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Repeated Intravenous Lidocaine Infusions for Patients with Fibromyalgia: Higher Doses of Lidocaine Have a Stronger and Longer-Lasting Effect on Pain Reduction

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Abstract

Objectives. To determine the effect of escalating doses of lidocaine infusion with or without added magnesium on pain levels and the duration of pain relief in patients with fibromyalgia (FM). **Methods.** A retrospective chart review of 74 patients diagnosed with FM who underwent at least three escalating doses of intravenous (IV) lidocaine infusions (5 mg/kg of body weight, 7.5 mg/kg, and 7.5 mg/kg of lidocaine + 2.5 g of magnesium sulfate) was conducted. Each patient's subjective impression of change in pain intensity and duration of pain relief after each treatment was recorded, along with an 11-point numeric rating scale (NRS) for pain intensity, immediately before and after each infusion. **Results.** Short-term lidocaine analgesia was evaluated by the reduction in NRS pain score according to the patients reported pre- (immediately before treatment) and post-treatment (immediately after treatment) values. There was a statistical difference in the NRS score reduction between doses 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.009$). Long-term analgesia was evaluated at follow-up visits by the patient's subjective impression of change in pain intensity and duration of pain relief. There was a statistical difference in the percentage of pain relief and the mean duration of pain relief between the treatments with 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.007$ and $P = 0.003$). Although there was a trend of greater response to magnesium sulfate as a beneficial adjunct to the lidocaine infusion, we were unable to find a statistically significant difference for any of the variables studied. **Conclusions.** This study demonstrated that escalating doses of IV lidocaine to 7.5 mg/kg safely and effectively reduced the pain with prolonged effect in a significant number of patients diagnosed with fibromyalgia. Larger, prospective clinical studies are required to confirm this finding.

Key Words: Lidocaine; Fibromyalgia; Chronic Pain; Neuropathic Pain

Chronic pain is a broad, multifaceted disorder that can cause a significant decline in quality of life [1]. Unlike acute pain, which alerts individuals of immediate physical harm such as an injury or an illness, chronic pain that lingers for months or years is maladaptive and may become a cause of disability [1]. Based on the 2010 American College of Rheumatology (ACR) criteria, fibromyalgia (FM) is classified as a chronic widespread pain lasting longer than three months, and it is confirmed with the use of the Widespread Pain Index (WPI) and somatic Symptom Severity (SS) scale [2]. FM affects an estimated 3–6% of the world population, with the lowest prevalence at the ages before 30 and the highest prevalence at the ages between 50 and 59 years; there is no significant difference in prevalence compared with older age of 60 and older [3,4]. It is more frequently diagnosed in

women, with a female-to-male ratio of approximately 3:1 [3,4]. Symptoms of FM syndrome most commonly include generalized chronic pain, fatigue, sleep disturbance, mood disorders, and impaired quality of life [5]. It is also characterized by a heightened pain response to pressure [6] and other systematic symptoms, including somatization symptoms [7] and post-traumatic stress disorder. Patients with FB frequently experience other types of chronic pain [8].

The pathophysiology of FM is multifactorial and is reflected in the complexity and variety of symptoms experienced by FM patients [9], but the consistent feature is altered pain processing [10] associated with peripheral and central nervous system influences [9]. The neurobiology of chronic widespread pain in patients with FM was reviewed in the article of Sluka and Clauw in 2016 [11]. The authors highlighted the heterogeneous nature of FM with multiple potential etiologies based on animal and human studies. According to the review, significant modifications in central nervous system factors result in accelerated pain and sensory processing in most patients with FM, whereas other studies demonstrated peripheral components contributing to generation of pain [11]. Clinical studies revealed that although many FM patients have stronger central components, peripheral components may be stronger in some individuals with FM, and mixed peripheral and central components may be present in others [11]. According to the review of Maslinska et al. published in 2018, several investigators of FM realize the far-reaching consequences of detecting features of small fiber neuropathy (SFN) in this disorder, and studies confirm that about 40%–50% of patients with FM are also diagnosed with SFN [12]. The role of alterations in the immune system resulting in an enhanced inflammatory state in the pathology of FM and other chronic pain conditions was also discussed in a review by Sluka and Claw [11]. Thus, similar to neuropathic pain, FM pain is considered to be generated by either the peripheral or central nervous system, or both [13]. Changes in the central nervous system and the experience of similar sensory phenomena, including allodynia and hyperalgesia, are common in both central neuropathic pain and FM [8,9]. This is consistent with the finding that FM responds to similar medications that target central neuropathic pain, including gabapentinoids, tricyclic antidepressants (TCAs), and serotonin norepinephrine reuptake inhibitors (SNRIs) [8].

