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Analgesic and Anti-Hyperalgesic Effects of Muscle Injections with Lidocaine or Saline in Patients with Fibromyalgia Syndrome

Roland Staud¹, Elizabeth E. Weyl¹, Emily Bartley², Donald D. Price³, and Michael E. Robinson²

¹Department of Medicine, University of Florida, Gainesville, USA

²Department of Clinical and Health Psychology, University of Florida, Gainesville, USA

³Department of Oromaxillary Surgery, University of Florida, Gainesville, USA

Abstract

Background—Patients with musculoskeletal pain syndrome including fibromyalgia (FM) complain of chronic pain from deep tissues including muscles. Previous research suggests the relevance of impulse input from deep tissues for clinical FM pain. We hypothesized that blocking abnormal impulse input with intramuscular lidocaine would decrease primary and secondary hyperalgesia and FM patients' clinical pain.

Methods—We enrolled 62 female FM patients into a double-blind controlled study of 3 groups who received 100 mg or 200 mg lidocaine or saline injections into both trapezius and gluteal muscles. Study variables included pressure and heat hyperalgesia as well as clinical pain. In addition, placebo factors like patients' anxiety and expectation for pain relief were used as predictors of analgesia.

Results—Primary mechanical hyperalgesia at the shoulders and buttocks decreased significantly more after lidocaine than saline injections ($p = .004$). Similar results were obtained for secondary heat hyperalgesia at the arms ($p = .04$). After muscle injections clinical FM pain significantly declined by 38% but was not statistically different between lidocaine and saline conditions. Placebo related analgesic factors (e.g. patients' expectations of pain relief) accounted for 19.9% of the variance of clinical pain after the injections. Injection related anxiety did not significantly contribute to patient analgesia.

Conclusion—These results suggest that muscle injections can reliably reduce clinical FM pain and that peripheral impulse input is required for the maintenance of mechanical and heat hyperalgesia of FM patients. Whereas the effects of muscle injections on hyperalgesia were greater for lidocaine than saline, the effects on clinical pain were similar for both injectates.

Corresponding author: Roland Staud, M.D., Department of Medicine University of Florida College of Medicine, Gainesville, FL 32610-0221, USA, Telephone: (352) 273-9681, Fax: (352) 392-8483, staudr@ufl.edu.

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Authors Contribution

R.S., E.E.W., E.B., D.D.P., and M.E.R. had substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; R.S., D.D.P., and M.E.R. draft the article or revised it critically for important intellectual content; R.S., E.E.W., E.B., D.D.P., and M.E.R. finally approved the version to be published.

Introduction

Fibromyalgia is a chronic musculoskeletal disorder whose pathogenesis is only partially understood. It is characterized by widespread pain, tenderness, stiffness, and non-refreshing sleep (Wolfe, 1990; Wolfe et al., 1997). Other symptoms include depression, anxiety, and pronounced fatigue (Wolfe, 1990). Although FM pain is widespread, most patients' pain is centered on several body areas including the shoulders, neck, and low back (Staud et al., 2004). Most FM patients demonstrate mechanical and thermal hyperalgesia which is highly predictive of their clinical pain intensity (Staud et al., 2012). This pronounced hypersensitivity has focused increasing interest on central nervous system mechanisms for FM including central sensitization and central disinhibition (Staud et al., 2003; Staud, 2012). However, preliminary evidence has suggested that such central pain processing abnormalities may be at least partially sustained by peripheral impulse input (Affaitati et al., 2011; Staud et al., 2009).

It is well known that chronic nociceptive input can result in central sensitization as well as increased pain and pain sensitivity. Thus, central sensitization of FM patients may rely on peripheral input for its development and maintenance. Possible nociceptive factors include muscle micro-traumas and peripheral ischemia of deep tissues associated with autonomic dysregulation and other factors that could lead to increased sensitivity and/or activation of muscle nociceptors (Vierck, Jr., 2006). Activated muscle nociceptors may be highly effective in sensitizing dorsal horn neurons and may contribute to widespread pain.

