

# Efficacy and Safety of Sodium Hyaluronate in the Treatment of Wilkes Stage II Disease

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**Purpose:** To show whether an intra-articular (IA) infiltration of 1 mL sodium hyaluronate (SH) into the temporomandibular joint (TMJ) would significantly reduce pain and improve joint function in Wilkes stage II disease, compared with the oral administration of a combination of methocarbamol and paracetamol.

**Patients and Methods:** Forty-one patients with Wilkes stage II disease were selected and randomly assigned to 2 groups. The experimental group received 1 IA infiltration of SH with assessments at days 14, 28, 56, and 84. The control group was given 2 tablets of a combination of methocarbamol 380 mg and paracetamol 300 mg every 6 hours for 4 weeks, with assessments at days 14 and 28.

**Results:** Forty-one patients were randomized into the study (SH: 20 patients, control drug: 21 patients). A statistically significant difference ( $P < .05$ ) was detected in favor of the SH group from day 56 onward for TMJ pain at rest, from day 14 onward for pain on jaw opening, and at days 28 and 56 for pain on mastication. The TMJ function was statistically significantly ( $P < .05$ ) better in the test group at all follow-up visits. The global evaluation of efficacy by both, the patients and investigators, was better for the test group. No adverse reactions were detected with SH.

**Conclusions:** An IA infiltration of SH showed better efficacy in reducing pain and improving joint function in Wilkes stage II disease, compared with the oral administration of methocarbamol-paracetamol tablets.

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Several lines of treatment have been described in the literature for temporomandibular joint (TMJ) dysfunction including physical,<sup>1</sup> surgical,<sup>2,3</sup> occlusal therapy using a splint,<sup>4</sup> arthrocentesis,<sup>5</sup> and arthroscopy<sup>6</sup> for

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lysis and lavage. The infiltration of the TMJ with sodium hyaluronate (SH) provides a less invasive method of treatment, with effective results.<sup>7</sup> A single intra-articular (IA) infiltration provided the best results in disk displacements with reduction<sup>8</sup> and after arthrocentesis,<sup>9</sup> although a decrease in pain and subjective improvement of symptoms also were seen in disk displacements without reduction.<sup>10</sup> Repeated IA infiltrations in the TMJ seemed to be more effective.<sup>11-13</sup> In comparative studies versus corticosteroids,<sup>14,15</sup> no statistical significance was observed between infiltration with SH or corticosteroids, although the infiltration with SH showed better long-term results, with no secondary effects.

The objective of our study was to investigate whether a single IA infiltration of 1 mL SH would significantly reduce pain and improve function in the TMJ, compared with the administration of 2 tablets of a combination of 380 mg methocarbamol and 300 mg paracetamol, every 6 hours for 4 weeks. The secondary objectives were the improvement of the restric-

tions to live a normal life, the evaluation of tolerability, and the consumption of analgesics.

## Patients and Methods

This was an open, randomized, single center, pilot study carried out in Seville (Spain). Male and female patients between 20 and 65 years of age with magnetic resonance imaging-confirmed Wilkes stage II disease<sup>16</sup> of at least 2-months' duration, were selected for this trial. The study protocol required patients to have TMJ pain greater than 3 cm on a 10-cm visual analog scale (VAS) at rest, on jaw opening, and on mastication. Major exclusion criteria included other painful TMJ conditions, infection of the affected joint or at the site of injection, concomitant osteoarthritis of other joints of sufficient severity to interfere with the assessment of the TMJ, previous surgery of the affected joint, and injection of SH or corticosteroids into the target TMJ during the previous 6 months.

Eligible patients were assigned randomly to 1 of 2 groups. The patients from the test group received 1 injection of 1 mL SH 1% (Ostenil mini, Laboratorios Masterfarm, Barcelona, Spain) into the upper joint space. The control group consisted of patients who took a commercial preparation of 380 mg methocarbamol plus 300 mg paracetamol, at a dose of 2 tablets every 6 hours for 4 weeks. After having received the IA product at baseline, the patients were followed up for 12 weeks, with visits at 14, 28, 56, and 84 days after the injection. For the control group, assessments were carried out 2 and 4 weeks after the first intake of methocarbamol-paracetamol, ie, at days 14 and 28.

The main efficacy parameters for this trial were pain at rest, on jaw opening, and on mastication, measured on a 10-cm VAS. In addition, the affected TMJ was evaluated using a 100-point questionnaire (0 = worst state, 100 = best state) addressing pain (maximum 40 points), function (45 points) and mastication (15 points). The secondary efficacy outcomes were the global judgments of efficacy evaluated by the patient and the investigator using a 5-point scale ranging from worse (0) to optimal (4). Tolerability to the treatment was evaluated by the patient and the investigator using a 5-point scale (0 = very bad, 1 = bad, 2 = acceptable, 3 = good, 4 = excellent). Adverse events were recorded at each visit by types and frequencies.

