Effect of Peripheral NMDA Receptor Blockade with Ketamine on Chronic Myofascial Pain in Temporomandibular Disorder Patients: A Randomized, Double-blinded, Placebo-Controlled Trial

Eduardo E. Castrillon, DDS, MSc, PhD
Clinical Teacher
Department of Clinical Oral Physiology
School of Dentistry
University of Aarhus, Aarhus, Denmark

Brian E. Cairns, PhD, RPh
Associate Professor, Canada Research Chair in Neuropharmacology
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, British Columbia, Canada

Malin Ernberg, DDS, PhD
Associate Professor
Department of Clinical Oral Physiology
Institute of Odontology
Kariolinska Institutet, Stockholm, Sweden

Kelun Wang, DDS, PhD
Associate Professor
Orofacial Pain Laboratory
Center for Sensory-Motor Interaction
Aalborg University, Aalborg, Denmark

Barry J. Sessle, BDS, MDS, BSc, PhD, DSc (hc)
Professor and Canada Research Chair
Faculty of Dentistry
University of Toronto
Toronto, Ontario, Canada

Lars Arendt-Nielsen, MScEE, PhD, Dr Med
Professor
Center for Sensory-Motor Interaction
Aalborg University, Aalborg, Denmark

Peter Svensson, DDS, PhD, Dr Odont
Professor and Chairman
Department of Clinical Oral Physiology
School of Dentistry
University of Aarhus, Aarhus, Denmark

Correspondence to:
Dr Eduardo Castrillon
Department of Clinical Oral Physiology
School of Dentistry, University of Aarhus
Vennelyst Boulevard 9
DK-8000 Aarhus C, Denmark
Fax: +45 86195665
E-mail: ecastrillon@odont.au.dk

Aims: *To investigate the effects of local intramuscular injection of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine on chronic myofascial pain and mandibular function in temporomandibular disorder patients.* ***Methods:*** *Fourteen myofascial temporomandibular disorder pain patients (10 women and 4 men) were recruited. The subjects completed 2 sessions in a double-blinded randomized and placebo-controlled trial. They received a single injection of 0.2 mL ketamine or placebo (buffered isotonic saline [NaCl], 155 mmol/L) into the most painful part of the masseter muscle. The primary outcome parameters were spontaneous pain assessed on an electronic visual analog scale and numeric rating scale. In addition, numeric rating scale of unpleasantness, numeric rating scale of pain relief, pressure pain threshold, pressure pain tolerance, completion of a McGill Pain Questionnaire and pain drawing areas, maximum voluntary bite force and maximum voluntary jaw opening were obtained. Paired* t *tests and analysis of variance were performed to compare the data.* ***Results:*** *There were no main effects of the treatment on the outcome parameters except for a significant effect of time for maximum voluntary bite force (analysis of variance;* P = .030*) and effects of treatment, time, and interactions between treatment and time for maximum voluntary jaw opening (analysis of variance;* P < .047*).* ***Conclusion:*** *These results suggest that peripheral NMDA receptors do not play a major role in the pathophysiology of chronic myofascial temporomandibular disorder pain. Although there was a minor effect of ketamine on maximum voluntary jaw opening, local administration may not be promising treatment for these patients.* J OROFAC PAIN 2008;22:122–130

Key words: experimental pain, glutamate, ketamine, muscle pain, orofacial pain, temporomandibular disorders, trigeminal physiology

The etiology and pathogenesis of myofascial temporomandibular disorders (TMD), which are characterized by symptoms of localized ongoing and activity-provoked masticatory muscle pain and are more common in women than in men, remain unclear.[1–3] It has been hypothesized that elevated levels of interstitial glutamate in the masseter muscle may play a role in the development and maintenance of myofascial TMD pain, in part based on previous findings that injection of glutamate into the human masseter muscle evokes pain, induces mechanical sensitization, and increases the amplitude of the jaw-stretch reflex.[4–7] Consistent with the idea that elevated glutamate levels could play a role in myofascial TMD mechanisms is the finding that gluta-

mate-evoked muscle pain is significantly greater in women than in men.[4,5,8] Moreover, some studies have demonstrated high levels of glutamate in patients with chronic painful tendinosis or trapezius myalgia.[9,10] Further, a recent animal study has suggested that a modest elevation of interstitial glutamate concentrations (~2 to 3 times above baseline) can excite and mechanically sensitize masseter muscle nociceptors.[11] Taken together, these findings suggest that glutamate, either alone or through its interactions with other algesic substances, may play an important role in the development and/or maintenance of chronic myofascial TMD pain conditions.