A recent study found that repeated lidocaine injections into myofascial trigger points at the shoulders reduced clinical FM pain and number of tender points (Affaitati et al., 2011), yet the mechanisms for this effect are unclear. Using quantitative sensory tests applied to forearms of FM patients, we found that a single 50 mg lidocaine but not saline injection into the trapezius muscle attenuated secondary heat hyperalgesia (Staud et al., 2009). This remarkable finding provides preliminary evidence that impulse input from muscle induces and maintains central sensitization associated with other tissues (i.e. skin) and distal sites.

To further test the importance of tonic peripheral impulse input for central sensitization in FM, we evaluated the effects of escalating doses of lidocaine on clinical pain and hyperalgesia of FM patients. In addition, we assessed not only the unique contributions of lidocaine and saline injections but also the role of placebo factors, including patients' expectations, on chronic pain mechanisms. Placebo factors have exerted strong effects on pain in previous studies of muscle injections with local anesthetics (Hong, 1994a; Hong, 1994b; Hong and Hsueh, 1996a; Hsieh et al., 2007; Kamanli et al., 2005; Scott et al., 2009). Specifically, patients' expectations for pain relief have been found to powerfully modulate analgesia (Price et al., 2008) similar to conditioned pain modulation from needle insertion into deep tissues (Yarnitsky, 2010).

2. Methods

2.1 Study Participants

Subjects were recruited from the local community and FM support groups. Informed consent was obtained from all participants and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The University of Florida Institutional Review Board approved the protocol and procedures for this study. Prior to testing, all subjects underwent a clinical examination and were excluded from the study if they had abnormal findings unrelated to FM. Use of analgesics, including non-steroidal anti-inflammatory drugs (NSAID) and acetaminophen, was not allowed during the study. All subjects were asked to discontinue analgesics for the duration of five drug half-lives before testing, except narcotics which had to be stopped at least two weeks prior to study entry. Low dose muscle relaxants and/or tricyclic antidepressants (10 mg/day) were permissible during the study for treatment of insomnia.

2.2 Inclusion and exclusion criteria

Inclusion criteria for participants were 1) adults over the age of 18; 2) the ability to give informed consent; 3) Subjects had to fulfill the 1990 American College of Rheumatology Criteria for FM including wide-spread pain (Wolfe et al., 1990). Exclusion criteria were 1) a relevant medical condition besides FM; 2) current participation in another research protocol that could interfere or influence the outcome measures of the present study; 3) the inability to give informed consent; 4) current use of analgesic drugs, hypnotic, or anxiolytic drugs.; 4) previous allergic reaction to lidocaine; 5) previous muscle injections with local anesthetics.

2.3 Experimental Design

This study used a parallel group design with 3 groups of FM subjects. All subjects were trained to rate threshold mechanical and suprathreshold heat pulses to the shoulders, arms, back, and legs. The subjects received experimental pain stimuli immediately before and 30 min after muscle injections into both shoulders and gluteal muscles. All experimental pain tests were counter-balanced to avoid order effects. The subjects were lying comfortably on a table during quantitative sensory testing but were asked to sit up during the muscle injections. The interval between heat and muscle stimuli was always 15 s or until pain after-sensations (AS) were no longer reported by the subjects.

2.4 Ratings of Experimental/Clinical Pain and Anxiety

A 15 cm mechanical visual analogue scale (mVAS; 0–10) was used for ratings of experimental and clinical pain (Price et al., 1994). This scale is anchored on the left with “no pain at all” and on the right with “the most intense pain imaginable”.

For ratings of anxiety a similar mVAS was used as for ratings of experimental pain. This scale, however, was anchored on the left by “no anxiety at all” and on the right by “most anxiety imaginable”.