The study protocol was approved by the Ethics Committee of the Virgen del Rocío Hospital, Seville, Spain, before the study started. All patients had to provide written informed consent before entering the study.

The statistical analysis was carried out using the Mann-Whitney *U* test for comparative analysis at each visit, whereas the Wilks' lambda test was applied for

the generalized linear model. The patients receiving the oral combination of methocarbamol and paracetamol ended their treatment on day 28. The values of this last visit were carried forward for their day 56 and day 84 visits because this group did not return for these visits. Results were considered statistically significant at *P* less than .05.

## Results

Forty-nine patients were screened and 41 were randomized into the study (SH: 20 patients, control drug: 21 patients). Both groups were homogeneous for gender (80.0% women in the SH group vs 76.2% in the control group), but not for age (mean  $25 \pm 11$  years in the SH group vs  $33 \pm 14$  years in the control group, *P* < .05). In the test group, the right TMJ was affected in 60% of the patients. In the control group, both TMJ were affected in 14.3%, the right TMJ in 23.8% and the left TMJ in 61.9% of the cases. All 20 patients from the SH group completed the trial, whereas in the combination drug group, 4 patients terminated the study prematurely.

In the test group, the mean VAS pain at rest decreased from  $6.8 \pm 2.3$  mm at baseline to  $3.5 \pm 3.9$  at day 84. In the control group, this value did not improve ( $6.6 \pm 2.3$  at baseline,  $6.5 \pm 3.5$  at day 28). Statistically significant differences (*P* < .04) were detected from day 56 in favor of the test group, which persisted up to day 84 (Table 1). The overall differ-

**Table 1. PAIN AT REST**

	SH Group (n = 20)			Control Group (n = 15)			<i>P</i>
	n	m	SD	n	m	SD	
Day 0	20	6.8	2.3	15	6.6	2.3	.735†
Day 14	20	4.7	3.5	15	6.3	2.6	.214†
Day 28	20	4.2	3.8	15	6.5	3.5	.076†
Day 56	20	3.4	3.9	15	6.5	3.5	.027*†
Day 84	20	3.5	3.9	15	6.5	3.5	.032*†
							.060‡
							.088§

NOTE. Pain at rest measured on a 10-cm VAS. Patients were treated with 1 intra-articular injection of SH or oral methocarbamol-paracetamol.

Abbreviation: SD, standard deviation.

\*Results considered significant (*P* < .05).

†Mann-Whitney *U* test was used for comparative analysis at each visit.

‡Wilks' lambda test was applied for generalized linear model between both groups.

§Wilks' lambda test was applied for generalized linear model all through the visits.

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ence between the groups was close to significance ( $P = .060$ , Wilks' lambda test).

The IA injection of SH produced an improvement in pain on jaw opening, with the mean VAS pain on jaw opening decreasing from  $7.0 \pm 2.2$  cm at baseline to  $3.6 \pm 3.8$  at day 84. In comparison, pain experienced by the control patients did not improve ( $7.9 \pm 2.1$  at baseline,  $7.7 \pm 3.6$  at day 28). Statistically significant differences ( $P < .04$ ) were detected from day 14 in favor of the test group, which persisted up to day 84. The overall difference between the groups was significant in favor of the test group ( $P = .007$ , Wilks' lambda test) (Table 2).

Pain on mastication decreased in the test group (mean  $4.0 \pm 3.6$  at baseline,  $2.8 \pm 3.9$  at day 84), with statistically significant differences compared with the control group at days 28 and 56. The overall difference between the groups was not significant ( $P = .071$ , Wilks' lambda test) (Table 3).

In the SH group, the evaluation score of TMJ function (100 points) improved from  $58.6 \pm 21.5$  points at baseline to  $72.8 \pm 31.0$  at day 84. In the control group, the administration of the control drug did not produce an improvement of the score, because it decreased from  $41.0 \pm 31.5$  to  $35.3 \pm 37.9$  at the end of the treatment course. Statistically significant differences ( $P < .02$ ) between the groups were observed at all follow-up visits and the overall difference was highly significant ( $P < .001$ , Wilks' lambda test) (Table 4).

**Table 2. PAIN ON JAW OPENING**

	SH Group (n = 20)			Control Group (n = 15)			<i>P</i>
	n	m	SD	n	m	SD	
Day 0	20	7.0	2.2	15	7.9	2.1	.199†
Day 14	20	5.0	3.5	15	7.8	3.0	.010*†
Day 28	20	4.2	3.7	15	7.7	3.6	.010*†
Day 56	20	4.0	4.0	15	7.7	3.6	.014*†
Day 84	20	3.6	3.8	15	7.7	3.6	.004*†
							.007*‡
							.070§

NOTE. Pain on jaw opening measured on 10-cm VAS. Patients were treated with 1 intra-articular injection of SH or oral methocarbamol-paracetamol.