Several lines of evidence suggest that many of the effects induced by elevated interstitial concentrations of glutamate are mediated through activation of peripheral *N*-methyl-D-aspartate (NMDA) receptors: Nociceptors that innervate the masseter muscle express NMDA receptors, NMDA application to the masseter muscle excites masseter nociceptive afferents, and glutamate-evoked masseter nociceptor discharge as well as glutamate-induced masseter nociceptor mechanical sensitization are attenuated by NMDA receptor antagonists.[11–14] In humans, local administration of the noncompetitive NMDA receptor antagonist ketamine has been shown to attenuate glutamate-evoked masseter muscle pain and glutamate-induced mechanical sensitization.[13,15] Also, peripheral NMDA receptors are localized to nerve structures in patients with chronic painful tendinosis.[9] Therefore, if elevated interstitial concentrations of glutamate in the masseter muscle contribute to pain in myofascial TMD patients, it would be predicted that local administration of an NMDA receptor antagonist should attenuate this pain.

Localized peripheral pain control in orofacial pain conditions may bring some advantages over approaches that target pain-related processes in the central nervous system. For example, higher local concentrations of the drug in the original site of pain would avoid systemic drug levels that may cause some adverse effect and would decrease the possibility of drug interactions, unless systemic absorption occurred.[16] Therefore, testing the effects of local application of peripheral NMDA receptor antagonists such as ketamine, a drug that was originally introduced as a general anesthetic, has recently been advocated.[17] For these reasons, the aim of the present study was to investigate the effects of local intramuscular injection of the NMDA receptor antagonist ketamine on chronic myofascial pain and mandibular function in TMD patients.

Materials and Methods

Volunteers

Ten female patients (mean age, 28.7 ± 2.0 years) and 4 male patients (mean age, 26.3 ± 2.5 years) with chronic myofascial TMD pain completed their participation in this study, which was performed at the Department of Clinical Oral Physiology in the School of Dentistry at the University of Aarhus, Denmark.

The study was approved by the local Ethics Committee at Aarhus University and conducted in accordance with the Helsinki Declaration. All the volunteers read and signed informed consent forms. For a patient to be included in the study, a diagnosis of myofascial TMD pain (1a or 1b) according to the Research Diagnostic Criteria for TMD (RDC/TMD)[18] and a history of characteristic pain intensity in the masseter muscle of more than 2 out of 10 on a numeric rating scale (NRS) over a 2-month period were required. The patients were not tested specifically for the presence of trigger points. Exclusion criteria were the presence of systemic musculoskeletal pain disorders such as fibromyalgia; signs or symptoms of systemic inflammatory joint disease, eg, rheumatoid arthritis[19]; other serious systemic diseases or malignancies; pregnancy; high blood pressure; or chronic administration of psychiatric, analgesic, or other medications that might influence the response to pain.

Experimental Protocol

A clinical examination according to the RDC/TMD criteria[18] was first performed by a single experimenter to confirm a diagnosis of myofascial TMD.[20] Then each subject participated in 2 sessions (separated by an interval of 12.2 ± 1.9 days), with the same experimenter in which they received either a single injection of 0.2 mL of ketamine (Ketalar 10 mmol/L; ~pH 7.0; Park Davis) or placebo (buffered isotonic saline NaCl 155 mmol/L, Alcon Lab) into the deep masseter muscle. One injection per session was given into the same masseter muscle by the same experimenter. The injection was made into the most painful point (as determined by palpation) of the masseter muscle over a 10-second period with a 27-gauge hypodermic needle and a disposable syringe. The treatment order was randomized between the 2 sessions by a clinical assistant, and neither the experimenter nor the volunteers were aware of the contents of the injections (double blind).

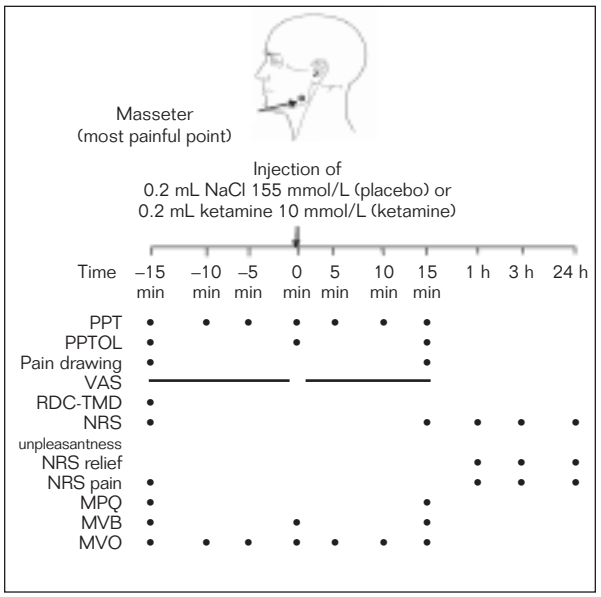

Fig 1 Schematic diagram of the experimental protocol.

The concentration of ketamine employed in the present study was based on the authors' previous work, which indicated that a concentration of 10 mmol/L ketamine selectively blocked glutamate-evoked masseter muscle pain in humans and nociceptor discharges in animals.[13,15] Figure 1 illustrates the experimental protocol.

