Use of Sodium Hyaluronate in Treating Temporomandibular Joint Disorders:  
A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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This study assessed the efficacy of high-molecular-weight sodium hyaluronate as a treatment for certain intracapsular temporomandibular joint (TMJ) disorders. One hundred twenty-one patients were studied at three test sites using a randomized, double-blind, placebo-controlled experimental design. Patients were selected on the basis of 1) confirmed diagnosis of either degenerative joint disease (DJD), reducing displaced disc (DDR), or nonreducing displaced disc (DDN); 2) nonresponsiveness to nonsurgical therapies; and 3) severe dysfunction as established by the Helkimo indices (HI), visual analog scales (VASs), and physical measurements of joint movement and joint noise (arthrophonometry [APM]). Subjects received a unilateral upper joint space injection of either 1) 1% sodium hyaluronate in physiologic saline (MedChem Products, Woburn, MA) or 2) USP physiologic saline. Clinical evaluations were performed using HI, VAS, and APM at weekly intervals for the first month and then at monthly intervals up to 6 months postinjection. Statistical analyses for both categorical and continuous variables were performed for each diagnostic category at each examination interval. For DJD, no difference in outcome was seen between treatment groups. For DDN, significant between-group differences were seen through 1 month; however, beyond this time point, the number of DDN patients was insufficient to draw meaningful conclusions concerning efficacy. For DDR, statistically significant within-group and between-group improvement in all three measures (HI, VAS, APM) was seen for the hyaluronate group compared to the saline group throughout the 6-month test period. At the month-2 and month-3 examination intervals, twice as many patients treated with hyaluronate (90%) showed improvement compared to patients given placebo. Further, only 3% of patients with DDR who were treated with hyaluronate relapsed compared with 31% of patients with DDR given placebo.

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The purpose of this study was to determine whether intra-articular administration of sodium hyaluronate to patients with severe temporomandibular joint (TMJ) disorders improves joint function and ameliorates pain. The underlying rationale was that sodium hyaluronate, an effective soft tissue lubricant, might offer a conservative, safe, and effective alternative to existing, less successful therapies for certain joint disorders. Until now, no well-designed, carefully controlled studies have been performed in humans to assess efficacy. The prevalence of true TMJ disease (as high as 7% in the general population by some estimates\textsuperscript{5}) of the joint's anatomy, proximity to the surface, access, and relative ease in diagnosis as well as the availability of widely accepted dysfunction indices\textsuperscript{5,7} all make the TMJ a suitable candidate for use in such experimental clinical trials. Current therapies typically rely on determining the disorder's origin as 1) intracapsular in nature (ie, true articular pathology), 2) extracapsular in nature, or 3) combined intracapsular and extracapsular origin. Because the cause of extracapsular disorders generally resides in muscles surrounding the joint, a variety of conservative (nonsurgical) therapies such as heat application, soft diet, and exercises are often effective.\textsuperscript{8} In contrast, intracapsular disorders are characterized by true pathology of the articular surfaces or by abnormalities in the mechanical relationship of articular structures.\textsuperscript{9} Such intracapsular abnormalities represent a temporomandibular variant of conditions common to other joints and include assorted degenerative joint disorders and internal derangements. Conservative approaches to treating symptomatic intracapsular disorders are not always successful and frequently occasion surgical and nonsurgical treatment (including administration of intra-articular corticosteroids).\textsuperscript{10,12} These therapies for intracapsular articular disease carry significant morbidity and justify the search for improved, low-risk approaches to managing intracapsular disorders of both the temporomandibular joint and other joints.

**Methods**

**Experimental Design**

A randomized, double-blind, placebo-controlled clinical protocol was used to determine whether joint pain and dysfunction decrease as a consequence of treatment with sodium hyaluronate as opposed to a saline placebo. Subjects were drawn from the patient populations of three investigational sites: 1) the Oral and Maxillofacial Surgery Unit, Massachusetts General Hospital (MGH), Boston, MA; 2) Oral and Maxillofacial Associates, Fargo, ND (OMS); and 3) the Temporomandibular Pain Clinic of the University of California, Los Angeles, CA (UCLA).

