Effects of Low-dose Intramuscular Ketorolac on Experimental Pain in the Masseter Muscle of Healthy Women

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Aims: *To investigate the effect of a low dose of intramuscular (im) ketorolac compared with lidocaine (LA) in a double-blinded, randomized, and controlled trial.* ***Methods:*** *Twelve healthy women participated in three sessions and received two injections into their right masseter muscle per session. The first injections contained hypertonic saline (HS, 5% in 0.2 mL) to induce muscle pain. The second injections were given 30 minutes later and contained, together with HS, either ketorolac (3 mg in 0.2 mL), LA (2% lidocaine in 0.2 ml), or HS alone (control). HS-evoked pain intensity was scored on a 0 to 10 electronic visual analog scale (VAS) measuring peak, duration, and area under the curve (AUC). Pressure pain thresholds (PPT), pressure pain tolerance levels (PPTOL), and pain on palpation (POP) were determined bilaterally on the masseter muscle before and 5, 15, and 25 minutes after the injections. Maximum jaw opening (MJO) was measured at baseline and every 10 minutes after. McGill Pain Questionnaire (MPQ) scores and the extent of the HS-evoked pain (pain drawings) were recorded at baseline, 2 minutes after the first and second injections, and every 10 minutes during the entire experimental session.* ***Results:*** *There were no differences between the three sessions in HS-evoked pain measures from the first injection ($P > .05$). During the second injection, HS + LA demonstrated significantly lower VAS peak, duration, and AUC scores than control and HS + ketorolac ($P < .001$). In the HS + ketorolac session, the VAS AUC was significantly lower than in the control session ($P < .005$). The sessions had no main effect on PPT, PPTOL, POP, MJO, or pain drawings ($P > .05$).* ***Conclusion:*** *A low dose of im ketorolac has a significant and immediate analgesic effect on HS-evoked jaw muscle pain but significantly less than LA. A local anesthetic-like effect may be the underlying mechanism.* J OROFAC PAIN 2010;24:398–407

Key words: experimental muscle pain, ketorolac, local anesthetics, NSAIDs, trigeminal nociception

Temporomandibular disorders (TMD) are estimated to affect 10% to 12% of the North American population.[1,2] A subgroup of these disorders is the myofascial TMD, in which the symptoms are characterized by pain and loss of function in the masticatory muscles. Women are highly overrepresented among patients with painful TMD.[3–5] Our knowledge about the pathophysiology of deep tissue pain, ie, myofascial TMD, is insufficient, and this is reflected, in part, in the frequent shortcomings of currently available treatment strategies.

Pharmacological treatment of musculoskeletal pain is often based on an empiric approach.[6] Despite the lack of clear signs of inflammation in myofascial TMD,[7] systemic nonsteroidal anti-inflammatory

drugs (NSAIDs) are commonly used as analgesics.[3,4] This is more due to clinical tradition than scientific evidence.[8–10] When administered systemically, NSAIDs may be associated with significant side effects such as gastrointestinal complications. These side effects are related to dose and duration of treatment.[11] The mechanism responsible for the analgesic effect of the NSAIDs, ie, the inhibition of the cyclooxygenase (COX), an enzyme involved in the conversion of arachadonic acid to prostaglandins,[11] is at the same time also responsible for the side effects. For this reason, NSAIDs should be applied in the lowest possible therapeutic dose for the shortest period of time, and it would be preferable to administer the drug locally at the painful site to avoid the systemic side effects.

The analgesic efficacy of NSAIDs in myositis is currently thought to result from the ability of these drugs to inhibit the synthesis of prostaglandins at the site of tissue injury.[11,12] Yet, NSAIDs may have other mechanisms than the inhibition of COX that contribute to their analgesic effect. Clinical research suggests that many NSAIDs are effective analgesics at concentrations below those required for anti-inflammatory activity.[12,13] This analgesic effect is then the result of a direct and local action on the excitability of nociceptors in the muscle.[14–16] Therefore, there is an increasing interest in topical NSAIDs for the treatment of musculoskeletal pain.[11,17] It has been demonstrated that both intramuscular (im) injection of 1 mg ketorolac and the recommended dose of 30 mg results in the same degree of analgesia, significantly different from placebo. However, while 30-mg ketorolac significantly reduces prostaglandin E2 (PGE2), 1-mg ketorolac has no effect on the PGE2 value.[14]

Diclofenac is one of the best studied topical NSAIDs for the treatment of muscle pain, including myofascial TMD.[17–19] Diclofenac (~100 μM), which is structurally similar to ketorolac, blocks sodium channels in the same way as conventional local anesthetics and thereby prevents neuronal depolarization and action potential conduction.[20] In rats, administration of a local anesthetic together with hypertonic saline (HS) into the masseter muscle was found to inhibit HS-evoked nociceptor discharge, and diclofenac caused an approximately 60% reduction in the HS-induced nociceptor discharge.[15] This further supports the hypothesis that certain NSAIDs may have local anesthetic-like effects.[15]

The aim of the present study was to investigate the effect of a low dose of intramuscular (im) ketorolac compared with lidocaine (LA) in a double-blinded, randomized, and controlled trial of HS-evoked masseter muscle pain[21,22] in women.