Patients with FM are often treatment-refractory or develop intolerable side effects to conventional oral medications. Intravenous lidocaine is known as a treatment with peripheral and central-mediated analgesic, anti-inflammatory, and antihyperalgesic effects [14,15]. Previous studies have reported that lidocaine is a safe and effective treatment when it is administered intravenously (IV) in order to produce clinically efficient analgesia in patients who suffer from a variety of pain disorders, including FM [16–22]. Lidocaine acts by blocking sodium channels in the neuronal cell membrane that, as studies suggest, may play a role in the pathogenesis of various chronic pain disorders [15]. In addition, lidocaine modulates or inhibits other channels, among them calcium, potassium, muscarinic and glycinergic signaling, releasing of endogenous opioids and ATP, and production of stimulatory amino acids, neurokinins, and thromboxane A2, which lead to lidocaine-induced analgesia [23]. An increasing number of placebo-controlled and comparative studies confirm that IV infusions of lidocaine are more effective than placebo in treating a broad spectrum of chronic pain disorders. This includes central and peripheral neuropathic pain [22,24–27], post-herpetic neuralgia and peripheral nerve injury [28,29], complex regional pain syndrome [30], persistent postsurgical pain [31], diabetic neuropathy [32], and fibromyalgia [16,17,19–21]. There is also evidence of its efficacy in treating cancer pain [33] and chronic, refractory pain in adolescent and young adult populations [34].

Intravenous magnesium has been shown to have beneficial effects on neuropathic back pain [35] and postherpetic neuralgia [36]. These effects are considered to be due to blockage of the N-methyl-D-aspartate (NMDA) receptors, and thus attenuation of central sensitization [37]. Nonopioid combinations of different medical products have been investigated for the use in patients with acute and chronic refractory pain to opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antineuropathic medicines, and other treatments. Intravenous combinations of lidocaine and magnesium showed positive results in patients with trigeminal neuralgia [38,39], postoperative pain [40], and chronic and refractory pain, including neuropathic pain [34].

Therefore, although there is supportive evidence for the use of IV lidocaine and its combination with magnesium, there is also a paucity of data regarding safety, effectiveness, and clear indications for IV lidocaine alone and in combination with magnesium in chronic pain. There is currently no established consensus for optimal infusion rates and doses or criteria for patient selection in terms of using lidocaine infusions for chronic pain [23,41]. The vast majority of studies have focused on short-term responses to IV lidocaine by measuring patients' levels of pain immediately after treatments; however, some studies in this area have reported the long-term effects of relief produced by IV lidocaine treatments [17–22,42].

The purpose of this study was to analyze our experience with escalating doses of lidocaine infusions for the treatment of patients with fibromyalgia. We hypothesized that higher doses of IV lidocaine may have a stronger and longer-lasting effect on pain reduction. We included the addition of magnesium to the highest dose of lidocaine, similar to a dosage protocol used elsewhere [38].

Methods

We conducted a retrospective chart review of patients at a community, referral-based pain management private

clinic staffed by physicians who specialize in pain management. Repeated IV lidocaine infusions are used in the clinic to alleviate pain in patients diagnosed with FM when other standard medications fail due to noneffectiveness or intolerable side effects. The study received approval from the institutional review board.

Study Participants and Chart Review

Our research team searched all 29,370 electronic medical records (EMRs) available at the clinic. First, we searched for target patients with diagnoses of FM. All included patients were diagnosed with FM in the clinic according to 2010 ACR criteria or had been diagnosed previously and then referred to the pain clinic by a rheumatologist.

This resulted in a pool of 727 patients. Out of this total, 526 patients were excluded because they were not treated with IV lidocaine. Further, 87 patients were excluded due to missing outcome data. This cohort of patients mostly included treatments before 2015, when the percentage and duration of pain relief were not recorded. Finally, 40 more patients were excluded due to having fewer than three infusions or having a dosage protocol that deviated from the predefined, escalating dosage investigated in this study. This resulted in 74 patients and 222 IV lidocaine treatments included in the final analysis (Figure 1). All patients signed a free informed consent form for using their electronic medical records for research purposes.

Lidocaine Infusions

During each treatment, patients had an IV access established in the forearm, and their ECG, BP, HR, and 02sat were monitored by a registered practical nurse. Patients received lidocaine infusions under a gravity drip, which lasted approximately 90 minutes. Participants in this study received regular treatments with multiple IV lidocaine infusions. Most of the included patients adhered to the schedule of lidocaine infusion treatments in our clinic once every two months, and we were able to collect follow-up data on the next lidocaine treatment visit or earlier if the patient had visits between the infusions. However, for several patients, follow–up data were collected >100 days after the treatment. The average number of days between infusion and follow-up data collection and the median, range, and number of patients with >100 days are presented in Table 1.

The number of infusions varied at each dose level. During the first infusion, 5 mg/kg of lidocaine was administered to each patient. Before escalating the dose or adding magnesium, each patient could have received several infusions at each dose level. If a patient had insignificant pain relief (<25% lasting less than two weeks) after the previous infusion and in the absence of serious side effects, the dose of lidocaine was increased to 7.5 mg/kg and subsequently to 7.5 mg/kg plus 2.5 g of magnesium sulfate. Only the first infusion at each dose level and corresponding follow-up data were taken into the final analysis.

The exact dose of lidocaine was calculated using an adjusted body weight calculator, available online (http://globalrph.com/ibw_calc.htm; Last accessed October 7, 2019). The calculator uses total body weight (TBW) to calculate an adjusted body weight (ABW) based on an ideal body weight (IBW) using the equation ABW (kg) = IBW (kg) + 0.4 (TBW (kg) − IBW (kg)) [43]. IBW was calculated as described by Devine [44]. Adjusted body weight was used to calculate the exact dose of lidocaine to reduce the risk of overdosing in case of obesity [43].