A detailed history was solicited from patients who complained of facial, jaw, or TMJ pain. If clinical examination and routine diagnostic procedures confirmed an intra-articular temporomandibular disorder, the level of dysfunction was assessed using standardized, numerical descriptors of temporomandibular dysfunction known collectively as the Helkimo indices.\textsuperscript{5,7} Prospective inclusion criteria further required that the patient 1) be 21 years of age or older, 2) possess a documented diagnosis of an intracapsular TMJ disorder, 3) exhibit severity at the level of Helkimo dysfunction class II or higher (severe dysfunction), and 4) prove refractory to conservative therapies for at least 2 months. Correspondingly, patients were excluded from the study who 1) were pregnant or lactating, 2) were unwilling or unable to return for follow-up, 3) possessed purely extracapsular disorders or showed evidence of a combination of different intracapsular disorders, 4) exhibited poor oral health or had received contraindicating therapies such as previous joint injections or surgery, or 5) lacked ability to follow instructions.

Among subjects meeting all the inclusion criteria and none of the exclusion criteria, the most important aspect of subject selection was accurate diagnosis of the underlying disorder. Three specific conditions were chosen for study: 1) degenerative joint disease (DJD), 2) displaced disc with reduction (DDR), and 3) displaced disc without reduction (DDN). In distinguishing these intracapsular conditions, standard clinical diagnostic criteria were used based on symptoms, clinical signs, and radiographic findings as outlined in Table 1.

**Test Preparations**

Patients who qualified for inclusion were divided into two groups: those who received a single injection of high molecular weight (1.5 - 2.0 \times 10^6 \text{Da}) sodium hyaluronate (10 mg/mL) solubilized in USP physiologic saline for injection (experimental group) and those who received a single control injection of physiologic USP saline alone (placebo group). The purified preparation of sodium hyaluronate used has been shown to be nonimmunogenic, noninflammatory, nontoxic, and nonpyrogenic by means of chemical, physical, and biologic assay. It is free of contaminants such as chondroitin sulfate, nucleic acids, and protein or other macromolecular constituents. All injections were made into the superior joint space, with the amounts injected being dictated by joint space volume. Injection technique followed standard clinical procedures.\textsuperscript{10,11,13-15} The control and hyaluronate solutions were both clear colorless fluids that were not distinguishable by visual inspection. Syringes were coded and randomized by the manufacturer and then used sequentially with only the identifying number (not the syringe content) known
## Table 1. Diagnostic Criteria

<table>
<thead>
<tr>
<th>Symptomology</th>
<th>Clinical Signs</th>
<th>Radiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degenerative joint disease</td>
<td>History of pain during range of motion and Tenderness over condyle</td>
<td>Limited range of mandibular movement and/or Crepitus</td>
</tr>
<tr>
<td>Displaced disc, reducing</td>
<td>Joint pain (variable) and Clicking</td>
<td>Joint tenderness (variable) and Reciprocal clicking and Jaw deviates toward side of click until click occurs then returns to midline</td>
</tr>
<tr>
<td>Displaced disc, nonreducing</td>
<td>Joint pain (variable) and Limited opening and Previous clicking with intermittent locking and Sensation that something in the joint blocks opening</td>
<td>Joint tenderness (variable) and Limited opening and Lateral movement toward opposite side and Jaw deviates toward affected side</td>
</tr>
</tbody>
</table>

To the participating clinicians, examiners, and investigators. In all cases, the clinicians injecting test substances and the examiners performing clinical evaluations were separate individuals. The ratio of test group to control group syringes was 2:1. Levels of dysfunction were measured 1) before treatment, 2) at weekly intervals for the first month after treatment, and 3) at monthly intervals to 6 months postinjection. This experimental design permitted “within-group” comparisons (preinjection versus postinjection) and “between-group” comparisons (hyaluronate versus control) for each diagnostic category and it allowed statistical comparisons of pain and dysfunction variables to be made longitudinally.

