative TMJ arthritis and rheumatoid arthritis to nonreducing disc displacement disorders.

The results of the present study showed that treatment using a cycle of 2 intra-articular injections of high

### Table V. The mean lateral excursion at different postoperative periods in comparison to preoperative lateral excursion (n = 34)

<table>
<thead>
<tr>
<th>Period</th>
<th>Mean right lateral excursion (mm)</th>
<th>P value</th>
<th>Mean left lateral excursion (mm)</th>
<th>P value</th>
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<td>—</td>
<td>7.3</td>
<td>—</td>
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<td>Postop 3 weeks</td>
<td>6.9</td>
<td>.32</td>
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<td>.66</td>
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<td>Postop 2 months</td>
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<td>.52</td>
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<tr>
<td>Postop 3 months</td>
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<td>Postop 6 months</td>
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<td>.17</td>
<td>8.3</td>
<td>.07</td>
</tr>
</tbody>
</table>

Paired-samples t test.

Fig. 4. Longitudinal change in TMJ clicking on the injected side at different postoperative periods (n = 34).
molecular weight hyaluronic acid 2 weeks apart was effective in diminishing pain intensity without significantly affecting the range of mouth opening. The precise mechanism by which hyaluronate alleviates symptoms remains unknown but may be a purely mechanical effect. However, the half-life of hyaluronate, known to be 13.2 hours in rabbit knee joints, cannot explain the beneficial effects of administered sodium hyaluronate, which can last for 6 months. One possible explanation is that damage to synovial surfaces and to the disc is mitigated through a short-term lubricating action of sodium hyaluronate and the repair of articular surface. The increase in mouth opening may be because of reduction of the frictional coefficient in the TMJ, thus enhancing the lubricating ability and not the mechanical effect of the liquid. The elimination of pain is mainly because of the analgesic, anti-inflammatory, and lubricating properties of the hyaluronic acid. Balazs commented that the analgesic effect was directly proportional to the molecular weight and, therefore, to the elastoviscosity of the solution, which was first reported by Miyazaki et al. It has been reported that synovial fluid aspirated from inflammatory joint disease or rheumatoid arthritis has a lower viscosity than patients with no disease. This was found to be correlated to either increased degradation of high molecular weight hyaluronate and/or a decrease in the concentration of high molecular weight hyaluronate in inflammatory disease. Therefore, the improvement in symptomatology and function most likely is linked with the intrinsic properties of high molecular weight hyaluronic acid as suggested by the results of the present study.

In this study, we noted that the pain intensity was significantly reduced even after the first injection despite Synvisc claim that there will be pain and inflammation for 3 days or longer. Mouth opening decreased in the first 4 weeks but improved in the subsequent follow-up period. This finding raises an interesting question about the effectiveness of a single dose versus 2 doses of intra-articular injection of high molecular weight sodium hyaluronate into the TMJ with a nonreducing disc displacement.

CONCLUSION

Based on this observational study, intra-articular TMJ injection of high molecular weight hyaluronic acid appears to be a safe and effective therapeutic method with a long-lasting effect (6 months to 1 year) in patients with nonreducing disc displacement.

The authors recommend the use of 2 injections of
high molecular weight hyaluronic acid given at 2-week intervals. This therapeutic option is in our opinion preferable to the use of nonsteroidal anti-inflammatory drugs and corticosteroids, which are known to have undesirable side effects.

The development and use of sodium hyaluronate, especially high molecular weight hyaluronate, in the treatment of TMJ internal derangement is an exciting therapeutic prospect that deserves further thorough investigation.

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