Variables

The patients' responses to treatment were recorded at every visit. Patients provided a rating of their pain on a simple 0–10 numeric rating scale (NRS), immediately before (pretreatment NRS score) and after (post-treatment NRS score) each treatment. The NRS is a well-established and widely used scale with high levels of reliability and validity [45]. Other dependent variables were each patient's subjective assessment of the percentage of change in pain intensity and duration of pain relief, if any, experienced after each treatment [46]. Patients' baseline characteristics included age, duration of pain (years), regular use of NSAIDs, opioids, and antineuropathic pain medications.

Statistical Analysis

The data for parametric variables are presented as mean (SD, 95% CI). Intertreatment differences were statistically evaluated using the Student t test. Intertreatment differences for nonparametric data (lidocaine responders) were evaluated by the McNemar test. All statistical tests were two-sided. The differences were considered statistically significant at $P < 0.05$. SPSS, version 25, was used for all analyses.
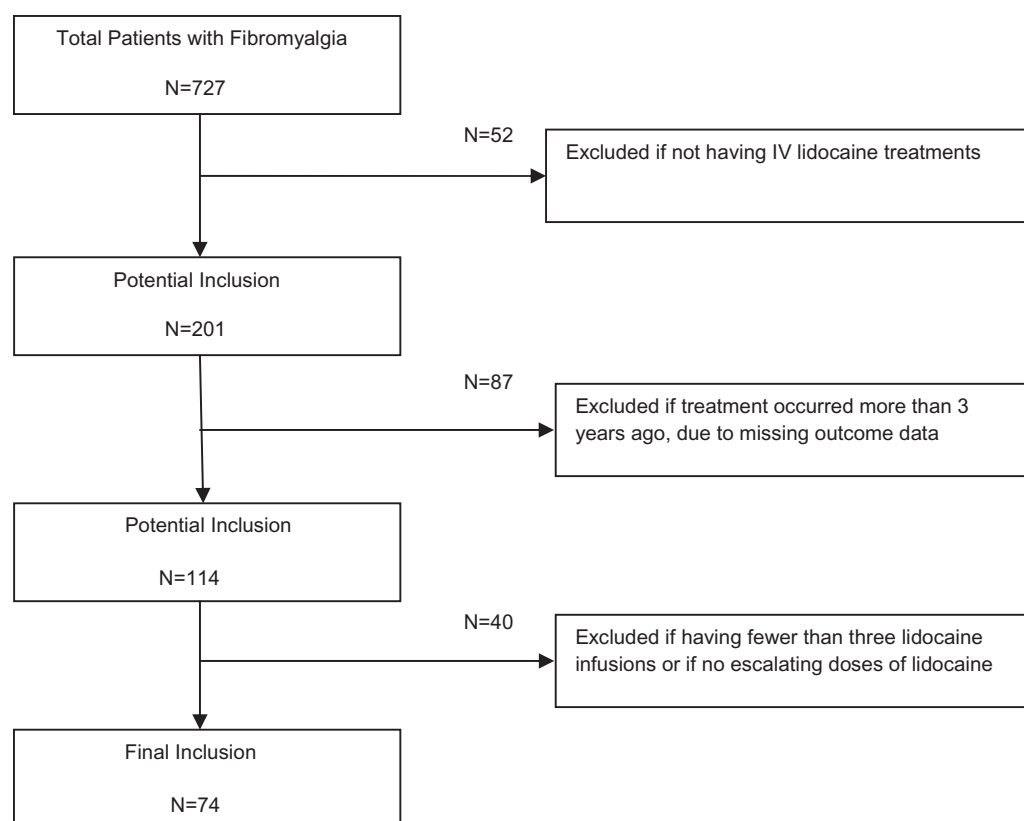
Results

Patient Identification

Seventy-four patients with FM had undergone at least three IV lidocaine infusions with escalating doses matching the targeted dose schedule. There were no serious adverse events recorded at the time of infusion for any of the patients. Side effects were reported during 24 (N = 222) infusions and included mild to moderate dizziness (18 cases), mild to moderate nausea (5 cases), shortness of breath (1 case), elevated blood glucose (1 case), headache (2 cases), and lip numbness (1 case). Patient baseline characteristics are displayed in Table 2.

Short- and Long-term Lidocaine Analgesia

Short-term lidocaine analgesia was evaluated by the reduction in NRS pain score according to the patients' reported pre- (immediately before treatment) and post-treatment (immediately after treatment) values. The average pretreatment NRS scores were 7.90 (SD = 1.76, 95% CI = 7.49–8.30), 8.01 (SD = 1.60, 95% CI = 7.63–

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┌─────────────────────────────┐
│ Total Patients with Fibromyalgia │
│         N=727                │
└─────────────────────────────┘
         │         N=52    ┌──────────────────────────────────────┐
         │────────────────→│ Excluded if not having IV lidocaine treatments │
         │                 └──────────────────────────────────────┘
         ▼
┌─────────────────────────────┐
│    Potential Inclusion       │
│         N=201                │
└─────────────────────────────┘
         │         N=87    ┌──────────────────────────────────────┐
         │────────────────→│ Excluded if treatment occurred more than 3 │
         │                 │ years ago, due to missing outcome data │
         │                 └──────────────────────────────────────┘
         ▼
┌─────────────────────────────┐
│    Potential Inclusion       │
│         N=114                │
└─────────────────────────────┘
         │         N=40    ┌──────────────────────────────────────┐
         │────────────────→│ Excluded if having fewer than three lidocaine │
         │                 │ infusions or if no escalating doses of lidocaine │
         │                 └──────────────────────────────────────┘
         ▼
┌─────────────────────────────┐
│      Final Inclusion         │
│         N=74                 │
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Figure 1. Only patients who had the three escalating doses of intravenous lidocaine less than three years ago were included in the final analysis.