### The Helkimo Indices, Arthrophonometry, Visual Analog Scales

Two indices devised and promulgated by Helkimo and coworkers served as semiquantitative numerical descriptors of joint pain and dysfunction. These were used both for the initial (preinjection) determination that the subject’s level of dysfunction was sufficiently severe to justify inclusion in the study and, subsequently, for assessing the subject’s response to the injected substances at periodic intervals. Details concerning these instruments for assessing joint dysfunction are available elsewhere; however, in essence, they comprise a clinical dysfunction index (CDI) for determining the functional state of the joint and an anamnestic index (AI) for describing the patient’s perception of the clinical problem and efficacy of treatment. The CDI ranks clinically demonstrable dysfunction and is derived from five dysfunction classes that, in turn, are calculated from a set of numerical scores. It ranks clinical dysfunction on the basis of 1) mobility, 2) impaired joint function, 3) pain on movement, 4) muscle pain, and 5) joint pain; each being judged according to either a two-grade or three-grade scale of severity.* As a means of enhancing the sensitivity of the mobility and noise parameters in the CDI, the actual linear values of mandibular displacement were recorded by arthrophonometry (APM) and analyzed separately as continuous measures. Also, joint noises were characterized in terms of either overall amplitude (for the DJD category) or location relative to mandibular displacement (for the DDR category).

AI was used to form a comprehensive opinion of the severity of subjective symptoms. This index is based on the patient’s report of symptoms of dysfunction elicited through methodical interview by a blinded clinical evaluator and by completion of a questionnaire. Ten variables were assessed: 1) presence or absence of temporomandibular joint noise, 2) feeling of fatigue in the jaws, 3) stiffness of the jaws on awakening, 4) stiffness during movement of the lower jaw, 5) difficulty in opening the mouth widely, 6) inability to open the mouth (locking), 7) inability to close the mouth (luxation), 8) pain on movement of the lower jaw, 9) pain in the region of the TMJ, and 10) pain in the cheek muscles. One point was assigned for each positive response. Finally, patients’ subjective impressions were assessed using three visual analog variables

* Modified from Helkimo’s discontinuous five-point scale.
(level of pain, level of jaw function impairment, and frequency of jaw noises), which were scored by the patient on a scale of 0 to 100 using standardized VAS methodology.19,20

**Ethics**

This investigation was conducted under Investigational Device Exemption (IDE) No. G88008 granted to MedChem Products, Woburn, MA. The experimental design was reviewed and approved by the Human Subjects Institutional Review Boards of each of the participating institutions and procedures were performed in accordance with the approved protocol.

**Statistical Analysis**

Changes in the dysfunction index and anamnestic index represent categorical variables that describe a patient's overall level of dysfunction and pain. Changes in the levels of classification between the preinjection examination and postinjection intervals reflect changes toward either improvement or relapse of condition and were analyzed statistically using nonparametric methods; specifically, the Pearson $\chi^2$ (BMDP, 4F).

The scores from the five sets of variables that make up the dysfunction class and the total score as well as relevant subsets were analyzed statistically using parametric methods. One subset was defined as the “total intracapsular score.” This score is the sum of the mobility, TMJ function, TMJ pain, and movement pain variables; in other words, all the variables with the exception of muscle pain. Muscle pain was selected out because it reflects an extracapsular condition not immediately relevant to the effects of the injection. The above comparisons were made using a matched-pair $t$-test model (BMDP, 3D) to determine within-group differences and an analysis of variance (ANOVA) model (BMDP, 2V) to determine between-group differences.

Arthrophonometric physical measurements related to mandibular displacement in each spatial dimension, and TMJ noise characteristics were analyzed separately using $t$ tests and ANOVAs.