Abbreviation: SD, standard deviation.

\*Results considered significant ( $P < .05$ ).

†Mann-Whitney *U* test was used for comparative analysis at each visit.

‡Wilks' lambda test was applied for generalized linear model between both groups.

§Wilks' lambda test was applied for generalized linear model all through the visits.

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**Table 3. PAIN ON MASTICATION**

	SH Group (n = 20)			Control Group (n = 15)			<i>P</i>
	n	m	SD	n	m	SD	
Day 0	20	4.0	3.6	15	4.3	2.8	.892†
Day 14	20	2.8	3.4	15	4.5	3.6	.117†
Day 28	20	2.4	3.4	15	5.5	4.1	.024*†
Day 56	20	2.8	3.7	15	5.5	4.1	.036*†
Day 84	20	2.8	3.9	15	5.5	4.1	.075†
							.071‡
							.208§

NOTE. Pain on mastication measured on 10-cm VAS. Patients were treated with 1 intra-articular injection of SH or oral methocarbamol-paracetamol.

Abbreviation: SD, standard deviation.

\*Results considered significant ( $P < .05$ ).

†Mann-Whitney *U* test was used for comparative analysis at each visit.

‡Wilks' lambda test was applied for generalized linear model between both groups.

§Wilks' lambda test was applied for generalized linear model all through the visits.

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## Discussion

Both groups were homogeneous for their demographic characteristics, except for age, as mean age was greater in the group treated with the combination methocarbamol and paracetamol. However, the

**Table 4. EVALUATION SCORE OF TMJ FUNCTION (100 POINTS)**

	SH Group (n = 20)			Control Group (n = 15)			<i>P</i>
	n	m	SD	n	m	SD	
Day 0	20	58.6	21.5	15	41.0	31.5	.127†
Day 14	20	67.7	26.5	15	35.7	35.0	.012*†
Day 28	20	75.6	29.6	15	35.3	37.9	.003*†
Day 56	20	71.5	29.7	15	35.3	37.9	.023*†
Day 84	20	72.8	31.0	15	35.3	37.9	.013*†
							<.001*‡
							<.001*§

NOTE. Evaluation of TMJ function using a 100-point questionnaire. Patients were treated with 1 intra-articular injection of SH or oral methocarbamol-paracetamol.

Abbreviation: SD, standard deviation.

\*Results considered significant ( $P < .05$ ).

†Mann-Whitney *U* test was used for comparative analysis at each visit.

‡Wilks' lambda test was applied for generalized linear model between both groups.

§Wilks' lambda test was applied for generalized linear model all through the visits.

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difference and range were not considered sufficiently relevant to carry out an adjustment of the statistical analysis for age. The different baseline measures of TMJ pain were homogeneous for the 2 study groups.

Five different parameters were used to evaluate the effectiveness of the experimental group compared with the control group: pain in the TMJ at rest, on jaw opening and on mastication, limitation of jaw opening, and the evaluation of TMJ function. In the group of patients treated with SH, pain decreased at all control visits compared with the group treated with the combination drug, although the differences between both treatments for the evolution of pain were not significant. These results were similar to the findings of Bertolami et al<sup>8</sup> and Hepguler et al<sup>17</sup> who used placebo as comparator. The objective of our study was to evaluate the effectiveness of a single infiltration of SH, because treatment courses involving more infiltrations at intervals of 7 days<sup>12,13,18</sup> or 15 days,<sup>11</sup> had already been studied for disk displacements without reduction. The evolution of pain at rest and on mastication did not show statistically significant differences between both treatments, although the results were very close to statistical significance. When comparing the visits, SH was the best treatment starting from the day 28 visit for the 3 pain measurements.

No treatment was better than the other for the limitation of jaw opening, as reported by Alpaslan and Alpaslan.<sup>9</sup> However, when the TMJ function was assessed, the SH infiltration was clearly superior. Although postinfiltration complications have been described in literature,<sup>19-23</sup> no serious adverse events were observed in our study.

One IA infiltration of SH was better than the oral administration of a combination of methocarbamol and paracetamol for the reduction of pain and for the functional improvement of the TMJ in Wilkes stage II disease. Similarly, the global judgment of efficacy of SH treatment was better than that with the combination of methocarbamol and paracetamol. The patients and the investigators assessed the tolerability as better with SH treatment than with the combination drug. No serious adverse events were detected during the treatment.

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