Table 1. Amount of days between infusion and follow-up data collection

Lidocaine Infusion	No. of Days Between the Infusion and Follow-up Data Collection			No. of Patients for whom Follow-up Data Were Collected >100 Days After the Infusion (%)
	Mean	Median	Range	
Lidocaine 5 mg/kg	65.72	62.00	7.00–530.00	5 (6.76)
Lidocaine 7.5 mg/kg	86.38	63.50	25.00–644.00	7 (9.46)
Lidocaine 7.5 mg/kg + 2.5 g Mg	90.97	64.00	28.00–379.00	12 (16.22)

Table 2. Patient baseline characteristics (N = 74)

Patient Characteristics
Age, mean (range) = 51.30 (30–88) y
Sex, % female = 79.73
Pain duration, mean (range) = 8.58 (0.5–34) y
NSAIDs, % patients = 31.08
Opioids, % patients = 54.05
Antineuropathics, % patients = 86.49

NSAIDs = nonsteroidal anti-inflammatory drugs. Antineuropathic medications included gabapentinoids, TCAs, and SNRIs.
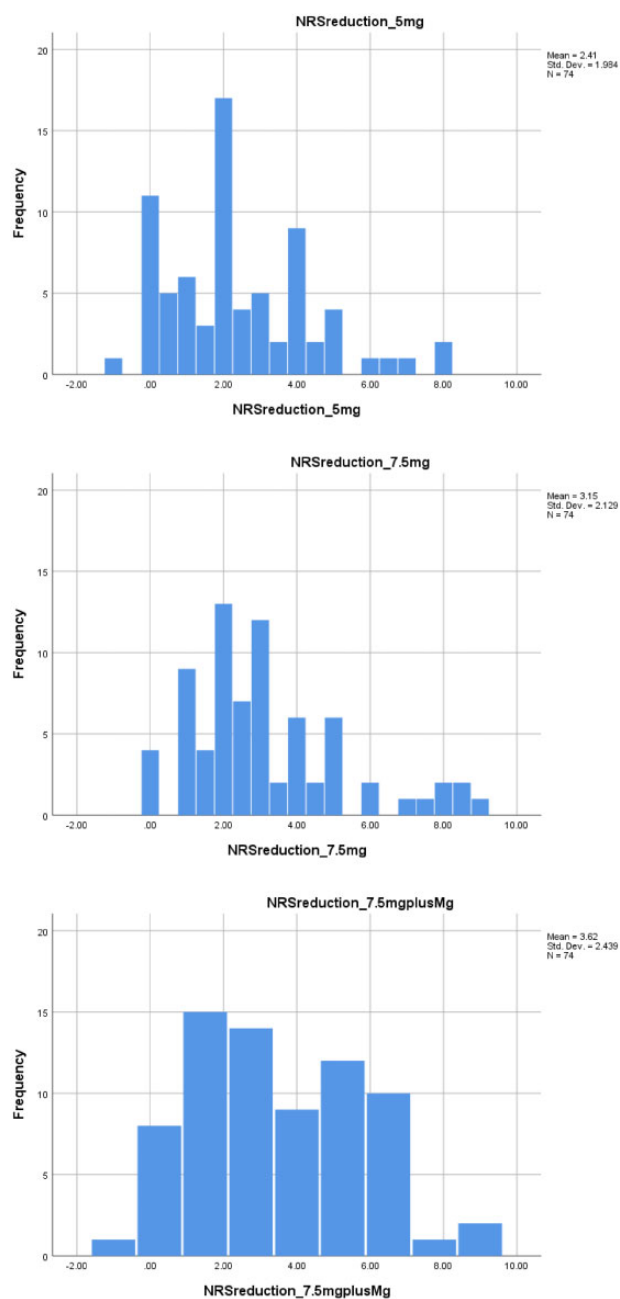
8.38), and 7.75 (SD = 1.73, 95% CI = 7.34–8.15) before the infusions of 5 mg/kg of lidocaine, 7.5 mg/kg of lidocaine, and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively. The mean reductions in NRS scores during lidocaine infusions were 2.41 ($P < 0.001$), 3.15 ($P < 0.001$), and 3.62 ($P < 0.001$) following 5 mg/kg of lidocaine, 7.5 mg/kg of lidocaine, and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively. The distribution of absolute NRS pain score reductions for all three treatments, as measured by pre- and post-treatment NRS scores, is presented in Figure 2.