Primary Outcome Parameters

Assessment of Pain Intensity. The volunteers continuously scored their pain intensity on a 10-cm electronic visual analog scale (VAS) with the lower extreme marked "no pain" and the upper extreme marked "most pain imaginable." Two separate recordings of 15 minutes were performed. The first started 15 minutes prior to injection and the second immediately after injection. Three parameters from the outputs of the electronic VAS were considered; the area under the curve (VAS AUC), the mean value of the pain rating during the time that the pain lasted (VAS mean), and the peak value of the pain rating (VAS peak). The VAS AUC was calculated by summation of all of the VAS recordings for each 15-minute epoch.

The patients were also asked to assess pain intensity prior to injection (–15 minutes) and after injection (1, 3, and 24 hours) on a 0-to-10 NRS. NRS pain was not assessed 15 minutes after injection but was determined instead from the electronic VAS data for the 15-minute postinjection time point (Fig 1).

Secondary Outcome Parameters

Assessment of Unpleasantness and Pain Relief. The patients were asked to assess with an NRS the intensity of the pain unpleasantness prior to injection (–15 minutes) and after injection (15 minutes and 1, 3, and 24 hours). In addition, the magnitude of pain relief in percentage (0% to 100%) was also registered on an NRS after injection (1, 3, and 24 hours).

Pressure Pain Threshold and Pressure Pain Tolerance. A pressure algometer (Somedic, Hörby, Sweden) was used to measure masseter muscle pressure pain threshold (PPT) and pressure pain tolerance (PPTOL) (kPa) bilaterally. During assessments, the patients were asked to keep their jaws at rest without tooth contact by maximum relaxation of the masticatory muscles. Pressure was applied with a 1-cm^2 diameter probe to the muscle at a rate of 30 kPa/s, and the volunteers pushed a button when they reached their PPT or PPTOL.[20] The PPTs and PPTOLs were determined from a single measurement every 5 and 15 minutes, respectively, except for the PPT at baseline (15 minutes prior to injection), which was the average of 2 repeated measurements (Fig 1).

McGill Pain Questionnaire and Pain Drawing. The volunteers were asked to fill out a Danish version of the McGill Pain Questionnaire (MPQ) form[21] and to draw the distribution of perceived pain on a lateral view of the face 15 minutes prior to the injection and 15 minutes after the injection (Fig 1). The pain drawings were digitized (Sigma Scan Pro 4.01.003) and expressed as arbitrary units.[22]

Maximum Voluntary Bite Force. The maximum voluntary bite force (MVB) was measured (kPa) between the incisors by asking the patient to bite on a bite-force transducer (Aalborg University, Aalborg, Denmark). They were encouraged to make their best effort to reach their maximum force and asked to release the pressure when this was reached. MVB was assessed 15 minutes prior to injection, immediately after the injection (0 min), and 15 minutes after the injection (Fig 1). The muscle pain evoked by the MVB task was assessed on a 0-to-10 cm NRS.

Maximum Voluntary Opening. The maximum voluntary opening (MVO) was recorded in millimeters with a metallic ruler between the incisal edges of the first incisors. The values of the vertical overlap between the incisors were added.[18] The recording was performed every 5 minutes from 15 minutes prior to the injection until 15 minutes after the injection (Fig 1). The muscle pain evoked by the MVO task was assessed on a 0-to-10 cm NRS.

Table 1 Baseline Clinical Characteristics of the Myofascial TMD Pain Patients Before the Placebo or Ketamine Session

	Placebo		Ketamine	
Baseline characteristics	Mean	SEM	Mean	SEM
Spontaneous pain (NRS 0 to 10)	4.0	0.5	3.6	0.5
Unpleasantness (NRS 0 to 10)	4.2	0.5	4.3	0.6
Maximum unassisted opening without pain (mm)	50.9	2.7	49.6	2.6
Maximum unassisted opening with pain (mm)	52.6	2.6	53.0	2.5
Maximum assisted opening with pain (mm)	53.8	2.7	54.1	2.7
Pain upon maximum opening (NRS 0 to 10)	4.4	0.5	3.9	0.6
No. of masticatory muscle sites with pain on palpation (0 to 20)	10.5	1.1	10.1	1.3
No. of TMJ sites with pain on palpation (0 to 4)	1.2	0.4	0.8	0.3

Mean age ± SEM, 28.3 ± 1.7 y; mean duration of myofascial TMD pain ± SEM, 8.0 ± 1.6 y. Two patients exhibited temporomandibular joint (TMJ) sounds.