2.5 Muscle Injections

Each subject received 2 muscle injections into the center of each trapezius muscle and 2 injections into the upper medial quadrants of both gluteus maximus muscles (see Figure 1). The order of injections was counterbalanced. These areas were selected because they correspond to frequently reported pain areas of FM patients. Study medication was prepared in syringes by nurses not involved in the injections. Each syringe used for muscle injections contained either 5 ml of 1% lidocaine (50 mg) or 5 ml of normal saline. To assess a dose effect of lidocaine on clinical pain and hyperalgesia the participants were randomized into 3 equally sized groups: a) group 1 received 4 lidocaine injections (Lidocaine 4); b) group 2 received 2 lidocaine + 2 saline injections (Lidocaine 2); and c) group 3 received 4 saline injections. The injections were conducted as subjects were seated on the examination table connected to a cardiac and automatic blood pressure/pulse monitor. The study physician provided the following instructions for the participants: “the injections that are you going to receive contain either a local anesthetic or placebo”. Then he slowly injected the content of each syringe into the designated muscles over 2 min in counter-balanced order (Figure 1).

30 min and 60 min after the muscle injections venous blood was drawn for analysis of lidocaine concentrations. These blood samples were immediately sent to the lab for analysis.

2.6 Expectations for Pain Relief and Treatment Allocation

Immediately after the 4 muscle injections the participants were asked to rate the overall pain level they expected to have after these injections, using the mVAS. They were also asked to indicate by forced choice whether they believed they had received active study medication or placebo.

2.7 Experimental Pain Stimuli

Experimental heat stimuli were applied to: a) 3 marked areas on the volar surface of both forearms (areas were separated by 3 cm); and b) the midpoint of the calf 5 cm lateral to the tibia over the anterior tibialis muscle. For each heat stimulus, the technician placed the thermode on each subject's skin using light pressure while the participant was resting comfortably on the examination table. Pressure stimuli were given to a) the midpoint of both trapezius muscles; b) web space between 1st and 2nd fingers of the hands; c) the medial upper quadrant of the gluteus maximus muscles; d) the midpoint of the calf 5 cm lateral to the tibial bone over the anterior tibialis muscle. Each heat and pressure stimulus was repeated 3 times in counterbalanced order. The interval between stimuli was always 10 s or until after-sensations were no longer reported by the subjects. All test areas were marked prior to stimulus application.

2.7.1 Heat Testing

2.7.1.1 Thermal probe: Precise heat pulses were generated by a Peltier thermode (Pathways; Medoc Advanced Medical Systems, Ramat Yishai, Israel). The heat probe is comprised of a Peltier element that provides fast heating rates of up to 10°C/s and cooling rates of up to 8°C/s. The thermode provides stimulation of a skin area of 3 × 3 cm (surface

area: 9 cm²). Special hardware and software allows precise temperature control. The thermal sensors of the thermode were calibrated before the experiments.

2.7.1.2 Heat Stimuli: The participants received three 10 s heat pulses of 44°C at each location. The temperature of the heat pulses increased from 35°C to 44°C over 6 s and was maintained at the peak temperature for 4 s. In addition, they received 10 s 45°C heat pulses at the same locations. The subjects were asked to rate the sensation intensities after each heat pulse using the mVAS. The average of all heat pulse ratings obtained at each location was used for statistical analyses.

2.7.2 Mechanical Pain Threshold Testing

2.7.2.1 Dolorimeter: A calibrated electronic dolorimeter (Wagner Force Measurement, Greenwich, CT) was utilized for 10 s pressure stimuli. The rubber tip of the dolorimeter was 1 cm in diameter.

2.7.2.2 Mechanical Stimuli: For testing of pressure pain thresholds the electronic dolorimeter was applied to a) the center of the shoulders (trapezius muscle), b) the gluteal muscles, c) both arms, and d) both legs using an ascending method of limits. Test locations were counterbalanced to prevent order effects. After the dolorimeter was placed on the target area, pressure was gradually increased by 0.5 kg/s until the subject reported pain for the first time. The average of 3 threshold ratings obtained at the same location was used for statistical analysis.