There was a statistical difference in the NRS score reduction between the doses 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.009$), whereas there was a trend but no statistical difference in the NRS score reduction between treatments with 7.5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg ($P = 0.082$) (Figure 3).
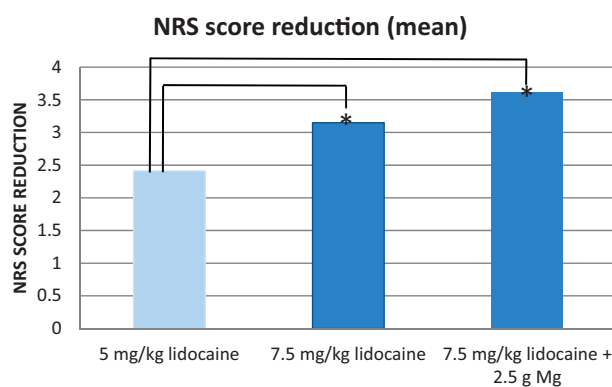
Twelve patients (16.22%) did not have any reductions in NRS scores or had their pain intensity scores increased after the infusion of 5 mg/kg of lidocaine, four (5.41%) and seven (9.46%) patients did not have any reduction in NRS score after the infusions of 7.5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively.

Long-term analgesia was evaluated at follow-up visits by the patient's subjective impression of change in pain

Figure 2. Distribution of analgesic response (reduction in numeric rating scale [NRS] score) to lidocaine infusions for all three treatments, as measured by the pre- and post-treatment NRS for each treatment. Positive numbers indicate pain reduction.

Figure 3. Average numeric rating scale score reductions demonstrate the level of short-term analgesia for three intravenous lidocaine treatments in patients with fibromyalgia. Significance was defined as *$P < 0.05$.
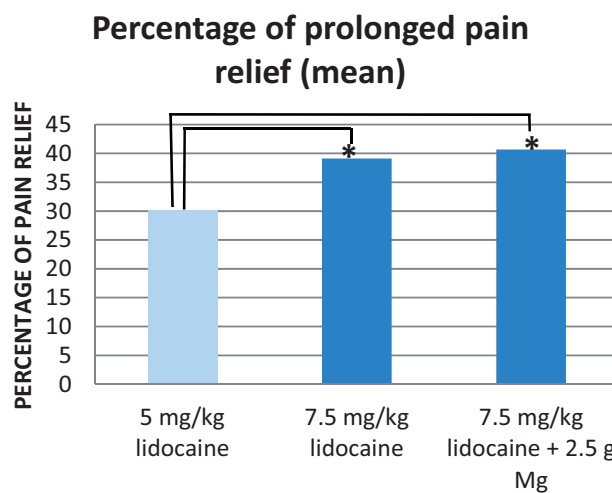

Figure 4. The mean percentage of pain relief reported by patients at follow-up. Significance was defined as *$P < 0.05$.

intensity and duration of pain relief. The mean reported percentages of prolonged pain relief were 30.23%, 39.11%, and 40.68% following 5 mg/kg of lidocaine, 7.5 mg/kg of lidocaine, and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively. There was a statistical difference in the percentage of pain relief between treatments of 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.007$), whereas there was no statistical difference in the percentage of pain relief between treatments of 7.5 mg/kg of lidocaine

and 7.5 mg/kg of lidocaine + 2.5 g Mg ($P = 0.799$) (Figure 4).

The mean duration of pain relief was 8.68, 14.05, and 17.54 days after treatments of 5 mg/kg of lidocaine, 7.5 mg/kg of lidocaine, and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively. The maximum duration of pain relief was up to 49 days after 5 mg/kg of lidocaine infusion and up to 90 and 75 days after infusions of 7.5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively. There was a statistical difference in the mean duration of pain relief between the treatments with 5 mg/kg and 7.5 mg/kg of lidocaine ($P = 0.003$), whereas the mean duration of pain relief between the treatments with 7.5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg did not reach statistical difference ($P = 0.091$) (Figure 5).

Table 3 shows pain score reductions (short-term analgesia), percentage of prolonged pain relief, and duration of pain relief (long-term analgesia) after each treatment.

Duration of pain relief (mean)
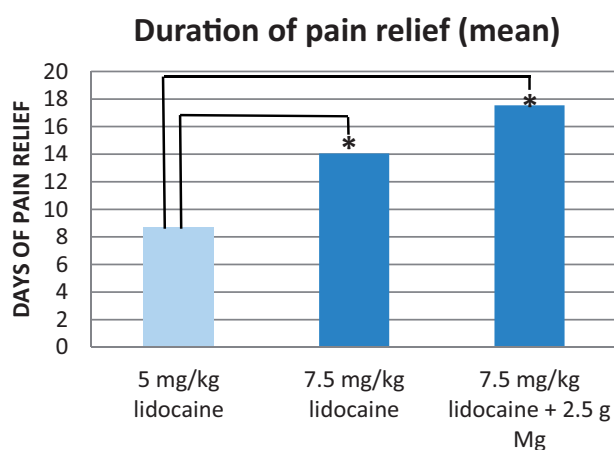
Figure 5. Average duration of pain relief (days) reported by patients at follow-up. Significance was defined as *P < 0.05.

The number of patients who did not experience prolonged pain relief was 15 (20.27%), 11 (14.86%), and 10 (13.51%) after 5 mg/kg of lidocaine, 7.5 mg/kg of lidocaine, and 7.5 mg/kg of lidocaine + 2.5 g Mg, respectively. One patient did not benefit from the lidocaine infusions at any dose level, having the same pain intensity NRS scores before and after infusion and no relief in pain; this patient discontinued lidocaine treatments after the third infusion.