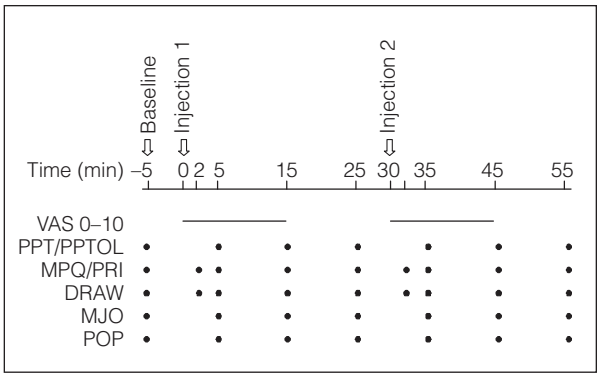

Fig 1 Illustration of the experimental protocol. Injection 1 = HS 5%; injection 2 = HS 5% alone (control) or in combination with either LA (lidocaine 2%) or ketorolac 15 mg/mL (3 mg in 0.2 mL). DRAW = pain drawing.

Materials and Methods

Subjects

Twelve healthy female volunteers using oral contraceptives participated in this study (mean age [± SEM] 25.6 ± 1.2 years). The volunteers were students and staff recruited from the Faculty of Health Sciences, Aarhus University, and the School for Dental Assistants, Hygienists, and Clinical Technicians, Aarhus. The women had no medical, physical, or psychological conditions, and they were without TMD according to the Research Diagnostic Criteria (RDC) for TMD.[23] The volunteers reported no history of side effects using NSAIDs or lidocaine. They were asked not to take any kind of analgesics during the 24 hours before an experimental session. The volunteers received written and oral information about the experiment before they signed an informed consent form in accordance with the guidelines of the Helsinki Declaration. The study was performed in the orofacial pain laboratory at the Department of Clinical Oral Physiology, School of Dentistry, Aarhus University, with the approval of The Central Denmark Region Committees on Biomedical Research Ethics (No. 20060199). All parts of the study were performed by the same female investigator (KHB).

Study Design

The study was performed in a randomized, double-blinded, and controlled crossover manner. All women participated in three experimental sessions with a minimum of 7 days between each session. One session lasted approximately 1 hour and each session was performed identically (Fig 1). The order of the

sessions was randomized by a computer. The study was performed in a quiet room at normal room temperature. The subjects were seated comfortably in a reclined position.

Hypertonic Saline Evoked Pain

Experimental pain was induced by injection of 0.2 mL sterile 5% HS into the deep central portion of the right masseter muscle by means of a 27-gauge hypodermic needle and disposable syringe.[24] HS has been shown to activate nociceptive type III and IV afferents and several studies have described somatosensory and motor responses to im HS injections.[15,25–29]

In each session, two injections were given (injection 1 and 2) (Fig 1). The first injection consisted of HS alone (5% in 0.2 ml). This injection served as an internal control for variation between sessions.[30] For the second injection, HS was given alone (control), in combination with LA (2% lidocaine in 0.2 mL), or in combination with ketorolac 15 mg/mL (3 mg in 0.2 mL). Blinding of both the volunteers and the examiner was achieved by administering the control, the active control LA, and the low dose of ketorolac from identical looking syringes, which were prepared by a dental nurse outside the examination room.

The volunteer estimated the pain intensity on a 0 to 10 electronic visual analog scale (VAS) collected on a PC at 1 Hz. The outcome parameters for the VAS recording were VAS peak (maximum pain 0 to 10 cm), VAS duration (pain offset time subtracted pain onset time, after terminated injection), and VAS area under the VAS-time curve (cm × seconds) (AUC).

Pressure Algometry

To test the sensitivity to deep stimuli applied to the masseter muscle, the pressure pain threshold (PPT) and the pressure pain tolerance level (PPTOL) were detected at baseline and every 10 minutes throughout the entire session (Fig 1). For this, an electronic pressure algometer (Somedic) was used with a probe diameter of 1 cm^2 and an increase in pressure application rate kept constant at 30 kPa/second.[24] The probe was applied perpendicular to the central segment of the masseter muscle. The subject's right masseter muscle was used as the experimental site and the subject's left masseter muscle served as a control. The PPT was defined as the amount of pressure (kPa) at which the subjects first perceived pain. The PPT measurement was repeated three times on each side with 1-minute intervals between each stimulus, and the average value was used for further analysis. The PPTOL was defined as the most painful pressure (kPa) that the subject would tolerate. This was measured only once on each side to reduce the number of episodes where the subject had to experience this high-intensity pressure stimulus and to avoid unnecessary sensitization. When either the PPT or the PPTOL was reached, the subject pressed a button to stop the stimulation. During pressure algometry, the subjects were asked not to clench their teeth and they were instructed not to contract their masseter muscles and to keep their jaw in as relaxed a position as possible.[24]