Because the AI is calculated from a subset of arbitrarily weighted scores, it was not subjected to statistical analysis; only group means were calculated. Matched-pair $t$ tests and ANOVAs were used to determine changes in the total score and an intracapsular component of the total score. Parametric statistics were also used to compare changes in the three different VASs.

Because each diagnostic group is characterized by different etiologies, pathologies, and clinical signs and symptoms, all analyses were made separately for each group.

**Results**

A total of 121 patients entered the study. Prior to analysis, 14 (all from OMS) were disqualified on the grounds that they either met specific exclusionary criteria or failed to meet inclusionary criteria. Mean ages, genders, duration of symptoms, and diagnoses are presented in Table 2.

**ASSESSMENT OF EFFICACY**

**DDR**

Changes in dysfunction class between the preinjection and postinjection assessments for the DDR group are summarized in Figure 1, which indicates the percentage of patients who improved or relapsed by at least one dysfunction class level, respectively, at each monthly examination interval relative to the preinjection examination. For the most part, improvement and relapse were limited to a single class shift for both the hyaluronate and placebo groups; however, the differences in the percentage of patients who showed improvement or relapse were consistently different for

**Table 2. Demographic Data for Patients Entered Into the Study**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>DDR</th>
<th>DDN</th>
<th>DID</th>
<th>Duration</th>
<th>Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronate</td>
<td>80</td>
<td>36.0</td>
<td>80</td>
<td>72</td>
<td>35</td>
<td>8</td>
<td>37</td>
<td>7.7</td>
<td>42</td>
</tr>
<tr>
<td>Placebo</td>
<td>41</td>
<td>40.7</td>
<td>7</td>
<td>35</td>
<td>15</td>
<td>6</td>
<td>20</td>
<td>7.9</td>
<td>22</td>
</tr>
</tbody>
</table>

* Total number of patients.
† Average age of patients at time of injection.
‡ Number of patients in each of the three diagnostic categories: displaced disc-reducing, displaced disc-nonreducing, degenerative joint disease.
§ Average duration of symptoms in years.
‖ Number of patients who received injection on right (R) and left (L) sides.
† Does not include one patient who experienced complication after injection of saline placebo and who exited before collection of any postinjection data.
The percentage of patients who relapsed at least one dysfunction class is equally revealing (Fig 1B). Whereas 7% to 30% (depending on the particular examination interval) of the patients receiving placebo relapsed at least one dysfunction class, only 3%, or one patient receiving hyaluronate, relapsed—and only at the month-1 interval. Taken together, both the number of patients improved and relapsed suggest a clinically as well as a statistically significant effect of hyaluronate on improvement in function.

FIGURE 1. Percentage of patients with DDR who improved (A) and relapsed (B) at least one dysfunction class level between preinjection visit and each monthly postinjection visit. Between-group statistical significance is indicated by an asterisk (*).

The two groups. Figure 1A shows that 72% to 90% of the patients administered hyaluronate improved at least one dysfunction class, depending on the particular visit, whereas, 42% to 73% of the placebo receiving placebo improved by this amount. The between-group differences were statistically significant for the month-2 and month-3 comparisons, where 87% and 90% of the patients administered hyaluronate improved in dysfunction class, compared with 42% and 50% of patients receiving placebo, respectively. In other words, at the month-2 and month-3 examination intervals, approximately twice as many patients receiving hyaluronate showed improvement in comparison with those receiving placebo.

