The efficacy of intra-articular sodium hyaluronate in patients with reducing displaced disc of the temporomandibular joint

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SUMMARY In this clinical trial, we examined the efficacy of intra-articular hyaluronic acid (HA) treatment in 38 patients with reducing displaced disc of the temporomandibular joint (TMJ). Subjects received two unilateral upper space injections of HA or physiological saline solution with 1 week apart. Efficacy was based on the following measurements: pain and sound intensity of the joint measured by visual analogue scale (VAS), modified Helkimo's clinical dysfunction index and the intensity of joint vibration during opening and closing the mouth measured by accelerometers. These measurements were performed before the first injection and 1 and 6 months after the last injection. In the treatment group (n = 19), all measurements improved significantly at month 1 and at month 6 compared with the baseline (P < 0.01). The same measurements, in the placebo group (n = 19), did not show any change, except for the pain intensity which improved at month 1 and month 6 (P < 0.05). The change in baseline measurements of all of the efficacy criteria at month 1 and at month 6 in the treatment group was significantly better compared with the change obtained with placebo at the same time intervals. This study demonstrates that intra-articular sodium hyaluronate (Orthovisc®) injection into the TMJ is an effective treatment for a reducing displaced disc.

KEYWORDS: intra-articular therapy, sodium hyaluronate (hyaluronan), temporomandibular joint

Introduction

Temporomandibular joint (TMJ) disorders may have intracapsular, extracapsular or combined intracapsular and extracapsular origins. Extracapsular disorders generally result from the muscles surrounding the TMJ. Thus, conservative therapies such as heat application, soft diet and exercise can often be effective in the treatment of these disorders (Clark & Merrill, 1992). In contrast, intracapsular disorders are the result of the pathology of the articular surfaces or abnormalities in the mechanical relationship of articular structures (Guralnick et al., 1978). The conservative treatment of the symptomatic intracapsular disorders are not always successful, surgical and non-surgical approaches including administration of intra-articular corticosteroids are often necessary (Agus et al., 1983). Because of the significant morbidity risk of these therapies for intracapsular articular disease, new improved approaches carrying low risk have been investigated. Reducing displaced disc (RDD) is one of the most prevalent intracapsular TMJ disorders and one for which no satisfactory treatment is currently available. There is limited data suggesting that intra-articular hyaluronic acid (HA) injections may offer a new prospect of approach in the treatment of TMJ disorders, including RDD (Kopp et al., 1985, 1987; Bertolami et al., 1993).

Hyaluronic acid is a linear polysaccharide consisting of repeating disaccharide units of glucuronic acid and N-acetyl glucosamine linked by B1-3 and B1-4 glycosidic bonds. It is available in the extracellular matrix of various mammalian tissues including skin, cartilage, umbilical cord, rooster comb and synovial fluid...
(Abantagelo & O’Regan, 1995). Intra-articular HA injections have been reported to have a beneficial effect in the treatment of knee, hip and shoulder disorders (Leardini et al., 1988; Bragantini & Molinaroli, 1994; Huskisson & Donnelly, 1999). Orthovisc®*, which has a molecular weight > 1000 kDa is a natural, non-crosslinked, extensively purified, high viscosity hyaluronan extracted from rooster combs. In this study, we have compared intra-articular injections of Orthovisc® and placebo in order to detect whether this compound is effective in the treatment of RDD of TMJ.

**Materials and methods**

This was a randomized, double-blind, placebo-controlled study with a 6-month follow-up period, comparing the efficacy of intra-articular injections of HA with intra-articular injections of placebo in patients with RDD of TMJ joint. Reducing displaced disc was diagnosed according to the standard clinical diagnostic criteria based on symptoms, clinical signs and radiographic findings (Bertolami et al., 1993). These criteria are summarized in Table 1. Patients over 21 years of age who were resistant to conservative treatment for at least 2 months and who fulfilled the standard clinical diagnostic criteria were included in this study. Those who were pregnant or lactating, exhibited poor oral health, received previous joint injections or surgery were excluded from the study. Written informed consent was obtained from all subjects.