Additional Measures

McGill Pain Questionnaire and Pain Rating Index. In order to estimate the sensory, discriminative, affective, and evaluative dimension of the pain experience, the subjects were asked to fill out a Danish version of the McGill Pain Questionnaire (MPQ)[31,32] at baseline, 2 minutes after the first and the second injection, and every 10 minutes during the entire experimental session. At the same time points, subjects were asked to illustrate, on an anatomical drawing, the extent of the experimentally induced pain from a lateral, frontal, and intraoral view (Fig 1). A total Pain Rating Index (PRI) was subsequently calculated[31] and the drawings were digitized (Sigma Scan Pro 4.01.003) to obtain a quantitative expression for the pain area including referred pain.[25]

Maximum Jaw Opening and Pain on Palpation. At baseline and at every 10 minutes, the maximum unassisted jaw-opening capability (MJO) without pain sensation was measured by the use of a ruler as the interincisal distance (in mm) plus the vertical overbite. The duration of each measurement was approximately 2 seconds (Fig 1). Pain on palpation (POP) was measured on both the experimental site and the control site at baseline and every 10 minutes throughout the session (Fig 1). This was done with a novel palpometer based on a spring-coil by which 1 kg of pressure was applied to the superior, the middle, and the inferior portion of the masseter muscle with a 1 cm^2 probe. Each measurement series took approximately 6 seconds (3 × 2 seconds) for each side. Prior to palpation, the subjects were asked to keep their mandible in a resting position, without the teeth touching, and to keep their muscles in a passive state. When palpated, the subjects were asked to indicate whether they felt pain or just pressure according to the RDC/TMD examination criteria scale in which "pressure only/no pain" is rated as "0," "mild pain" as "1," "moderate pain" as "2," and "severe pain" as "3."[23]

Table 1 HS-evoked Pain Scores (Mean ± SEM)

	VAS peak pain		VAS duration		VAS AUC	
Session	Injection 1	Injection 2	Injection 1	Injection 2	Injection 1	Injection 2
LA	6.5 ± 0.4	1.3 ± 0.3*	294 ± 39	75 ± 23*	956 ± 78	76 ± 24*
Ketorolac	6.3 ± 0.5	5.1 ± 0.4	275 ± 26	208 ± 23	887 ± 92	555 ± 74*
Control	6.3 ± 0.6	5.9 ± 0.6	252 ± 20	246 ± 21	881 ± 97	855 ± 110

*Significant different from injection 1 ($P < .05$).

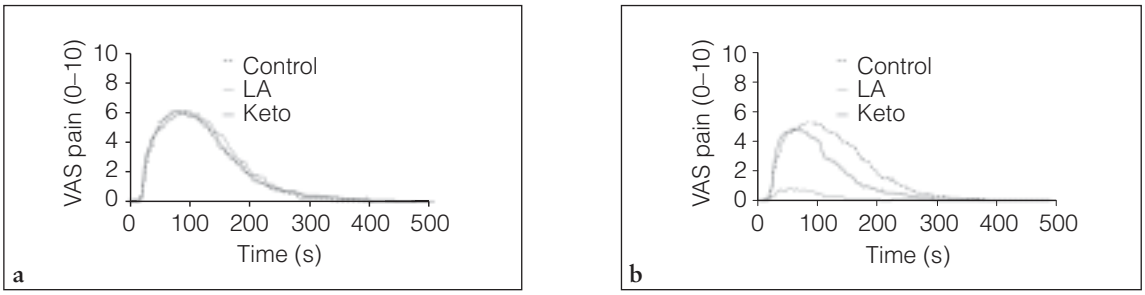

Fig 2 Mean HS-evoked pain scores on a VAS (0 to 10) (n = 12). *(a)* injection 1 contained HS (5% in 0.2 mL). *(b)* injection 2 contained together with the HS either ketorolac (keto, 3 mg in 0.2 mL), LA (lidocaine 2% in 0.2 mL), or HS alone (control).