2.8 Tender Point Testing

Nine paired TPs as defined by the ACR Criteria (Wolfe et al., 1990) were assessed by a trained investigator using the Wagner dolorimeter. The dolorimeter was placed on the examination site, and pressure was gradually increased by 1kg/s. The subjects were instructed to immediately report when the sensation at the examination site changed from pressure to pain. Pressure testing was stopped at that moment and the result recorded as positive (1) if maximal pressure was 4 kg. If no pain was elicited at 4 kg the test results were recorded as negative (0).

2.9 Data Analysis

Statistical analyses were calculated using SPSS 20.0 software (SPSS, Inc., Chicago, IL). Clinical pain, age, and TPs were analyzed by one-way ANOVAs. The effects of muscle injections on experimental mechanical and heat pain ratings of FM subjects were analyzed by MANOVA to assess the overall effects of muscle injections on pain ratings. Subsequently, significant effects of muscle injections on individual experimental pain ratings were analyzed by repeated measures ANOVAs, to examine relative effects of peripheral and central factors. Significant main and interaction effects were decomposed with t- tests. Hierarchical linear regressions were performed to assess the contributions of placebo factors to clinical and experimental pain ratings.

3. Results

We enrolled 62 female subjects into this study who fulfilled the 1990 ACR Criteria for FM. The subjects were randomly allocated to 3 groups: 20 participants received 4 lidocaine, 21 participants received 2 lidocaine + 2 saline, and 21 participants received 4 saline injections. The mean age (SD) of study participants was 45.8 (14.8) years. A one-way ANOVA demonstrated no significant age differences between the 3 groups ($p > .05$) (Table 1). The average (SD) number of tender points of FM subjects was 17.5 (1.2) (Table 1) and was not significantly different between groups ($p > .05$).

3.1 Effects of Treatments on Clinical and Experimental Pain Ratings

The treatments included: Saline 4, Lidocaine 2 + Saline 2, and Lidocaine 4. The subjects underwent testing of pressure pain thresholds and 10 s heat pulses. Only the results from the 44°C heat pulse comparisons are reported here because the 45°C heat pulse comparisons did not provide systematically different results. Furthermore, because heat and mechanical pain ratings did not significantly differ between the subjects' right and left side ($p > .05$) the results of both sides were collapsed and averages were used for subsequent analyses.

3.1.1 Effects of Treatments on Mechanical and Heat Hyperalgesia—All subjects received 2 muscle injections into the shoulders (trapezius muscles) and 2 muscle injections into the low back (gluteal muscles). Before and after the injections pressure pain thresholds and heat pain ratings were obtained at the shoulders, low back, arms, and legs. A MANOVA was used to test the effects of muscle injection on heat and pressure pain ratings at the shoulders, arms, legs, and low back. Within subjects' factors were heat pain ratings at the arms and legs and pressure pain ratings at the shoulders and low back. Between subjects' factor was time (2). There was a significant time ($(F(1,59) = 51.6; p < .001)$) and time x treatment effect ($(F(1,59) = 6.8; p = .01)$) noted, indicating that lidocaine was more effective than saline in reducing heat and mechanical hyperalgesia. After repeated measures ANOVA did not show significantly different effects on heat or mechanical hyperalgesia (time x lidocaine dose interactions: $p > .05$) between Lidocaine 2 or Lidocaine 4 injections the results of both lidocaine conditions were collapsed for further analysis. Several repeated measures ANOVAS of experimental pain ratings were performed with time (2) as the within and treatment (2) as the between subjects' factor to decompose the effects of muscle injections on mechanical and heat hyperalgesia.