The patients were randomly divided into two groups and subjected to intra-articular injection with HA (HA group, n = 19) or saline (placebo group, n = 19). Although the HA and control solutions, were coded and randomized by the manufacturer, were both clear colourless fluids that were not visibly distinguishable, it was still necessary to use a blind observer because of the differences in viscosity between the drug and placebo. Thus, different physicians carried out the administration of the intra-articular injections and the efficacy assessments. Neither was aware of the treatment given. A volume of 0.5 mL of HA (15 mg mL⁻¹, Orthovisc®) or physiological saline solution was administered into the superior joint compartment of the TMJ with the mouth opened maximally and was repeated 1 week later.

### Table 1. Diagnostic criteria for reducing displaced disc of the TMJ

<table>
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<tr>
<th>Symptoms</th>
<th>Temporomandibular joint pain (variable)</th>
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<td>Physical signs</td>
<td>Joint tenderness (variable)</td>
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<td>Radiographic findings</td>
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<td></td>
<td>Jaw deviates toward side of click until click occurs then returns to midline</td>
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<td>Magnetic resonance imaging shows displaced disc that reduces on opening</td>
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Clinical evaluation was carried out before the first injection and at 1 and 6 months after the final injection. The level of TMJ pain was measured by VAS (0 = no pain, 10 = constant and severe pain), as well as the severity of joint sound (click) (0 = no sound, 10 = a joint sound that is easily perceptible from outside by another person). The patients were also evaluated by a modified Helkimo’s clinical dysfunction index (Kurita et al., 1997). According to the modified Helkimo’s clinical dysfunction index, pain on movement of the mandible, TMJ pain, maximal mouth opening, signs of TMJ sound and disc derangement, and muscle pain in masticatory muscles are scored between 0 and 5. Treatment response in this index is as follows: 1 – total remission, if the index components all went down to the 0 or 1 level; 2 – partial remission, if one index component was at a level >1; 3–unchanged, if none of the components went up or down; 4 – exacerbated, if one or more of the index components went up (Kurita et al., 1997).

The severity of TMJ vibrations and pain measured by VAS, and the TMJ vibration amplitudes recorded at different periods were compared using Friedman test to determine the within group differences and Mann–Whitney U-test to determine between-group differences. The improvement frequencies of both groups according to the Helkimo’s clinical dysfunction index were compared with the χ² test.

Temporomandibular joint vibrations were captured by two small accelerometers (Dytran, 3115AS†) fixed over each joint with a double-sided tape. Each accelerometer was placed about 1–1.5 cm front of tragus over the skin on the articular eminence. This site was reported to be the best site for detecting TMJ vibrations with accelerometers (Yoshida et al., 1994). Vibration recording instrumentation consisted of an

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electronic goniometer, two accelerometers, an amplifier deck, a custom designed table to keep the head upright for mandibular angle detection, an IBM compatible computer with a 12 bit data acquisition card (Advantech PCL-812PG) to digitize the signals and a software to record and analyse vibrations and angle (Fig. 1). Amplification gain was set between 200 and 500 and vibrations were sampled at 2 kHz for each channel within 5–1000 Hz filter range. The sampling rate and filter settings were in the suggested range for vibration recording with accelerometers (Yoshida et al., 1994). The accelerometers were factory calibrated to 10 mV g⁻¹, and had almost a flat response up to 10 kHz. The experimental set-up was calibrated as 1 V RMS (root mean square) amplitude corresponding to 100 m s⁻² acceleration.

Each patient was seated upright on a comfortable chair which was closely placed to the experiment table. Patients were instructed to open and close their mandible at every 1-s period for 20 s. Two channel TMJ vibration signals and one channel TMJ angle data were stored on a computer hard disc during this 20-s period, and was repeated for about 5–8 times. Jaw opening and closing angular velocity of each record was almost equal to each other. Very slow or incomplete cycles of jaw opening or closing were rejected and extracted from calculations.