Statistical Analysis

The present study was designed to be able to detect a decrease in pain of at least 25%. Power analyses indicated that 10 subjects would be needed to detect such a difference with an intraindividual variability of 20% and a risk of type I and II errors of 5% and 20%, respectively. Data were normalized to obtain the relative changes after injections. This was done by dividing the values obtained after the injections by the values obtained at baseline (15 minutes prior to the injections). Paired *t* tests were used for comparing sessions (placebo or ketamine injection) at baseline and for relative changes. Two-way repeated measures analysis of variance (ANOVA) with time and treatment as factors were used to determine whether there was an effect of treatment on primary and secondary outcome parameters. Tukey tests were used for post-hoc comparison when appropriate. Post-hoc Pearson correlation analyses were applied to test at 15 minutes post-ketamine injection (the time point that showed the strongest effect of ketamine in a previous study[15]) for an association between VAS relative changes and for changes from PPT or PPTOL baseline values in the ketamine session. The level of significance was set at $P < .05$.

Results

Baseline Values

Baseline clinical characteristics of the patients are shown in Table 1. There were no significant differences in clinical characteristics between patients first receiving the placebo injection and those first receiving the ketamine injection ($P > .423$; Table 1). Furthermore, there were no significant differences between the placebo and ketamine sessions in the baseline values (–15 minutes) of the various primary and secondary outcome parameters ($P > .139$; Table 2).

Primary Outcome Parameters

VAS Pain Intensity. Paired *t* tests were used to compare the relative changes of the VAS parameters: VAS AUC, VAS mean, and VAS peak values between treatments. There were no significant differences in these parameters between the ketamine and placebo sessions ($P > .483$).

NRS and VAS Pain. For statistical comparison purposes 8 different time point values were analyzed together with respect to NRS and VAS pain. NRS pain values from –15 minutes (baseline) and 1, 3, and 24 hours were analyzed, as were electronic VAS scores from 0, 5, 10, and 15 minutes (Fig 2). All the values were normalized to baseline. The test showed that there were no significant effects of treatment, time, or the interaction of treatment and time (Fig 2; ANOVA; $P > .761$).

Secondary Outcome Parameters

NRS Unpleasantness and NRS Pain Relief. ANOVAs of the relative changes of the NRS unpleasantness and the values of NRS pain relief did not reveal any significant treatment or time effect (ANOVAs: $P > .147$).

PPT and PPTOL. ANOVA of the PPT relative change values showed a significant effect of time (ANOVA: $P = .004$) but no effect of treatment and no interaction between treatment and time. Moreover, there was no significant effect of time or treatment on PPTOL (ANOVAs: $P > .072$).

Table 2 Baseline Primary and Secondary Outcome Parameters Values of the Myofascial TMD Pain Patients

	Placebo		Ketamine	
Baseline parameters	Mean	SEM	Mean	SEM
Primary outcome parameters				
VAS AUC (0 to 10,000)	2793.7	451.8	3181.5	485.7
VAS peak (0 to 10)	3.5	0.5	3.9	0.6
NRS pain (0 to 10)	4.0	0.5	3.6	0.5
Secondary outcome parameters				
NRS unpleasantness (0 to 10)	4.2	0.5	4.3	0.6
PPT (kPa)	134.5	12.4	135.8	12.9
PPTOL (kPa)	294.9	29.6	281.0	32.9
Pain drawing area (arbitrary units)	105.3	24.2	139.6	32.8
MPQ total scores (0 to 112)	11.5	2.0	12.1	2.4
MVB (kPa)	19.4	2.2	19.1	2.2
MVO (mm)	49.5	2.5	48.4	2.7

There were no significant differences in these baseline values between placebo and ketamine sessions ($P > .139$).

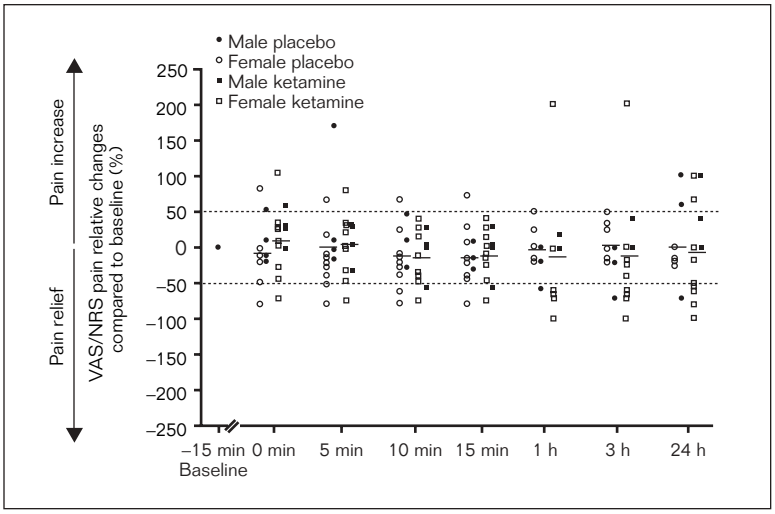

Fig 2 The horizontal black lines represent the mean values (n = 14) of the relative changes in NRS/VAS pain as a response to the placebo (NaCl 155 mmol/L) or ketamine (10 mmol/L ketamine) injection into the most painful part of the masseter muscle. There was no significant effect of sessions or time (ANOVAs: $P > .686$). Values at –15 minutes, 1 hour, 3 hours, and 24 hours were NRS pain scores, while those at 0 minutes, 5 minutes, 10 minutes, and 15 minutes were values obtained from the electronic VAS scores. Dotted lines represent 50% of relief and increase of pain after injections. There were 4 female patients with a decrease of ≥ 50% of their baseline pain levels of pain after 1, 3, and 24 hours following the injection of ketamine. One female patient reported a 200% increase 1 and 3 hours following the injection of ketamine.