3.1.1.1 Treatment Effects on Mechanical Pain Thresholds

3.1.1.1.1 Shoulders: Mechanical pain thresholds increased after the *Shoulder* injections in FM subjects after both saline and lidocaine injections (Figure 2). There was a significant effect of time ($F(1,55) = 47.9; p < .001$; partial $\eta^2 = .63$) and time x treatment interaction noted ($F(1,55) = 9.2; p = .004$), demonstrating that lidocaine increased mechanical pain thresholds at the shoulder more than saline.

3.1.1.1.2 Low back: Again, a repeated measures ANOVA showed a significant main effect of time ($F(1,57) = 11.7; p = .001$) indicating that mechanical pain thresholds increased after the muscle injections (Figure 3). In addition, the time x treatment interaction was significant

($F(1,57) = 6.3$; $p = .02$), indicating that pressure pain threshold increased significantly more after lidocaine than saline injections.

3.1.1.1.3 Arms: A repeated measures ANOVA was used to assess the effects of muscle injections on mechanical hyperalgesia at the arms. Within subjects' factor was time and between subjects' factor was treatment. A significant main effect of time indicated that mechanical pain threshold at the arms increased after muscle injections ($F(1,56) = 7.6$; $p = .008$). However, the time $\times$ treatment interaction was not significant ($p > .05$) demonstrating that lidocaine and saline were similarly effective (Figure 4).

3.1.1.1.4 Legs: Similar to the arms, mechanical pain thresholds at the legs were tested with repeated measures ANOVAs. Mechanical pain thresholds significantly increased after the injections ($F(1,56) = 8.2$; $p = .006$) (Figure 4). However, the time $\times$ treatment interactions were not significant ($p > .05$) demonstrating that lidocaine and saline were similarly effective on mechanical hyperalgesia at the legs.

3.1.1.2 Treatment Effects on Heat Pain

3.1.1.2.1 Arms: A repeated measures ANOVA with time as within subjects' factor and treatment as the between subjects' factor demonstrated a significant main effect of time indicating that heat pain ratings at the arms decreased after muscle injections ($F(1,46) = 18.6$; $p < .001$). There was also a significant time $\times$ treatment interaction noted ($F(1,46) = 4.3$; $p = .04$) (Figure 5). These findings demonstrate that lidocaine injections decreased heat pain ratings at the arms significantly more than saline.

3.1.1.2.2 Legs: Similar to the arms, heat pain ratings at the legs was tested with repeated measures ANOVA. Heat hyperalgesia significantly decreased after the injections ($F(1,55) = 95$; $p < .001$) (Figure 5). However, the time $\times$ treatment interactions was not significant ($p > .05$) demonstrating that lidocaine and saline were similarly effective on heat pain at the legs.

3.1.2 Treatment Effects on Clinical Pain—Average (SD) overall clinical pain ratings of all FM participants at the beginning of the trial were 6.1 (3.8) mVAS units (Figure 6). A one-way ANOVA did not show significantly different pain ratings between FM subjects assigned to the different treatment groups ($F(2,61) = 3.0$; $p > .05$). Thirty minutes after the muscle injections, the subjects' average overall clinical pain ratings were reduced to 3.8 (1.8) mVAS units. A repeated measures ANOVA of clinical pain ratings with time as within subjects' factor and treatment modality as between subjects' factor showed a significant effect of time ($F(1,54) = 110.4$; $p < .001$) but demonstrated no significant effect of treatment modality ($F(2,54) = .7$; $p > .05$) or time $\times$ treatment modality interaction ($F(2,54) = 1.3$; $p > .05$) indicating that FM subjects' clinical pain improved regardless of treatment modality.

3.2 Effects of Expectation and Anxiety (Placebo Factors) on Pain Relief

Immediately before the muscle injections the FM subjects were asked to rate how anxious they felt and immediately after the injections they were asked to rate how much pain relief they expected. On average, they expected their pain to be reduced by 1.6 (2.4) mVAS units

which corresponds to 28.7 (59.9) % improvement of their pain. A one-way ANOVA demonstrated that expectations of all FM treatment groups were similar across saline, 100 mg lidocaine, and 200 mg lidocaine treatments ($F(2,59) = .1$; $p > .05$). Additionally, no significant differences in mean anxiety levels were found across all 3 groups ($F(2,59) = .26$; $p > .05$).