FIGURE 2. Difference in score (mean score improvement) for patients with DDR between preinjection visit and each monthly postinjection visit. Values for total dysfunction score (A) and total intra­capsular dysfunction score (B) are shown. Upward deflection of the curve indicates improvement in condition. The mean differences for both sets of scores show a clear divergence in the rate of improvement after month 1, with statistically significant between-group hyaluronate effect appearing at the month-2 and month-5 intervals. Between-group (ie, hyaluronate group vs placebo group) statistical significance is indicated by an asterisk (*).
Table 3. Mean Differences in Criterion Measures of Dysfunction Index, Anamnestic Index, and Physical Measurements in the DDR Diagnostic Category

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of HA Patients</td>
<td>30</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td>24</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>No. of PL Patients</td>
<td>13</td>
<td>11</td>
<td>12</td>
<td>14</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total dysfunction</td>
<td>HA</td>
<td>2.4*</td>
<td>2.3*</td>
<td>2.8*</td>
<td>2.7*</td>
<td>3.9*</td>
<td>3.5*</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>1.8‡</td>
<td>1.2</td>
<td>1.8‡</td>
<td>2.2‡</td>
<td>1.4(‡)</td>
<td>1.9</td>
</tr>
<tr>
<td>Intracapsular dysfunction</td>
<td>HA</td>
<td>0.8‡</td>
<td>1.0‡</td>
<td>1.4*</td>
<td>1.1*</td>
<td>1.7*</td>
<td>1.7*</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>0.9‡</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8‡</td>
<td>0.5(‡)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mandibular deviation</td>
<td>HA</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3‡</td>
<td>0.3‡</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>0.2</td>
<td>0.1</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Noise location</td>
<td>HA</td>
<td>2.8‡</td>
<td>2.4‡</td>
<td>1.8</td>
<td>4.0‡</td>
<td>4.0</td>
<td>-1.5</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>1.1</td>
<td>2.1</td>
<td>1.1</td>
<td>-1.5(‡)</td>
<td>-1.4</td>
<td>-4.5</td>
</tr>
<tr>
<td>Total anamnestic</td>
<td>HA</td>
<td>4.0*</td>
<td>1.3‡</td>
<td>1.6*</td>
<td>1.3*</td>
<td>1.3‡</td>
<td>1.9‡</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>0.7</td>
<td>0.9</td>
<td>0.3</td>
<td>0.1(‡)</td>
<td>0.3</td>
<td>0.2(‡)</td>
</tr>
<tr>
<td>Intracapsular anamnestic</td>
<td>HA</td>
<td>0.8*</td>
<td>0.8*</td>
<td>1.0*</td>
<td>0.8*</td>
<td>0.8*</td>
<td>2.2*</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>0.4</td>
<td>0.6</td>
<td>0.1(‡)</td>
<td>0.1(‡)</td>
<td>0.2(‡)</td>
<td>0.0(‡)</td>
</tr>
<tr>
<td>Visual analog noise</td>
<td>HA</td>
<td>13.9‡</td>
<td>9.0</td>
<td>11.1‡</td>
<td>12.9‡</td>
<td>14.0‡</td>
<td>19.1‡</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>6.7</td>
<td>-1.2</td>
<td>-2.4</td>
<td>0.9</td>
<td>1.3</td>
<td>-8.1(‡)</td>
</tr>
</tbody>
</table>

Scores for the HA patients appear above those for the placebo (PL) patients. Positive values indicate an improvement in score, negative values indicate a worsening in score. P value without parentheses indicates within-group significance; P value in parentheses indicates between-group significance. *P = <.001; ‡P = <.05; †P = <.01.

These differences also appear in both the total dysfunction scores and total intracapsular dysfunction scores (Fig 2 and Table 3). The mean differences for both variables showed a clear divergence in the rate of improvement after month 1, with a statistically significant between-group hyaluronate effect for both sets of scores appearing at the month-2 and month-5 intervals. Consistently greater hyaluronate effects were observed for all the individual variables, with the exception of TMJ pain (data not shown); however, none of these was statistically significant between groups.