A computer program was developed in our laboratory by using a data acquisition program (DASYLab) to segment the vibrations according to jaw opening and closing cycles and to calculate the RMS vibration amplitudes. Every peak was detected independently and its RMS value was calculated by using the following formula then the results were added to each other to calculate the vibration amplitude for each segment.

\[ V_{\text{rms}} = \sqrt{\frac{1}{T} \int_{0}^{T} V(t)^2 \, dt} \]

Other measures, such as jaw angle of vibration onset or correlation of jaw opening and closing speed and vibration amplitude, and the number of detected peaks in a segment can also be recognized and calculated by the developed program.

**Results**

Baseline characteristics of the active treatment and control groups were comparable (Table 2). All patients in both groups completed the treatment course and 6-month follow-up.

Pain and sound intensity of the TMJ measured by VAS, modified Helkimo’s clinical dysfunction index and

| Table 2. Patient characteristics at baseline (n = 19) |
|---------------------------------|---------------------------------|
| Age (year) (mean ± s.d.)        | 31.94 ± 12.67                   | 31.10 ± 11.25*                   |
| Sex (F/M)                       | 13/6                            | 13/6*                           |
| Duration of symptoms (months) (mean ± s.d.) | 18.52 ± 20.11                   | 21.26 ± 18.31*                   |
| Pain intensity (VAS) (mean ± s.d.) | 6.68 ± 1.56                     | 5.73 ± 1.82*                     |
| Sound intensity (VAS) (mean ± s.d.) | 8.0 ± 1.63                      | 7.15 ± 1.60*                     |
| Helkimo’s index (score) (mean ± s.d.) | 6.47 ± 0.96                     | 6.15 ± 0.83*                     |

*P < 0.05.

vibration intensity during opening and closing the mouth measured by accelerometers showed greater reductions at month 1 and month 6 in the HA group compared with the placebo group, with statistically significant within group differences in the HA group being observed for all these individual parameters at the same time intervals ($P < 0.05$) (Figs. 2–4). Within group analysis of the placebo group showed no significant difference except for the joint intensity measured at month 1 and month 6 compared with the baseline value.

Evaluation of patients by modified Helkimo’s clinical dysfunction index in the HA group showed improvement (total or partial remission) in 17 patients (89.5%) at 1 month and 12 patients (63%) at 6 months. In the placebo group, only four (21%) and five (26%) patients at month 1 and month 6, respectively, showed improvement (total or partial remission) (Fig. 3). The difference between the two groups was significant at both time intervals ($P < 0.001$ and $P < 0.05$, respectively).

Discussion

Temporomandibular joint disorders contain a group of conditions affecting the TMJ, masticatory muscles or both. These conditions are characterized by pain in the pre-auricular region aggravated by chewing and other jaw functions. Physical examination findings may include limitation of jaw movement, joint sounds, palpable muscle tenderness or joint pain (Mohl, 1993). Although patients with TMJ disorder may often respond to conservative treatments such as heat application, soft diet and exercise, some have prolonged intra-articular pain and tenderness in spite of the treatment. Surgical treatment is an alternative, but with a significant risk of morbidity. As a non-surgical treatment alternative, intra-articular corticosteroid injections may be tried. However, this kind of treatment is known to exert deleterious effects on joints (Sevastik & Lemperg, 1969). Thus, there is a requirement to search for alternative therapeutic agents in these disorders.