Hierarchical linear regression was used to assess the effects of expected pain relief and anxiety on clinical pain intensity after the muscle injections. Both factors were entered in separate blocks. The combination of expectations and anxiety accounted for 19.9 % of the variance in clinical pain intensity of FM subjects (Table 2). However, only the contributions of expectations for pain relief were statistically significant ($p = .003$).

3.3 Drug Allocation Concealment

In order to test whether FM subjects had correctly guessed their treatment allocation they were asked after the muscle injections by forced choice whether they had received active study medication or placebo. A one-way ANOVA demonstrated no significant effects of treatment on subjects' estimates ($F(2,59) = .033$; $p > .05$). This confirms that the subjects were unable to detect whether they had received active study medication or placebo during this study.

3.4 Lidocaine Blood Levels

Blood lidocaine concentrations were tested 30 min and 60 min after the muscle injections (Table 3). A repeated measures ANOVA demonstrated that blood lidocaine concentrations were significantly higher after Lidocaine 4 than Lidocaine 2 injections ($F(2,58) = 54.7$; $p < .001$). The analysis also indicated that lidocaine blood levels slightly decreased from 30 min to 60 min ($F(1,58) = 18.5$; $p < .001$).

4. Discussion

Muscle injections with lidocaine significantly reduced clinical pain as well as mechanical and heat hyperalgesia of FM patients. For hyperalgesia this effect was significantly greater after lidocaine compared to saline injections. However clinical pain was similarly reduced after lidocaine or saline injections, suggesting different contributions of additional factors to overall analgesia compared to hyperalgesia of FM patients.

4.1 Anti-Hyperalgesic Effects of Lidocaine

Our study demonstrated large effects of lidocaine injections on mechanical and heat hyperalgesia of FM patients. In comparison to saline, lidocaine muscle injections (2 into the trapezius and 2 into the gluteal muscles) of FM patients resulted in significantly greater overall reductions of mechanical and heat hyperalgesia of study participants. Lidocaine injections increased pressure pain thresholds at both shoulders and low back. Similar reductions were detected for secondary heat hyperalgesia at both arms. These effects were not different between 100 mg and 200 mg lidocaine injections, suggesting ceiling effects. Importantly, FM patients were unable to distinguish lidocaine from saline injections indicating successful blinding of study participants to treatment allocation. These results

extend our previous observations of FM patients after a single 50 mg lidocaine injection into one shoulder muscle that resulted in reduced mechanical hyperalgesia at the shoulder and heat hyperalgesia at the ipsilateral arm (Staud et al., 2009). The present study adds further support for the important role of peripheral impulse input for dynamically maintaining central sensitization in FM patients, similar to other chronic pain conditions (Gracely et al., 1992; Maixner et al., 1998).

Our results indicate that lidocaine injections had mostly local and not systemic effects because reductions of mechanical and heat hyperalgesia were limited to several specific body areas and not global.

4.2 Contribution of Multiple Factors to Clinical Pain Reduction

Overall, muscle injections resulted in 38% reduction of clinical pain. Similar effect sizes have been reported as clinically significant in pharmacological pain trials of FM and neuropathic pain patients (Farrar et al., 2010). These analgesic effects, however, were not dependent on lidocaine but were also observed after saline injections. Inclusion of a “Natural History” condition in our study allowed estimating placebo effects on clinical pain ratings related to muscle injections. Our analyses demonstrated that 19.9 % of clinical pain reductions were related to placebo related factors including expectations for pain relief and anxiety (Table 2). Thus other factors may have contributed large amounts of the variance (approx. 80%) to pain relief and reductions of hyperalgesia. Such factors likely included activation of endogenous analgesic mechanisms associated with “injection procedures” such as stress analgesia (Butler and Finn, 2009) and/or conditioned pain modulation (Yarnitsky, 2010).