Statistical Analyses

The number of subjects was based on a paired design sample size calculation. The authors wished to be able to detect a 25% reduction in VAS pain and PPT measures, and the intraindividual coefficient of variance of the psychophysical measures was estimated to 20%, giving a minimum of 10 healthy subjects. VAS pain scores (absolute values of VAS peak pain, VAS pain duration, and VAS pain AUC) were tested with the use of analyses of variance (ANOVAs) with session (control, ketorolac, LA) and injection (injection 1 versus injection 2) as repeated measurement factors. The PPT, PPTOL, and MJO data were tested with the use of ANOVAs with session (control, ketorolac, LA) and time (0, 5, 15, 25, 35, 45, and 55 minutes) as repeated measurement factors. MPQ/total PRI and the pain drawings were analyzed with ANOVAs with session (control, ketorolac, LA) and time (0, 2, 5, 15, 25, 32, 35, 45, and 55 minutes) as repeated measurement factors. When appropriate, the Tukey HSD test and the Holm-Sidak test were used for post-hoc analyses. McNemar's test for paired binary data was used to test POP. Results are presented as means ± standard error of the mean (SEM). Values of $P < .05$ were considered statistically significant.

Results

All subjects completed the study and no major side effects were observed.

HS-evoked Pain

Table 1 shows the absolute values of the HS-evoked pain scores (VAS peak, VAS duration, and the VAS AUC) from the first and second injections. Between the three sessions, there were no differences in HS-evoked pain scores from the first injection (VAS peak, VAS duration, and VAS AUC) (ANOVA: $P > .05$) (Fig 2a).

Analysis of the second injection revealed a significant main effect of session in all VAS pain parameters (VAS peak, VAS duration, and VAS AUC) (ANOVA: $P < .01$). Tukey post-hoc tests demonstrated that the VAS peak, VAS duration, and the VAS AUC in the LA session were significantly lower than in the ketorolac and control sessions (Tukey: $P < .05$). There was also a significant difference between the first and second injections with regard to all VAS pain parameters (ANOVA: $P < .001$). The Tukey post-hoc test demonstrated that the VAS peak, VAS duration, and the VAS AUC in the second injections were significantly reduced compared with the first injections (Tukey: $P < .001$). A signifi-

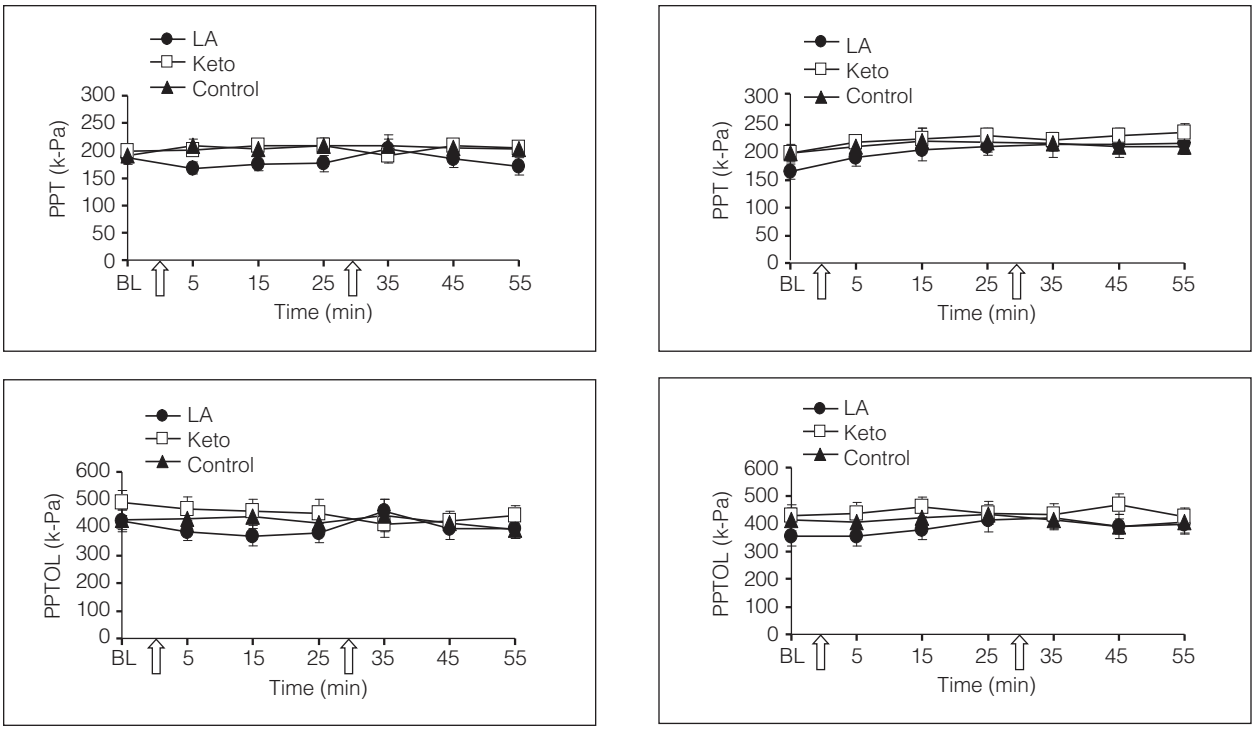

Fig 3 Mean (± SEM) values of LA (lidocaine 2% in 0.2 mL) or ketorolac (keto, 3 mg in 0.2 mL) of the PPT and PPTOL on the injection side *(left column)* and the control side *(right column)*. The arrows indicate the time of the injections. BL = baseline. At all time points, the mean PPT on the control side was significantly increased from the mean baseline PPT value (Tukey: $P < .05$).