Pain Drawings and MPQ. The relative changes of pain drawing area and MPQ total scores were compared with paired *t* tests. No significant effect of treatment was observed ($P > .364$).

MVB and MVO. The relative changes of MVB showed a significant time effect (ANOVA: $P = .030$) but no effect of treatment or any interaction between time and treatment. For MVO, there was a significant effect of treatment and time as well as interactions between treatment and time (ANOVAs: $P < .047$). Tukey post-hoc analyses showed differences between the 2 different treatments at 0, 5, 10, and 15 minutes (Tukey: $P < .31$). Moreover, in the ketamine session, there were significant differences between baseline and 5, 10, and 15 minutes (Tukey: $P < .008$; Fig 3).

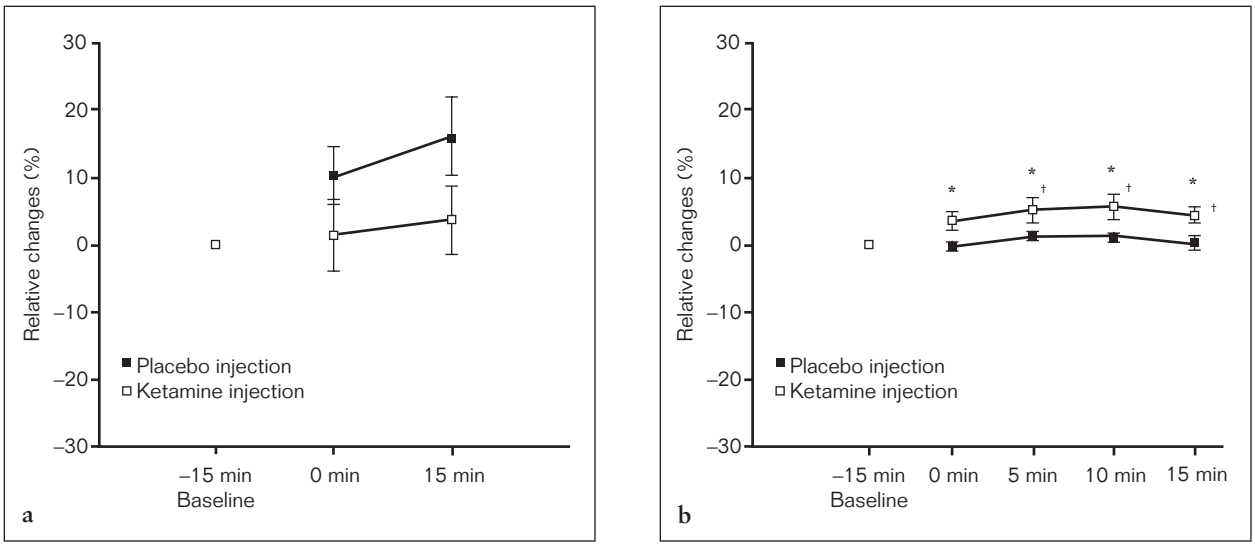

Fig 3 Mean values (± SEM; n = 14) of the relative changes of *(a)* MVB and *(b)* MVO in response to the 2 different types of injections (isotonic NaCl 155 mmol/L [placebo] or ketamine 10 mmol/L) into the most painful part in the masseter muscle. There was a time effect for MVB (ANOVA: $P = .030$). For MVO, there was a session effect (ANOVA: $P = .046$), a time effect (ANOVA: $P < .001$), and significant interaction between time and session (ANOVA: $P = .032$). Post-hoc analyses showed differences between groups at all time points (Tukey: $P < .031$; indicated by an asterisk) and differences from baseline in reaction to the ketamine injection (Tukey: $P < .007$; indicated by †).

Correlation

At 15 minutes post-ketamine, the time point that showed the strongest effect of ketamine in the authors' previous study,[15] post-hoc Pearson correlation analyses revealed no associations between PPT or PPTOL baseline values and the relative VAS changes in the ketamine session ($P > .520$).