4.3 Analgesic Factors Related to Muscle Injections

We have previously demonstrated limited but specific effects of a single 50mg lidocaine injection into the trapezius muscle on primary mechanical and secondary heat hyperalgesia of FM patients (Staud et al., 2009). Although hyperalgesia was significantly reduced, a single lidocaine injection did not change clinical FM pain ratings. This lack of effectiveness of lidocaine on clinical pain ratings is puzzling because hyperalgesia represents an important mechanism for clinical pain (Coderre et al., 1993; Mannion and Woolf, 2000; Staud et al., 2012). A single lidocaine injection however may have resulted in analgesic effects too small to be reliably detected. Although our present study showed significant reductions of clinical FM pain ratings after 4 muscle injections, these effects were likely the results of several analgesic factors, including placebo factors and effects of local mechanical tissue stimulation from injections. Since many of these factors can contribute to pharmacological analgesia (Benedetti et al., 2005) they may have interfered with our ability to detect statistical differences between lidocaine and saline analgesia in the case of clinical pain. These findings do not necessarily imply that peripheral impulse input is irrelevant for FM pain and hyperalgesia. Analgesia related to muscle injections with lidocaine has been reported in other studies with different study designs (Affaitati et al., 2009; Affaitati et al., 2011; Giamberardino et al., 2011). Our experimental design and analyses, however, were unique in providing estimates of placebo-related factors within all groups of subjects including those receiving saline or lidocaine

4.4 Tonic Peripheral Impulse Input in FM

Widespread mechanical and heat hyperalgesia are not only the hallmarks of FM (Desmeules et al., 2003; Graven-Nielsen and Arendt-Nielsen, 2010; Hurtig et al., 2001; Sorensen et al., 1998; Staud et al., 2010) but can also predict large amounts of the variance in clinical FM pain (Staud et al., 2012). Although no consistent deep tissue abnormalities have been identified in FM patients, local muscle changes including blood flow abnormalities have been reported (Park et al., 2000; Staud, 2007; Vierck, Jr., 2006). Such abnormalities could be responsible for increased peripheral impulse input necessary for initiation and maintenance of FM hyperalgesia and pain. Worsening of FM pain and muscle hyperalgesia has been reported with isometric exercise (Kosek and Lundberg, 2003; Staud et al., 2005) and reductions of overall FM pain were demonstrated after rest (Staud et al., 2010). The critical importance of peripheral impulse input for FM pain and hyperalgesia is also attested by the fact that lidocaine has been effectively utilized for the treatment of FM pain using either local injections (Hong and Hsueh, 1996b) or intravenous infusions (McCleane, 2000; Posner, 1995). In some placebo controlled studies intravenous lidocaine reduced clinical FM pain by more than 50 % and this effect lasted for up to 7 days (Sorensen et al., 1995). These studies, however, were not designed to separately evaluate the peripheral and central nervous system (CNS) contributions to analgesia.

4.5 Study Limitations

The dose dependent increase of serum lidocaine levels observed after the muscle injections raises concerns about systemic analgesic effects related to this medication. It is noteworthy, however, that lidocaine produced significant reductions in mechanical and heat hyperalgesia at the shoulders, arms, and low back areas but not at the legs. Such local anti-hyperalgesic effects argue against systemic effectiveness of lidocaine. Although it is puzzling that heat hyperalgesia at the legs was not significantly decreased after lidocaine in comparison to saline injections, the basis for such differential effects of local anesthesia in different body areas needs to be addressed in future studies.

4.6 Conclusions

Muscle injections can effectively reduce mechanical and heat hyperalgesia as well as clinical pain of FM patients. The anti-hyperalgesic effects of lidocaine support the combined roles of tonic peripheral impulse input and central sensitization in FM and other forms of chronic pain. While lidocaine effects on mechanical and heat hyperalgesia were demonstrated in our study, other factors may have obscured the superiority of lidocaine compared to saline injections on clinical pain ratings. Such interfering factors include placebo analgesia as well as analgesia related to needle insertion and deep tissue injections.