cant session × injection interaction was also found (ANOVA: $P < .001$). The post-hoc test revealed significantly lower VAS peak pain, VAS duration, and VAS AUC scores from the second injection in the LA session compared with both the control and the ketorolac session (Tukey: $P < .001$) and a significantly reduced VAS AUC from the second injection in the ketorolac session compared with the control session (Tukey: $P = .005$, Fig 2b). The overall HS-evoked pain reduction by ketorolac was 37% compared with 82% by LA (Table 1). ANOVAs on the normalized (to baseline) VAS values (VAS peak pain, VAS duration, and VAS AUC) were performed as an additional analysis. These results did not differ from the results on absolute VAS values and are therefore not reported.

Pressure Algometry

The absolute PPT and PPTOL values are seen in Fig 3. The PPT on the experimental side demonstrated no significant session (ANOVA: $P = .131$) or time effect (ANOVA: $P = .648$). There was no main effect of session detected on the PPT on the control side (ANOVA: $P = .277$), but a main effect of time was found (ANOVA: $P < .001$). A Tukey post-hoc test revealed that at all time points the mean PPT on the control side was significantly increased from the mean baseline PPT value (Tukey: $P < .05$).

The PPTOL measurements did not show any significant main effect of session (ANOVA: $P > .05$) or time (ANOVA: $P > .05$) on either side.

Additional Measures

MPQ and PRI. The subjects used several words from the MPQ to describe the HS-evoked peak pain. The most frequently used words by at least 30% of the subjects are presented in Table 2.

The mean sensory, affective, evaluative, miscellaneous, and total PRI scores are presented in Table 3. At baseline, none of the subjects reported any pain and consequently all the PRI scores were zero. The averaged total PRI of the HS-evoked pain showed both a session (ANOVA: $P = .019$) and a time (ANOVA: $P < .001$) effect. A post-hoc analysis revealed that 2 minutes after the first and second injections, the total PRI scores were significantly higher than baseline values (Tukey: $P < .001$). The PRI values from the LA session were significantly lower than the control session (Tukey: $P = .020$). A significant session × time interaction was also detected (ANOVA: $P < .001$). The post-hoc test indicated that

Table 2 The Most Frequently Used Words on the MPQ (%)

	LA		Ketorolac		Control	
Words	Injection 1	Injection 2	Injection 1	Injection 2	Injection 1	Injection 2
Taut	75.0*	8.3	66.7*	66.7*	66.7*	58.3*
Pressing	58.3*	16.7	58.3*	50.0*	66.7*	66.7*
Aching	16.7	8.3	41.7*	8.3	33.3*	33.3*
Spreading	16.7	0.0	16.7	16.7	33.3*	50.0*
Tight	50.0*	8.3	16.7	25.0	33.3*	33.3*
Nagging	33.3*	0.0	16.7	16.7	33.3*	16.7
Tender	25.0	33.3*	41.7*	58.3*	25.0	33.3*
Pounding	25.0	8.3	25.0	8.3	25.0	33.3*
Annoying	16.7	0.0	16.7	8.3	25.0	33.3*
Hot	16.7	0.0	33.3*	33.3*	16.7	25.0

The numbers with * are words used by at least 30% of the 12 subjects to describe the HS-evoked peak pain.

Table 3 PRI of the HS-evoked Pain (Mean ± SEM)

	LA		Ketorolac		Control	
	Injection 1	Injection 2	Injection 1	Injection 2	Injection 1	Injection 2
Sensory	8.1 ± 1.3	1.9 ± 0.8*	6.3 ± 0.8	6.3 ± 1.0	8.3 ± 1.0	8.5 ± 1.2
Affective	0.2 ± 0.1	0.0 ± 0.0	0.3 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
Evaluative	1.2 ± 0.4	0.0 ± 0.0	0.8 ± 0.4	0.4 ± 0.3	0.8 ± 0.4	0.5 ± 0.2
Miscellaneous	1.9 ± 0.7	0.1 ± 0,1	2.1 ± 0.5	2.3 ± 0.8	3.3 ± 0.7	2.0 ± 0.6
Total score	11.3 ± 1.8	2.0 ± 0.9*	9.5 ± 1.4	9.2 ± 1.6	12.5 ± 1.4	10.8 ± 1.4

At baseline, none of the subjects reported any pain and consequently all the PRI scores were zero. * = significantly different from injection 1 ($P < .05$).

there were lower total PRI scores in the LA session (Tukey: $P < .001$) 2 minutes after the second injection compared with both the control session and the ketorolac session.