For the excluded patients (N = 40), who did not have all escalating doses of lidocaine as predefined for the study, the mean reductions in NRS scores immediately after lidocaine infusions were 2.64 (SD = 2.65, 95% CI = 1.68–3.66), 2.66 (SD = 1.90, 95% CI = 1.94–3.50), and 4.30 (SD = 2.71, 95% CI = 3.16–5.38) after 5 mg/kg of lidocaine (N = 28), 7.5 mg/kg of lidocaine (N = 25), and 7.5 mg/kg of lidocaine + 2.5 g Mg (N = 25), respectively. At follow-up, the mean reported percentage of prolonged pain relief was 33.50% (SD = 33.53%, 95% CI = 20.26–48.50%), 41.84% (SD = 29.59%, 95% CI = 28.43–54.99%), and 41.00% (SD = 26.67%, 95% CI = 26.23–55.71%) after 5 mg/kg of lidocaine (N = 20), 7.5 mg/kg of lidocaine (N = 19), and 7.5 mg/kg of lidocaine + 2.5 g Mg (N = 15), respectively. The mean duration of pain relief was 12.43 days (SD = 14.68, 95% CI = 6.03–19.57), 17.50 days (SD = 15.64, 95% CI = 11.30–24.23), and 15.73 days (SD = 18.55, 95% CI = 5.46.71–26.01) after 5 mg/kg of lidocaine (N = 20), 7.5 mg/kg of lidocaine (N = 19), and 7.5 mg/kg of lidocaine + 2.5 g Mg (N = 15) treatments, respectively.

Lidocaine Responders

We defined short-term lidocaine responders as those patients who had at least 25% reduction in NRS pain intensity score immediately after the treatment. After the first treatment with 5 mg/kg of lidocaine, 41 patients (55.4%) met the criterion for short-term responders. After the treatments with 7.5 mg/kg of lidocaine and
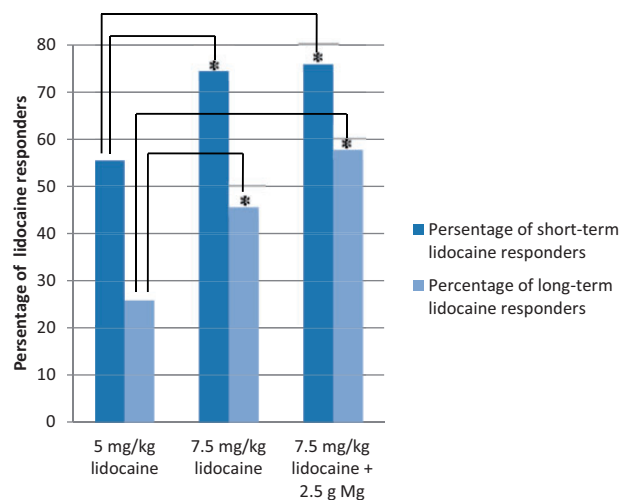
Figure 6. Percentage of short-term and long-term responders among the patients with fibromyalgia treated with different doses of intravenous lidocaine. Significance was defined as *P < 0.05.

7.5 mg/kg of lidocaine +2.5 g Mg 55 (83.8%), 56 (75.7%) patients met the criterion for short-term responders, respectively. There was a statistical difference in the number of short-term lidocaine responders between the treatments with 5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine (P = 0.011), as well as between the treatments with 5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg (P = 0.007). There was no statistical difference in the number of short-term lidocaine responders between the treatments with 7.5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg (P = 1.000) (Figure 6).

Among 40 excluded patients, the criterion for a short-term lidocaine responder was met by 16 patients (57.14%, 95% CI = 37.2–75.5%) on the dose of 5 mg/kg of lidocaine (N = 28), 15 patients (57.69%, 95% CI = 36.9–76.6%) on the dose of 7.5 mg/kg of lidocaine (N = 25), and 20 patients (76.92%, 95% CI = 56.4–91.0%) on the dose of 7.5 mg/kg of lidocaine + 2.5 g Mg (N = 25).

We defined long-term lidocaine responders as those patients who reported at least 25% pain relief lasting for at least 14 days. During the reviewed treatment period, 17 (25.8%) patients met criteria for long-term responders after treatment with 5 mg/kg of lidocaine, 30 (45.5%) patients after treatment with 7.5 mg/kg of lidocaine, and 38 patients (57.6%) after treatment with 7.5 mg/kg of lidocaine + 2.5 g Mg. Twelve infusions were included in the analysis as missing data, because not all the information was collected on follow-up visits and patients were lost to follow-up. There was a statistical difference in the number of long-term lidocaine responders between the treatments with 5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine (P = 0.022), as well as between the treatments with 5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine +

2.5 g Mg ($P = 0.001$). There was no statistical difference in the number of long-term lidocaine responders between the treatments with 7.5 mg/kg of lidocaine and 7.5 mg/kg of lidocaine + 2.5 g Mg ($P = 0.096$) (Figure 6).

Among 40 excluded patients, seven patients (35.00%, 95% CI = 15.0–55.0%) met criteria for long-term responders after treatment with 5 mg/kg of lidocaine (N = 20), nine patients (47.40%, 95% CI = 26.3–68.4%) after treatment with 7.5 mg/kg of lidocaine (N = 19), and eight patients (53.33%, 95% CI = 26.6–78.7%) after treatment with 7.5 mg/kg of lidocaine + 2.5 g Mg (N = 15).