Parallel, and even more consistent, improvements in patients receiving hyaluronate were apparent in the anamnestic measures, which showed the patients’ own evaluations of pain and dysfunction (Fig 3). Unlike the DJD and DDN groups (discussed below), whose anamnestic indices reflected minimal if any change, 12% to 25% (depending on the particular examination interval) of the hyaluronate patients showed an improvement in anamnestic index. In contrast, no patients receiving placebo showed improvement. Anamnestic and intracapsular anamnestic scores shown in Table 3 and in Figure 4 demonstrate that the mean differences in both sets of scores consistently diverge between the hyaluronate and placebo groups—beginning at month 1 and continuing through month 6, with five of the six monthly intervals showing statistically significant between-group hyaluronate effects. As with the intracapsular dysfunction scores, the intracapsular anamnestic scores are the more important clinically because they reflect those variables unequivocally linked to the known pathophysiology of the intracapsular conditions being studied.

Similarly, the individual physical events most clinically relevant to the DDR category are joint noise and mandibular deviation. Figure 5 depicts the mean score improvement in the visual analog noise scale and shows a consistent divergence in mean score differences be-
HYALURONATE USE IN JOINT DISORDERS

A at which the click occurs represents an improvement of condition. Noise location showed a greater degree of improvement for the hyaluronate patient group from the week-1 through the month-2 examination intervals, with statistically significant within-group differences appearing at the weeks 1 and 2 intervals and statistically significant within-group and between-group differences appearing at the month-1 interval. Importantly, because of instrumentation problems, the total population size (N) was considerably lower at all examination intervals for this variable than for any of the other variables.

Differences in mean mandibular deviation measurements are also shown in Table 3. With the exception of the week-1 interval, all comparisons showed a slightly greater reduction in mandibular deviation for the hyaluronate group, with statistically significant within-group differences appearing at the week-3 and months 1, 4, and 5 examination intervals. A possibly related hyaluronate effect also appears for ipsilateral displacement, with statistically significant within-group differences being present at all examination intervals except week 1 (data not shown).

In summary, the results for the DDR patient group suggest efficacy for high-molecular-weight sodium hyaluronate in treating this disorder. The total and intracapsular scores from both the dysfunction and anamnestic indices, as well as the variables that are the most clinically relevant (joint noise and mandibular deviation), showed a consistent and statistically significant improvement for the hyaluronate patient group in comparison with the placebo group.

FIGURE 4. Improvement in mean total anamnestic score (A) and intracapsular anamnestic score (B) between preinjection visit and each monthly postinjection visit for the DDR diagnostic category. Between-group statistical significance is indicated by an asterisk (*).

The noise location variable, as measured by APM (Table 3), reflects differences in the location of the onset of the TMJ "click" in relation to the displacement of the mandible. Changes in the location of the click reflect changes in the degree of displacement of the disc, with click occurrence at a greater level of displacement (late opening click), indicating a more advanced displacement. Thus, a reduction in the displacement level at which the click occurs represents an improvement of condition. Noise location showed a greater degree of improvement for the hyaluronate patient group from the week-1 through the month-2 examination intervals, with statistically significant within-group differences appearing at the weeks 1 and 2 intervals and statistically significant within-group and between-group differences appearing at the month-1 interval. Importantly, because of instrumentation problems, the total population size (N) was considerably lower at all examination intervals for this variable than for any of the other variables.

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DDN

The analysis of the DDN data focused on changes observed during the first month postinjection because the patient N beyond this period was too small to provide meaningful comparisons. The percentage of patients who improved at least one dysfunction class level during the first month postinjection was clearly greater for the hyaluronate group than for the placebo group. Improvement ranged from 30% at week 1 to 100% at week 4, with the latter statistically significant between groups. The same degree of improvement in patients receiving hyaluronate also was shown at the month-2 examination interval. The percentage of patients receiving placebo who improved, on the other hand, ranged from a low of 17% at weeks 1 and 3 to a high of 40% at weeks 2 and 4. Although the percentage of improvement in the patients receiving hyaluronate was substantial and statistically significant at the week-4 interval, the analyses were based on only 10 to 13 patients, depending on the particular examination interval. With respect to relapse, 33% to 50% of the scores of patients receiving placebo were lower during the 1-month postinjection period, whereas one patient receiving hyaluronate relapsed one level but only at the week 1 examination.