Pain Drawings. When the subjects were asked to draw the spatial extent of the HS-evoked peak pain, the pain occurred only on the experimental side in all of the sessions at all time points (Tables 4a and 4b and Figs 4a to 4c).

In both the control and the ketorolac sessions, 12 out of 12 subjects reported pain on the lateral aspect of the face (Tables 4a and 4b and Fig 4a) at the second injection. In the LA session, 7 out of 12 subjects reported pain on the lateral aspect of the face (Tables 4a and 4b and Fig 4a). There was no main effect of session (ANOVA: $P = .216$), but a significant main effect of time (ANOVA: $P < .001$) on the pain drawing area. A post-hoc analysis revealed that 2 minutes (peak pain) after both the first and second injections, the average pain drawing area was significantly larger than at baseline (Tukey: $P < .001$). There was a significant session × time interaction (ANOVA: $P = .002$). The Tukey post-hoc test showed that 2 minutes after the second injection, the average pain drawing area was significantly reduced in the LA session compared with both the control and the ketorolac sessions (Tukey: $P < .01$) (Tables 4a and 4b and Fig 4a).

In the control session, 3 out of 12 subjects reported pain on the frontal aspect of the face (Tables 4a and 4b and Fig 4b). Two out of 12 subjects in the ketorolac session and 1 out of 12 subjects in the LA session reported frontal pain. There were no differences between sessions (ANOVA: $P = .495$) when the average area of the frontal pain drawing at the second injections were analyzed (Tables 4a and 4b and Fig 4b).

In both the control and the ketorolac sessions, 8 out of 12 subjects reported intraoral pain at the second injection (Tables 4a and 4b and Fig 4c). In the LA session, only 1 out of 12 subjects reported intraoral pain (Tables 4a and 4b and Fig 4c). There were, however, no significant differences between sessions (ANOVA: $P = .305$) when the average area of the intraoral pain drawing at the second injections were analyzed (Tables 4a and 4b and Fig 4c).

MJO and POP. There was no significant main effect of session on the MJO (ANOVA: $P = .846$). A significant main effect of time was found (ANOVA: $P < .001$). A post-hoc test detected that, apart from 5 minutes after the first injection, the average MJO was

Table 4a Area of Pain Drawing (Mean ± SEM) (mm^2)									
	Control			Ketorolac			LA		
	Lateral pain	Intraoral pain	Frontal pain	Lateral pain	Intraoral pain	Frontal pain	Lateral pain	Intraoral pain	Frontal pain
Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Peak injection 1	9.9 ± 2.4	7.0 ± 4.5	0.6 ± 0.4	11.2 ± 2.8	6.8 ± 3.3	1.0 ± 0.6	11.4 ± 3.1	4.8 ± 2.8	1.2 ± 0.8
15 min	1.1 ±1.0	0.0 ± 0.0	0.4 ± 0.4	1.1 ± 0.5	0.6 ± 0.6	0.0 ± 0.0	1.7 ± 0.7	0.4 ± 0.4	0.3 ± 0.2
25 min	0.6 ± 0.4	0.0 ± 0.0	0.1 ± 0.1	0.5 ± 0.3	1.2 ± 1.2	0.0 ± 0.0	1.1 ± 0.9	0.0 ± 0.0	0.2 ± 0.2
Peak injection 2	10.7 ± 2.4	7.1 ± 4.4	0.9 ± 0.6	8.5 ± 1.3	5.4 ± 3.0	0.4 ± 0.3	2.6 ± 1.7*	0.5 ± 0.5	0.3 ± 0.3
45 min	1.0 ± 0.7	0.0 ± 0.0	0.3 ± 0.3	2.1 ± 0.9	0.2 ± 0.2	0.0 ± 0.0	1.0 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
55 min	1.4 ± 0.8	0.0 ± 0.0	0.1 ± 0.1	1.5 ± 0.6	0.0 ± 0.0	0.0 ± 0.0	0.5 ± 0.3	0.0 ± 0.0	0.0 ± 0.0

Table 4b Frequency of Subjects Reporting Pain (%)									
	Control			Ketorolac			LA		
	Lateral pain	Intraoral pain	Frontal pain	Lateral pain	Intraoral pain	Frontal pain	Lateral pain	Intraoral pain	Frontal pain
Baseline	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Peak injection 1	91.7	83.3	25.0	100.0	66.6	33.3	100.0	58.3	25.0
15 min	16.6	0.0	8.3	50.0	8.3	0.0	50.0	8.3	16.7
25 min	25.0	0.0	8.3	33.3	8.3	0.0	33.3	0.0	8.3
Peak injection 2	100.0	66.7	25.0	100.0	66.6	16.7	58.3	8.3	8.3
45 min	25.0	0.0	8.3	58.3	8.3	0.0	41.7	0.0	8.3
55 min	33.3	0.0	8.3	58.3	0.0	0.0	33.3	0.0	8.3

Subjective description of the extent of HS-evoked pain on an anatomical drawing. There were no reports of pain at any time in the control side (n = 12). Peak injection 1 and peak injection 2: Peak pain on 0–10 VAS. *Significantly different from ketorolac and control ($P < .05$).