Summarized data for short- and long-term response to lidocaine infusions with escalating doses are presented in Table 4.

Discussion

This retrospective study of 74 patients indicates that lidocaine infusions safely and effectively reduce pain in a significant number of patients diagnosed with fibromyalgia. These patients did not experience success with conventional medications and physical therapy.

Table 3. Lidocaine Treatment (included patients): average reductions in NRS scores, mean percentage of pain relief at follow up, and mean duration of pain relief.

Treatments	5 mg/kg	7.5 mg/kg	7.5 mg/kg+2.5 g magnesium
Variables			
NRS score reduction, mean ± SD	2.41 ± 1.98	3.15 ± 2.13*	3.62 ± 2.44*, †
95%CI	1.95–2.87	2.65–3.64	3.05–4.18
Prolonged pain relief, mean ± SD, %	30.23 ± 28.90	39.11 ± 27.43*	40.68 ± 26.51*, †
95%CI	23.08–37.39	32.36-45.85	34.16–47.2
Duration of pain relief, mean ± SD, d	8.68 ± 11.31	14.05 ± 15.04*	17.54 ± 15.46*, †
95%CI	5.90–11.46	10.35–17.75	13.74–22.34

CI = confidence interval; NRS = numeric rating scale.

*statistical significance found, compared with the dose 5 mg/kg lidocaine.

†no statistical significance found, compared with 7.5 mg/kg lidocaine without added magnesium.

According to the dose of lidocaine by itself and with the addition of Mg, patients reported an average reduction of their NRS scores by 2.41–3.62 points immediately after the lidocaine infusion that corresponded to 30.51–46.71% of short-term pain relief. This trend of pain relief was closely maintained at follow-up, with patients reporting an average pain relief from 30.23% to 40.68% depending on what lidocaine treatment they received. Previous studies have reported that pain reduction from 20% to 50% has a clinically meaningful impact [47]. Lastly, in our study the length of pain relief was relatively sustained in duration. Patients reported an average of 8.68–17.54 days of relief depending on the dose of lidocaine and the addition of Mg. The maximal duration of pain relief was reported up to 90 days.

Prolonged analgesic effect following IV lidocaine has been previously reported in a number of studies. The largest study that explored the long-term benefits of lidocaine infusions in patients with neuropathic and non-neuropathic chronic pain was published by Iacob et al. in 2018 and revealed that 41% of patients reported pain relief of more than seven days [42]. For patients with FM, prolonged analgesic effect was identified in two case studies in 1995 for up to 30 days [18] and in 2015 for up to five weeks [22]. In a retrospective study of 50 FM patients, Raphael et al. reported average pain relief of 11.5 ± 6.5 days after a six-day course of IV lidocaine treatment [20]. In an open trial, Shafranski et al. presented reductions in patients' visual analog scale (VAS) pain scores and Fibromyalgia Impact Questionnaire (FIQ) scores immediately after the five-day course of IV lidocaine and 30 days after their fifth infusion [21]. In two controlled studies, prolonged pain relief was demonstrated by Sorensen et al. in 1995 and McCleane in 2000 with maintained decreasing VAS scores up to four weeks and four to seven days, respectively [17,19]. Thus, the analgesic effect of IV infusions of lidocaine is significantly longer than the biological half-life of lidocaine (approximately 120 minutes) as well as the biological half-life of its active metabolites (up to 12 hours) [23]. Vlainich et al. discussed the long-term effect of lidocaine analgesia and suggested that a reduction in medullary

Table 4. Short- and long-term responses to lidocaine infusions

Response to Lidocaine Infusion	Lidocaine Infusion Treatment		
	5 mg/kg Lidocaine	7.5 mg/kg Lidocaine	7.5 mg/kg Lidocaine +2.5 g Mg
Short-term lidocaine responders, No. (%)	41 (55.4)	55 (74.3)*	56 (75.7)*, †
95% CI, %	43.2–66.3	64.9–83.8	66.2–83.8
Long-term lidocaine responders, No. (%)	17 (25.8)	30 (45.5)*	38 (57.6)*, †
95% CI, %	15.2–37.8	33.4–57.6	45.9–69.7

CI = confidence interval.

*Statistical significance found, compared with the dose 5 mg/kg lidocaine.

†No statistical significance found, compared with 7.5 mg/kg lidocaine without added magnesium.

sensitization is responsible for the extended duration of pain relief [48].