The significant differences in functional improvement between the hyaluronate and placebo groups were also evident, in the total scores for weeks 2 to 5, the muscle soreness scores for weeks 1 to 4, the movement pain score for week 3, and the total intracapsular score for weeks 2 to 4 (Fig 6). Although improvement for the other variables was also greater for the patients receiving hyaluronate in almost every other comparison, none was statistically significant between groups. The only exception to this general rule was for the function variable, which showed a slight overall placebo effect.

The improvement for the hyaluronate patient group that was evident on the basis of the dysfunction index was not as clear in either the anamnestic or intracapsular anamnestic scores, although it did appear in the visual analog pain and visual analog function scores. Both anamnestic scores showed little within-group and between-group difference during the initial 4-week period. However, both the visual analog pain and visual analog function scores consistently improved for the hyaluronate patient group and progressively relapsed for the placebo group, with significant between-group differences occurring at week 3 for the pain scores and week 4 for the function scores. The visual analog noise scores did not show significant differences either within or between groups; however, this would not be expected because joint noise is not commonly a component of DDN.

Physical measurements generally showed a consistent improvement for the hyaluronate group and a worsening for the placebo group, with mandibular protrusion at week 4 and ipsilateral displacement at week 5 showing between-group statistical significance. Vertical opening differences improved up to 5 mm for the hyaluronate group, with a maximum between-group difference of 8 mm at week 5; however, presumably because of the small N, these differences were not statistically significant either within groups or between groups.

DJD

Although within-group and between-group changes were observed for the DJD category of patients, most patients, both those who received hyaluronate and those given placebo, improved at least one classification level at each examination interval throughout the 6-month duration of the study. In all cases, the differences between the groups were slight and none was statistically significant.

On average, approximately 10% to 40% of all patients with DJD who received placebo relapsed at least one dysfunction class throughout the 6-month period of the study. Fewer patients receiving hyaluronate relapsed (10% to 15%), but none of the between-group differences was statistically significant. The absence of any between-group differences in dysfunction improvement was also reflected in the scores of the individual variables as well as the total dysfunction scores and total intracapsular dysfunction scores. The same pattern emerged from a comparison of the anamnestic and visual analog scores, where statistically significant
within-group improvement appeared for both groups, but, with the exception of isolated 5-month and 6-month placebo effects, no between-group significant differences appeared. Likewise, the physical measurements of mandibular displacement and noise amplitude showed comparable levels of improvement for the two groups.

An overall improvement in patients with DJD did occur over the study period; however, it appears that such improvement was independent of the injection of high molecular weight sodium hyaluronate into the joint capsule of the experimental patient group. High molecular weight sodium hyaluronate does not appear to be an effective means of treating degenerative TMJ disease.

**ASSessment of Safety**

A total of 13 adverse events occurred in 10 patients. Most were mild in nature, self-limiting, and of short duration. Such occurrences consisted primarily of discomfort at the injection site and/or localized swelling. Seven of the 13 events occurred in six patients who received hyaluronate; six occurred in four patients who received placebo. The duration of the event was generally 1 day. Of those receiving hyaluronate, the severity of the event was identified as mild in five cases, moderate in 1, and severe in 1. Of the patients receiving the saline placebo, the severity of the event was identified as mild in four patients and severe in two. All adverse events associated with both hyaluronate and placebo groups have resolved. It therefore appears that injection of hyaluronate into the TMJ is a safe procedure and essentially indistinguishable from a saline placebo in its likelihood of producing adverse occurrences.