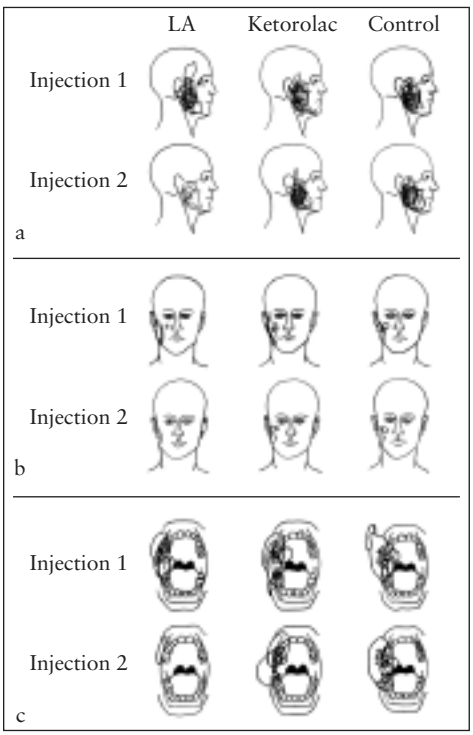

Fig 4 Illustrations of the subject-based drawings of the spatial extent of the HS-evoked peak pain from the two injections in the three sessions. The first injection contained HS (5% in 0.2 mL). In the second injection, HS was coadministered with either ketorolac (3 mg in 0.2 ml), LA (lidocaine 2% in 0.2 mL), or HS alone (control). Fig 4a illustrates the lateral presentation of the pain; Fig 4b, the frontal presentation of the pain; and Fig 4c, the intraoral presentation of the pain.

significantly reduced from the average baseline value at all time points (Tukey: $P < .05$). There was no significant session × time interaction (ANOVA: $P = .887$).

There was a significant difference between POP at the experimental site and control site (McNemar's test, $P = .014$). When palpated with 1 kg of pressure, 8 out of 12 subjects experienced pain at the experimental site versus 2 out of 12 subjects at the control site. The vast majority of the positive pain scores were rated as "1" (mild). However, there were no significant differences between any of the sessions in POP (McNemar's test, $P > .05$).

Discussion

The main finding in the present study was that im injection of ketorolac, at a dose lower than required for anti-inflammatory activity, did significantly and immediately reduce the experimental HS-evoked masseter muscle pain in healthy women. To the authors' knowledge, this is the first human study to describe the effect of an NSAID in this manner.

Methodological Issues

The randomized, double-blinded, and controlled design is a major strength of this study. The volunteers acted as their own controls with the use of a paired design carried out in a crossover manner. The first injection in each session contained HS alone and was performed to minimize the interindividual variation between sessions. Yet, some methodological considerations have to be discussed.

This study included female volunteers only. This was done due to the higher prevalence of myofascial TMD in women than in men,[4] and to eliminate the variability caused by gender differences in pain perception.[33] In addition, a previous animal study did not find significant sex-related differences in the local anesthetic-like effect of the NSAID diclofenac on masseter muscle nociceptors in rats.[15] Alterations in the level of the female sex hormone estrogen during the menstrual cycle may have caused variation in muscle pain sensitivity.[34] To reduce the influence of this variation, only women taking oral contraceptives were included.[33,35,36] Future studies in which pain sensitivity and the anesthetic-like effect of a low dose of im NSAID are compared between men and women will be of interest.

The primary outcome in this study is based on experimentally evoked pain from injection of HS into the masseter muscle of healthy subjects, a reliable and valid experimental pain model in which the pain sensation is characterized by a diffuse pain sensation in the deep structures much like clinical muscle pain.[22] The reliability of the HS-evoked pain was also demonstrated in the present study, with no significant differences between the first injections in the three sessions. Furthermore, the words chosen to describe HS-evoked pain areas were in accordance with previous clinical studies.[26] Obviously, the discrepancy between an acute experimental pain model and chronic pain in patients suffering from myofascial TMD has to be considered. Comparisons of pain evoked by a controlled painful stimulus in a controlled environment with pain in patients suffering from chronic pain have apparent limitations.[22,26,37] Yet, human experimental pain models serve as important connections between animal experiments and clinical pain studies in patients.[37] Based on this, it is proposed that future studies examine the effects of low doses of im ketorolac on pain in myofascial TMD patients. These patients do not have any clinical signs of inflammation but may respond to the anesthetic-like action of ketorolac independent of the COX-inhibition.