Our data showed that the higher dose of lidocaine at 7.5 mg/kg produced a greater analgesic response than the 5 mg/kg dose. By escalating lidocaine dosage, our patients experienced a further mean reduction of 8.82% in NRS scores immediately following treatment and reported 8.88% more pain relief across five additional days. In another clinical population of patients with diabetic neuropathy, Viola et al. compared doses of 5 mg/kg and 7.5 mg/kg in a placebo-controlled study and found only a tendency of greater response to higher doses; however, this did not reach significance for any of the scores measured [32]. It is important to note that we did not find that the higher dose of IV lidocaine (7.5 mg/kg) was associated with a higher frequency of adverse reactions. Raphael et al. reported that 42% of FM patients had adverse effects, of which two were serious during six consecutive daily infusions of escalating doses of IV lidocaine up to 550 mg over six hours [20]. However, the authors did not provide relevant information regarding on which day of the treatment or at what dosage of IV lidocaine the adverse events occurred. In a controlled study with healthy volunteers where the mean dose of lidocaine infused (range) was 763 (311–1072) mg, lidocaine produced significantly more adverse effects than in control groups, and such reactions as light-headedness, sedation, perioral numbness, metallic taste, dry mouth, and muscle twitching were dose-dependent [49]. Other studies revealed that it was not only the higher dose of lidocaine that was responsible for increasing incidence of adverse effects, but also the rate of IV infusion. Hutson et al. reported in a retrospective analysis that patients with neuropathic pain treated with IV lidocaine at a trial rate of 16.7 mg/min (500 mg over 30 minutes) experienced side effects in 88% of cases vs 3.3% of cases when the rate was reduced to 8.8 mg/min [50].

In our study, the mean dose of lidocaine infused (range) was 334.86 (222–584) mg for treatment with 5 mg/kg and 503.59 (337.5–876) mg for treatment with 7.5 mg/kg and was performed over a 90-minute IV infusion. Therefore, the mean infusion rate (range) was 3.72 (2.5–6.5) mg/min and 5.6 (3.75–9.73) mg/min for treatments with 5 mg/kg and 7.5 mg/kg, respectively. Thus, both the higher dose of lidocaine (7.5 mg/kg) and the infusion rate (maximum 9.73 mg/min) were relatively low in comparison to other studies where the higher doses and infusion rates resulted in increased incidences of adverse reactions. The rates of the adverse events experienced by patients included in the study were 10.3% and 10.8% for 5 mg/kg and 7.5 mg/kg respectively. All reactions were mild to moderate, did not include any major cardiovascular events, and resolved shortly after the infusion.

Although there was a trend of greater response to magnesium sulfate as a beneficial adjunct to the lidocaine infusion, we were unable to find a statistically significant difference for any of the variables studied in the clinical population of patients suffering from FM. In a study of the therapeutic effect of IV lidocaine on chronic pain in adolescents and young adults, co-administration of magnesium with lidocaine infusion also did not show any clear differences in the degree of pain relief in comparison with lidocaine infusion without magnesium [34]. Intravenous magnesium by itself provided a greater pain relief than placebo for the treatment of neuropathic pain [36], but co-administration of lidocaine and magnesium for neuropathic pain in other publications is limited to one case study and one preliminary report [38,39].

Separating patients into lidocaine responders and nonresponders showed that the number of long-term responders became appreciably greater with increased dosage, from 25.8% of patients after treatment with 5 mg/kg of lidocaine to 45.5% of patients after treatment with 7.5 mg/kg of lidocaine. A maximal number of patients (57.6%) met the predefined criteria of being a long-term lidocaine responder ($\geq$25% pain relief for $\geq$14 days) when the IV treatment included 7.5 mg/kg of lidocaine and 2.5 g Mg. We do not exclude a cumulative effect of repetitive infusions, as most of the patients included in this study received more than one infusion at each dose level. It was previously shown that the decrease in pain intensity correlated with the number of lidocaine infusions delivered for the treatment of patients with neuropathic pain [23]. We also do not exclude a placebo effect that may have a significant impact on treatment efficacy in FM patients. A meta-analysis of randomized controlled studies (RCTs) revealed that patients with FM who received a placebo experienced superior improvements in their pain than those receiving no treatment [51].

In conclusion, the flat doses of lidocaine 5 mg/kg and 7.5 mg/kg for treatment of patients with FM reduced pain with prolonged effect and did not cause serious adverse reactions when infused over 90 minutes. During the initial infusion, it is recommended to administer 5 mg/kg of IV lidocaine. If the patient is able to tolerate the lidocaine treatment but the pain relief is not significant, the dose of IV lidocaine can be increased to 7.5 mg/kg for subsequent infusions to reach a clinically meaningful effect. Adding 2.5 g of magnesium sulfate as an adjuvant to the infusion with 7.5 mg/kg of lidocaine was also beneficial for some patients and can be recommended in order to increase and/or prolong pain relief.

The limitations of our study are related to the general limitations of retrospective chart reviews. Additionally, our study has limited documentation of the reasons why some patients received fewer than three infusions or had different doses of IV lidocaine among 40 patients excluded from the final analysis. It is possible that some of these patients did not experience pain relief and declined infusions. It is equally possible that patients achieved satisfactory pain relief with a different dose schedule or decided to repeat the same dose. The cumulative effect of

repetitive infusions at each dose level, which may play a role in pain score reduction and in the duration of pain relief, was not examined in this study. In addition, as in all retrospective chart reviews, the lack of a control group cannot eliminate the possibility of the placebo effect, conditioning effect, or other biases. Lastly, there is a potential recall bias due to a longer period of time before the collection of the follow-up data, which limits the power of the conclusions that can be made. It is therefore clear that the attempt should be made to conduct a randomized, double-blind, placebo-controlled study. A properly designed IV lidocaine dose–response study in FM patients with frequently scheduled patient-reported outcomes should be conducted. These reported outcomes should include pain relief diaries, analgesic medication consumption, and use of other concurrent treatments for a prolonged period of time following the infusion.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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