**Discussion**

Sodium hyaluronate is the sodium salt of hyaluronic acid. It is a high-molecular-weight polysaccharide and a major natural component of synovial fluid. The importance of hyaluronate to the lubrication of synovial tissues has been established, but its function in relation to the occurrence of joint diseases is not precisely known. 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 surface. Although not considered a lubricant for cartilage under high load, 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 has been reported to prevent intra-articular adhesions and elicits little if any immune response when injected into humans or animals. The administration of hyaluronate into intra-articular sites can be viewed as an extension of existing methods—especially those involving the injection of agents like corticosteroids into joint spaces. However, unlike intra-articular corticosteroids, which are known to exert deleterious effects on joints, hyaluronate is not known to induce damage or to elicit tissue reactions. This is not surprising given hyaluronate’s status as a ubiquitous, naturally occurring, structural component of connective tissue matrices. Even repeated injections of hyaluronate into the joints of experimental animals have been shown to result in only transient infiltration of polymorphonuclear leukocytes, plasma cells, and mononuclear macrophage-like cells into the synovial membrane. Under such conditions, hyaluronate does not produce clinical signs of inflammation.

Despite its apparent safety, the efficacy of hyaluronate in treating specific intracapsular disorders in human joints has remained an open question. This uncertainty justified the present clinical trial. Realistic expectation of therapeutic benefit was based on several lines of reasoning, including 1) the known physical properties of high molecular weight hyaluronate in aqueous solution that favor its use as a tissue lubricant—a characteristic considered desirable in alleviating friction-induced joint symptoms; 2) an extensive literature that demonstrates amelioration of joint symptoms by intra-articular injection of sodium hyaluronate in animal joints and in human joints other than the TMJ; 3) beneficial effects attributed to hyaluronate when injected into the human TMJ, though this conclusion is tempered by partial or inadequate controls in previous work; and 4) a well-established safety record when high molecular weight hyaluronate has been used extensively in other common nonarticular therapeutic applications—primarily in ophthalmologic surgery.

In the present work, the primary beneficial effect (≥6 months in duration) was seen for the DDR category of patients. This condition is typified by pain, noise (reciprocal clicking), and mandibular deviation. In comparison with the placebo substance, hyaluronate’s clinical benefit was evidenced by 1) an increased percentage of patients who improved by at least one full dysfunction class, 2) a markedly lower incidence of relapse, 3) improvement in objective dysfunction scores (both total and intracapsular), and 4) marked subjective improvement as perceived by patients through anamnestic scores (total and intracapsular) and visual analog measures. For these individuals, a single intra-articular injection of sodium hyaluronate offered...
clear and consistent benefit for at least 6 months. These results were both statistically significant and clinically important, particularly in light of DDR’s status as one of the most prevalent intracapsular temporomandibular disorders (41% in this study), and one for which no satisfactory treatment currently exists.

The precise mechanism by which hyaluronate alleviates symptoms of DDR is unknown, but it may be a purely mechanical effect. The administered exogenous hyaluronate is unlikely to be physically present in bulk form within the joint space for the full 6-month period during which efficacy is seen, particularly in view of a half-life (t½) of only 13.2 hours in other joint spaces. What is certain is that the beneficial effects of sodium hyaluronate persist beyond the period of the test substance’s probable presence. A possible explanation might be that damage to synovial surfaces and to the disc is mitigated during acute discal obstruction through a short-term lubricating action of sodium hyaluronate. The effects of persistent trauma to the intracapsular articular surfaces as the disc and mandibular condyle are repetitively reduced and displaced with each opening/closing cycle may be minimized at a critical point in time. Hansson has indicated that, in DDR, the condyle continuously traumatizes the posterior loose tissue of the disc (bilaminar zone), or the junction between the disc and capsule, and inflammation occurs. Due to intra-articular swelling, the disc remains out of place. A vicious cycle is begun and it must be interrupted before tearing of the attachment or ligament occurs. The results of this study suggest that recovery (for at least 6 months) becomes possible when the obstruction/trauma cycle is broken by a single injection of sodium hyaluronate, presumably because of the latter’s properties as a lubricant. Effects also might be attributable to hyaluronate’s properties as a boundary layer lubricant, which could, in principle, persist for a protracted period of time. This view is attractive in light of recent evidence for cell surface hyaluronate receptors (such as CD44) that recognize and bind hyaluronate at the molecular level.

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References