Discussion

Glutamate by itself or through its interactions with other algesic substances may play an important role in the development and/or maintenance of chronic myofascial TMD pain conditions due to the activation of peripheral NMDA receptors. In animal models of masseter muscle pain, glutamate, or NMDA-induced activation of these receptors can be attenuated by NMDA receptor antagonists,[11–13,23] and in humans, local administration of the noncompetitive NMDA receptor antagonist ketamine has been shown to attenuate acute glutamate-evoked masseter muscle pain and glutamate-induced mechanical sensitization.[13,15] Moreover, some studies have demonstrated the presence of high levels of glutamate in patients with chronic painful tendinosis or myalgia in the trapezius muscle.[9,10] Therefore, it was logical that local administration of an NMDA receptor antagonist should attenuate pain in myofascial TMD patients. The results of this study showed that although some individual patients showed clinical pain relief, intramuscular injection of the NMDA receptor antagonist ketamine did not have a statistically significant effect on perceived pain intensity, NRS unpleasantness, NRS pain relief, pain drawing area, MPQ total scores, PPTs, or PPTOLs in chronic myofascial TMD pain patients. These findings contrast with the authors' earlier findings that local administration of ketamine attenuates acute pain and mechanical sensitization experimentally induced by glutamate injection into the masseter muscle of healthy humans.[15] These various findings are in line with previous studies which reported potent and long-lasting inhibition of the development of secondary hyperalgesia following an injection of the NMDA receptor antagonist ketamine on experimental cutaneous thermal injuries[24] but a lack of effect after the application of topical ketamine in patients with cutaneous (neuropathic) pain.[25]

The findings of the present study could be interpreted to suggest that activation of peripheral NMDA receptors may not play an important role in the maintenance of myofascial pain in TMD patients. However, limitations to this interpretation related to other glutamatergic-initiated effects and the concentration, volume, and disposition of intramuscularly injected ketamine need to be carefully considered before entirely ruling out a role for peripheral NMDA receptors in chronic myofascial TMD pain. For example, it has been suggested that only a brief elevation of intramuscular glutamate concentration is sufficient to trigger a cascade of events within the muscle and alter the response properties of muscle afferent fibers.[15] Furthermore, although the activation of peripheral NMDA receptors alone may be sufficient to induce mechanical sensitization upon injection of glutamate into the masseter muscle, this does not exclude the possibility of a contribution by other receptor mechanisms. There is evidence that non-NMDA receptors as well as metabotropic glutamate receptors may also contribute to glutamate-induced mechanical sensitization of the masseter muscle[12,26] and that elevated interstitial levels of glutamate in the masseter muscle could result in the release of neuropeptides[27]; these are mechanisms that could affect mechanical sensitivity without ongoing NMDA receptor activation and thus not be amenable to NMDA receptor blockade.

In the case of the concentration and volume of ketamine, the values used (10 mmol/L, 0.2 mL) for injection into the masseter muscle in this study were based on evidence from the authors' previous experimental studies, which indicated that this concentration of ketamine, when coinjected with glutamate, could significantly attenuate acute glutamate-evoked muscle pain and glutamate-induced mechanical sensitization of the masseter muscle in men and attenuate glutamate-evoked nociceptor discharge in male and female rats.[13,15] However, a recent study using this concentration of ketamine with glutamate found that it did not significantly attenuate either acute glutamate-evoked muscle pain or glutamate-induced mechanical sensitization in healthy young women.[7] The majority of chronic myofascial TMD pain sufferers in the present study were women. Although the number of male volunteers in this study was too small to determine any gender difference, it is possible that the absence of significant effects of ketamine on muscle pain resulted from too low a concentration being employed and that a higher concentration of ketamine might have shown more remarkable results. The problem with this approach is that while the present study demonstrated that 10 mmol/L ketamine does not exert nonselective, local anesthetic-like actions,[13] it is possible that higher concentrations of ketamine probably would exert local anesthetic effects and thus would have confounded interpretation of the data collected.[28]

The site of injection of ketamine in the current study was determined by palpation of each subject's masseter muscle to identify the area with the greatest hyperalgesic action. A limitation of this approach is that the relatively small volume of ketamine may not have permitted distribution of ketamine to a sufficient number of painful sites within the muscle to effect a significant decrease in the overall pain ratings. Indeed, injection of a similar volume of local anesthetic into the masseter muscle of TMD sufferers has previously been found to be no more effective than isotonic saline in reducing pain and mechanical sensitivity in myofascial TMD sufferers.[29,30] Another related factor may be the rapid clearance of ketamine from the masseter muscle. The blood flow in the masseter muscle is 3 times higher than in somatic muscles, and the clearance of other injected chemicals, such as glutamate (t1/2 ~100 seconds) is rapid, which suggests that ketamine may have been cleared from the masseter muscle at a rapid rate, limiting its ability to interact with peripheral NMDA receptors within the muscle.[31–33]

Another factor to consider for effects of ketamine is that there may be sex-related differences in pain perception mediated through activation of peripheral NMDA receptors. As already mentioned, acute glutamate-evoked masseter muscle pain is significantly attenuated by coinjection of ketamine in healthy young men but not in healthy young women.[7,13] In female but not male rats, the magnitude of masseter nociceptor discharge acutely evoked by activation of peripheral NMDA receptors is positively correlated with serum estrogen levels, a phenomenon that appears to be due to an estrogen-mediated increase in the number of masseter nociceptors that express NMDA receptors.[14] If this effect also occurs in women, it might explain not only why women report a greater intensity of pain than men after injection of glutamate into the masseter muscle but also why higher doses of ketamine might be required in women to adequately attenuate pain related to increased interstitial concentrations of glutamate. Unfortunately, there were too few male myofascial TMD patients in the present study to permit the analysis of sex-related differences in the effects of ketamine. However, the individual results of male volunteers in this study did not

reveal any major pain-relieving effects from the ketamine injection (Fig 2).