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Bulleted statements**What's already known about this topic?**

- The role of peripheral nerve impulse input for FM pain and hyperalgesia is not well understood. Mostly indirect evidence is available suggesting deep tissue nociception as relevant for clinical FM Pain.

What does this study add?

- This study demonstrates that nerve impulse input from muscles significantly contributes to clinical FM pain and hyperalgesia.
- However, analgesic factors other than lidocaine injections seem to be equally effective in reducing clinical FM pain.

Figure 1.

Experimental design of muscle injections: Three groups of FM subjects were treated either with 4 Lidocaine (Lidocaine 4), 4 Saline (Placebo), or 2 Lidocaine + 2 Saline injections (Lidocaine 2). All subjects received 2 injections into the trapezius muscles and 2 injections into the gluteal muscles.

Figure 2.

Effects of lidocaine or saline injections on pressure pain thresholds (PPT) at the shoulders. PPTs of FM subjects significantly increased after saline or lidocaine injections ($p < .001$). However, PPT increase was significantly greater after lidocaine than saline injections ($p = .004$).

Figure 3. Effects of lidocaine or saline injections on pressure pain thresholds (PPT) at the gluteal muscles. PPTs of FM subjects at the gluteal muscles significantly increased after lidocaine ($p < .001$) but not after saline injections ($p > .05$).

Figure 4. Effects of lidocaine or saline injections on pressure pain thresholds (PPT) at the arms and legs. None of the injections had a significant effect on PPTs at the arms or legs (all $p > .05$) of FM subjects. ns = non-significant

Figure 5.

Effects of lidocaine or saline injections on heat pain ratings at the arms and legs. All subjects received 10 s 44 C ramp and hold heat pulses at the arms and legs. Only the lidocaine but not saline injections significantly decreased heat pain ratings of FM subjects at the arms ($p < .001$). Neither lidocaine nor saline had a significant effect on heat pain ratings at the legs ($p > .05$). ns = non-significant

Figure 6.

Average (SD) clinical pain ratings of FM subjects before and 1 hour after saline, 100 mg lidocaine (Lidocaine 2), or 200 mg lidocaine (Lidocaine 4) injections into the shoulders and buttocks. Clinical pain ratings of FM subjects significantly decreased during all treatment conditions ($p < .001$). However, the effects of saline and lidocaine conditions on clinical pain were not statistically different ($p > .05$).

Table 1

Demographics

	Saline (4 saline injections) mean (SD)	Lidocaine 2 (2 lidocaine + 2 saline injections) mean (SD)	Lidocaine 4 (4 lidocaine injections) mean (SD)	p – Value [*]
Age (years)	44.9 (15.3)	46.0 (16.3)	47.2 (13.0)	> .05
Tender Points	17.6 (1.0)	17.6 (.7)	17.4 (1.2)	> .05

^{*} Results of one-way ANOVA

Table 2

Linear Regression Analysis

Block	Variable	R ²	F Change	p
1	Expectation	.147	9.84	< .003
2	Anxiety	.051	3.59	> .05
Beta (standardized)		t		
1	Expectation	-.332	-.717	< .009
	Anxiety	-.232	-1.90	> .05

Dependent Variable: Clinical Pain

Final Model: $R^2 = .199$, $F = 6.94$; $p = .002$

Table 3

Lidocaine Blood Levels after Injections

	Blood Level (µg/ml) at 30 min Mean (SD)	Blood Level (µg/ml) at 60 min Mean (SD)	p –Value*
Saline	< .1	< .1	
Lidocaine 2	.6 (.3)	.5 (.2)	< .001
Lidocaine 4	.9 (.3)	.7 (.3)	

* Lidocaine dose x time interaction was statistically significant (p < .001)