NSAIDs in Pain Management

The experimental HS-evoked muscle pain was significantly and immediately reduced by coadministration of a low dose of ketorolac into the masseter muscle tissue, although to a lesser extent than LA. In this group of women, the overall HS-pain experience, illustrated by the VAS-AUC measures, was significantly reduced by ketorolac as compared with control. ANOVAs on the normalized (to baseline) VAS values (VAS peak pain, VAS duration, and VAS AUC) were performed. These results did not differ from the results on absolute VAS values and therefore indicate that the obtained results are very robust.

Intramuscular injection of HS evokes nociceptor discharge and causes localized and referred muscle pain in human subjects without signs of gross inflammatory change.[15,24,25,38,39] Clinical research suggests that many NSAIDs, including ketorolac, are also effective analgesics at concentrations below those required for anti-inflammatory activity.[12–14] These findings support the suggestion that alternative mechanisms may contribute to the peripheral analgesic properties of NSAIDs when used in humans. Since the administered dose of ketorolac in the present study was less than that required to inhibit COX in humans, the inhibitory effect of ketorolac on HS-evoked muscle pain might reflect a local anesthetic-like action. However, in addition to a similar local anesthetic-like action, the NSAID diclofenac can exert a selective, competitive inhibition of peripheral N-methyl-d-aspartate (NMDA) receptors, which does not require inhibi-

tion of prostaglandin synthesis.[16] Ketorolac may also share this property, as it has been shown to inhibit the excitatory effect of NMDA on spinal cord nociceptive neurons.[40] Future experiments in both animals and humans will be required to elucidate the analgesic mechanisms of intramuscularly injected ketorolac.

Words from the MPQ used to describe the peak pain from the first injection were similar in all three sessions and consistent with the words used from the pain experienced after the second injection in the control session. The ketorolac session differed from the control in the subjective description of the peak pain experience, but LA differed notably from both ketorolac and control. This superior effect of LA was also demonstrated in the PRIs in which the LA session significantly reduced the PRI total scores compared with both the ketorolac and the control sessions. When the subjects were asked to draw the extension of the HS-evoked pain, LA produced a significantly reduced pain area when compared with both the ketorolac and the control sessions.

Future topics to be investigated are the potential effects of different doses and subgroups of NSAIDs. It would, however, be of significant clinical benefit if NSAIDs could be administered locally to treat muscle pain, as this could greatly reduce or even eliminate possible systemic adverse effects.

Mechanical Sensitivity

The present study found that the PPT and the PPTOL levels were not significantly affected by injection of HS into the masseter muscles of the healthy subjects, which is in agreement with previous studies.[24] As an additional analysis, ANOVAs performed on the normalized (to baseline) PPT and the PPTOL values produced results that did not differ from the results on absolute PPT and PPTOL values and are therefore not reported.

However, when palpated with 1 kg of pressure, the majority of subjects experienced pain according to the RDC/TMD examination criteria scale at the experimental site and not at the control site. This suggests a slight sensitization.[22] No POP differences were found between sessions, probably due to a marginal increase in mechanical sensitivity. It should be noted that the absolute PPT and PPTOL measures were unable to detect this slight and probably subclinical sensitization of the injected muscle site. Standardization of clinical palpation procedures therefore could be of importance to detect low-levels of mechanical sensitization.

Previously, it has been shown that injection of HS followed by LA into the masseter muscles of healthy subjects increases the PPT and PPTOL levels.[24] In this study, co-injection of LA with HS did not significantly increase PPT and PPTOL, and there were indications of a slight relative sensitization of the experimental site, since an increase in PPT and PPTOL over time was found at the control site, in agreement with previous studies.[41–43] This relative sensitization as indicated by the PPT and PPTOL measures is in accordance with the palpation results (see above). In a previous animal study that investigated the effect of co-injection of HS with lidocaine on masseter muscle nociceptors, there was no significant effect of lidocaine on mechanical threshold.[15] Animal research indicates that co-injection of hypertonic solutions with lidocaine significantly shortens the duration of local anesthesia.[44] This is thought to result from the large edema produced by intramuscular injection of hypertonic solutions, which dilutes the concentration of the injected local anesthetic, and the pronounced increase in muscle blood flow produced by injection of hypertonic solutions, which leads to a more rapid clearance of the local anaesthetic from the injection site.[44]

The clinical impact of the present findings is not clear because the study in healthy subjects was designed to address the possible mechanisms of action of locally administered ketorolac. Nevertheless, the present findings indicate that it would be worthwhile to pursue studies to test the dose-response relationship for locally injected ketorolac in various orofacial pain conditions.

Conclusions

A low dose of ketorolac (im) had a significant and immediate analgesic effect on HS-evoked jaw muscle pain, but this effect was significantly less than im LA. There were no robust effects on mechanical sensitivity. A local anesthetic-like effect could be one explanation for the analgesic effects of im ketorolac, although other mechanisms may also contribute to this effect.

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