An additional consideration is that even though it has been suggested that human experimental models of pain applied to the orofacial area are valuable and can provide clinically relevant information, the myofascial TMD patients and the characteristics of their persistent pain experience are more complex than acute experimental pain. Those differences could be due to the fluctuation of pain, the chronicity of the pain, psychosocial distress, functional disabilities, and concomitant pain conditions that may influence their pain perception.[34] Such factors limit the direct comparison of the results obtained from clinical experiments on this type of patient with experimental pain in healthy human subjects.[34] Pain is influenced by a multitude of factors, including psychologic factors, that have been shown to be important determinants of the pain experience.[35,36] It has been reported that patients suffering from myofascial TMD pain dysfunction or atypical facial pain are more likely to show elevations in psychometric scales for hypochondriasis and depression.[36] It has also been shown that psychosocial variables, such as coping strategies, may have implications for the underlying physiology of pain and the prediction of important clinical outcomes, including pain severity and disability.[37] All these factors suggest awareness and caution when comparing the results of the current study with those obtained from human experimental pain models.

A final point of discussion is the interpretation of the results from the secondary outcome parameters, namely MVB and MVO. There were significant increases of MVB over time, but no difference between treatments. It is unclear why this occurred. On the other hand, there was a significant effect of time and treatment on MVO, with a significant improvement in this parameter after treatment with ketamine when compared with placebo control. While this is the first documentation that MVO may be influenced by NMDA receptor mechanisms in humans, it is consistent with findings in rats that a peripherally applied NMDA receptor antagonist reduces jaw-muscle clenching activity induced by elevated glutamate levels in deep craniofacial tissues.[38] However, alternative mechanisms such as changes in contractile properties of the muscle or modulation of non-nociceptive reflex circuitries could also be considered. Although the effect of ketamine used in the present study on MVO was statistically significant, the improvement in MVO was very small (< 5%); thus, the clinical significance of this finding is not clear.

Conclusions

In summary, there were no major effects of the local injection of ketamine on masseter muscle pain in chronic myofascial TMD pain patients. These results suggest that peripheral NMDA receptors do not play a major role in the pathophysiology of chronic myofascial TMD pain. Although there was a significant effect of ketamine on MVO, the clinical significance of this finding is not clear. The current findings do not support the treatment of chronic myofascial TMD pain patients with local injections of ketamine.

Acknowledgments

This research was supported by the US National Institutes of Health (grant DE 15420). The skillful help of Bente Haugsted is greatly appreciated.

References

1. Lobbezoo F, Drangsholt M, Peck C, Sato H, Kopp S, Svensson P. Topical review: New insights into the pathology and diagnosis of disorders of the temporomandibular joint. J Orofac Pain 2004;18:181–191.
2. Sessle BJ. Factors bearing on causes and of management orofacial pain [editorial]. J Orofac Pain 2006;20:189.
3. Sessle BJ. Animal models of chronic orofacial pain [editorial]. J Orofac Pain 2007;21:5.
4. Svensson P, Cairns BE, Wang K, et al. Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. Pain 2003;101:221–227.
5. Cairns BE, Wang K, Hu JW, Sessle BJ, Arendt-Nielsen L, Svensson P. The effect of glutamate-evoked masseter muscle pain on the human jaw-stretch reflex differs in men and women. J Orofac Pain 2003;17:317–325.
6. Wang K, Sessle BJ, Svensson P, Arendt-Nielsen L. Glutamate evoked neck and jaw muscle pain facilitate the human jaw stretch reflex. Clin Neurophysiol 2004;115: 1288–1295.
7. Castrillon E, Cairns BE, Ernberg M, et al. Effect of peripheral NMDA receptor blockade on glutamate-evoked masseter muscle pain and mechanical sensitization in women. J Orofac Pain 2007;21:216–224.
8. Cairns BE, Hu JW, Arendt-Nielsen L, Sessle BJ, Svensson P. Sex-related differences in human pain and rat afferent discharge evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2001;86:782–791.
9. Alfredson H, Forsgren S, Thorsen K, Lorentzon R. In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee. J Orthop Res 2001;19: 881–886.
10. Rosendal L, Larsson B, Kristiansen J, et al. Increase in muscle nociceptive substances and anaerobic metabolism in patients with trapezius myalgia: Microdialysis in rest and during exercise. Pain 2004;112:324–334.