Since the first therapeutic studies of HA in knee osteoarthritis in the early 1970s, intra-articular injections of HA have been tried in various joint disorders including TMJ (Rydell & Balazs, 1971; Peyron & Balazs, 1974; Kopp et al., 1985; Kopp et al., 1987; Leardini et al., 1988; Bragantini & Molinaroli, 1994; Huskisson & Donnelly, 1999). In those few studies carried out in various TMJ disorders, improvement in subjective symptoms and clinical findings was obtained (Kopp et al., 1985; Kopp et al., 1987; Bertolami et al., 1993; Sato et al., 1997). In the study performed by Bertolami et al. (1993), the primary beneficial effect was seen for the RDD category of TMJ disorders. In their study, a clear and consistent beneficial effect lasting for 6 months was reported in patients with RDD with a single intra-articular injection of HA. Our study confirm their findings. With two intra-articular injections of HA, 1 week apart, we detected improvement at month 1 and month 6 compared with the baseline evaluation for all of the outcome measures including pain and sound intensity.

intensity measured by VAS, the modified Helkimo's clinical dysfunction index and the intensity of joint vibration measured by accelerometer. In the placebo group, only pain intensity measured by VAS showed a significant improvement compared with the baseline measures. However, VAS scores of pain intensity at month 1 and month 6 were significantly lower in the HA group compared with the control group.

The decrease seen in the intensity of joint vibration measured by the accelerometer in the HA group provide further objective evidence indicating the effectiveness of such treatment. Recording and analysing the TMJ vibrations is a non-invasive and easily applicable method which can provide objective data to evaluate the effectiveness of treatment for TMJ disorders. The TMJ vibrations before and after intra-articular application of HA were recorded by arthrophonometry in one study (Bertolami et al., 1993). However, in this study joint vibrations were characterized in terms of location relative to mandibular displacement for the RDD category.

In our study, TMJ vibration during opening and closing the mouth was measured by an accelerometer which has been accepted as a reliable method for measuring amplitudes of TMJ vibrations (Yoshida et al., 1994). Although accelerometers are considered as low frequency sensors because of skin thickness and its resonance, the frequency range can be considered sufficient to measure vibration amplitudes. Miniature condenser microphones or electronic stethoscopes placed over the TMJ are frequently used techniques to record sounds. To capture TMJ sounds using accelerometers may be more convenient than the microphones, as microphones can easily be affected by environmental sounds. Thus, patients could be instructed during recording as no interference from the instructor’s voice was expected.

If there was no sense of clinically palpated vibration during recording, instrumentation did not show any signal of vibration except for very low amplitude background noise which was caused by electronic amplifier circuits. Duration of every peak was measured

Fig. 4. Temporomandibular joint vibration amplitudes in placebo group (A and B) and hyaluronan group (C and D) according to jaw opening (A and C) and closing (B and D) cycles before and after treatment.
by the computer with 0.5 ms resolution and its RMS value was calculated by integrating as described in the materials and methods. Then, every peak RMS value was added to find the total vibration RMS amplitude of the segment. By this way, only the signals produced from the TMJ was evaluated.

The precise mechanism by which HA alleviates symptoms of RDD is unknown. It provides lubrication for the articular surfaces and is largely responsible for synovial fluid viscosity. As it has a short half life, restoration of viscosity is improbable to explain the prolonged symptomatic relief. A purely mechanical effect, through interruption of the obstruction and/or trauma cycle of the disc by short-term lubricating action of sodium hyaluronate has been suggested to be responsible for the long lasting symptomatic improvement (Bertolami et al., 1993).

Hansson (1992) has indicated that, in patients with RDD, constant trauma by the condyle to the posterior loose tissue of the disc or to the junction between the disc and capsule leads to inflammation which may lead to intra-articular swelling and to displacement of the disc. Hyaluronic acid has been reported to reveal anti-inflammatory effects (Brandt et al., 1976; Sato et al., 1988; Punzi et al., 1989). The interruption of this vicious circle by the anti-inflammatory effects of HA may be another mechanism contributing to the prolonged symptomatic relief obtained in RDD patients with intra-articular HA injections.

In conclusion, intra-articular HA is a safe and effective therapeutic approach with a long lasting effect for at least 6 months in patients with RDD.

References


effect is enhanced in rheumatoid arthritis patients. *Arthritis Rheumatism*, 31, 63.


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