11. Cairns BE, Dong X, Mann MK, et al. Systemic administration of monosodium glutamate elevates intramuscular glutamate levels and sensitizes rat masseter muscle afferent fibers. Pain 2007;132:33–41.
12. Cairns BE, Gambarota G, Svensson P, Arendt-Nielsen L, Berde CB. Glutamate-induced sensitization of rat masseter muscle fibers. Neuroscience 2002;109:389–399.
13. Cairns BE, Svensson P, Wang K, et al. Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2003;90: 2098–2105.
14. Dong XD, Mann MK, Kumar U, et al. Sex-related differences in NMDA-evoked rat masseter muscle afferent discharge result from estrogen-mediated modulation of peripheral NMDA receptor activity. Neuroscience 2007;146:822–832.
15. Cairns BE, Svensson P, Wang K, et al. Ketamine attenuates glutamate-induced mechanical sensitization of the masseter muscle in human males. Exp Brain Res 2006; 169:467–472.
16. Sawynok J. Topical and peripherally acting analgesics. Pharmacol Rev 2003;55:1–20.
17. Annetta MG, Iemma D, Garisto C, Tafani C, Proietti R. Ketamine: New indications for an old drug. Curr Drug Targets 2005;6:789–794.
18. Dworkin SF, LeResche L. Research Diagnostic Criteria for Temporomandibular Disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
19. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31:315–324.
20. Svensson P, Arendt-Nielsen L, Nielsen H, Larsen JK. Effect of chronic and experimental jaw muscle pain on pain-pressure thresholds and stimulus-response curves. J Orofac Pain 1995;9:347–356.
21. Drewes AM, Helweg-Larsen S, Petersen P, et al. McGill Pain Questionnaire translated into Danish: Experimental and clinical findings. Clin J Pain 1993;9:80–87.
22. Svensson P, Graven-Nielsen T, Arendt-Nielsen L. Mechanical hyperesthesia of human facial skin induced by tonic painful stimulation of jaw muscles. Pain 1998;74: 93–100.
23. Dong XD, Mann MK, Kumar U, et al. Sex-related differences in NMDA-evoked rat masseter muscle afferent discharge result from estrogen-mediated modulation of peripheral NMDA receptor activity. Neuroscience 2007;146:822–832.
24. Warncke T, Jorum E, Stubhaug A. Local treatment with the N-methyl-D-aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action. Neurosci Lett 1997;227:1–4.
25. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: A randomized, double-blind, placebo-controlled trial. Anesthesiology 2005;103:140–146.
26. Ro JY, Capra NF, Lee JS, Masri R, Chun YH. Hypertonic saline-induced muscle nociception and c-fos activation are partially mediated by peripheral NMDA receptors. Eur J Pain 2007;11:398–405.
27. Hargreaves KM, Swift JQ, Roszkowski MT, Bowles W, Garry MG, Jackson DL. Pharmacology of peripheral neuropeptide and inflammatory mediator release. Oral Surg Oral Med Oral Pathol 1994;78:503–510.
28. Brau ME, Sander F, Vogel W, Hempelmann G. Blocking mechanisms of ketamine and its enantiomers in enzymatically demyelinated peripheral nerve as revealed by single-channel experiments. Anesthesiology 1997;86:394–404.
29. McMillan AS, Blasberg B. Pain-pressure threshold in painful jaw muscles following trigger point injection. J Orofac Pain 1994;8:384–390.
30. Tschopp KP, Gysin C. Local injection therapy in 107 patients with myofascial pain syndrome of the head and neck. ORL J Otorhinolaryngol Relat Spec 1996;58: 306–310.
31. Palmer GM, Cairns BE, Berkes SL, Dunning PS, Taylor GA, Berde CB. The effects of lidocaine and adrenergic agonists on rat sciatic nerve and skeletal muscle blood flow in vivo. Anesth Analg 2002;95:1080–1086.
32. Cairns BE, Gambarota G, Dunning PS, Mulkern RV, Berde CB. Activation of peripheral excitatory amino acid receptors decreases the duration of local anesthesia. Anesthesiology 2003;98:521–529.
33. Gambarota G, Philippens M, Cairns BE, Dong XD, Renema WK, Heerschap A. MRS assessment of glutamate clearance in a novel masticatory muscle pain model. NMR Biomed 2005;18:345–351.
34. Svensson P. What can human experimental pain models teach us about clinical TMD? Arch Oral Biol 2007;52: 391–394.
35. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1975;1:277–299.
36. Rollman GB, Gillespie JM. The role of psychosocial factors in temporomandibular disorders. Curr Rev Pain 2000;4:71–81.
37. Turk DC, Okifuji A. Psychological factors in chronic pain: Evolution and revolution. J Consult Clin Psychol 2002;70:678–690.
38. Cairns BE, Sessle BJ, Hu JW. Evidence that excitatory amino acid receptors within the temporomandibular joint region are involved in the reflex activation of the jaw muscles. J Neurosci 1998;18:8056–8064.