

# Evaluating the Effectiveness of Escalating Intravenous Infusions of Lignocaine and Ketamine in Reducing Pain and Disability for Fibromyalgia Syndrome: A Prospective Observational Study

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## ABSTRACT

**Introduction:** Fibromyalgia is a chronic syndrome characterised by widespread musculoskeletal pain accompanied by fatigue, disability, sleep, memory and mood issues. The pain of fibromyalgia is difficult to manage and has no complete remission. While there is no cure for fibromyalgia, a variety of medications have been tried to minimise symptoms and improve general health. Hence, a trial was conducted to evaluate lignocaine and ketamine as pharmacological modalities to treat fibromyalgia.

**Aim:** To evaluate effectiveness of intravenous (i.v.) lignocaine-ketamine infusions in reducing pain and disability in fibromyalgia syndrome.

**Materials and Methods:** A prospective observational study was conducted at Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India, between March 2021 and March 2022, on patients aged between 18-60 years diagnosed with fibromyalgia syndrome. Sixty patients were included in the study. Escalating doses of i.v. lignocaine of 5 mg/kg, 6 mg/kg and 7 mg/kg followed by escalating doses of i.v. ketamine of 0.4 mg/kg, 0.5 mg/kg and 0.6 mg/kg were administered on alternate days over a period of 12 days. Infusions were given in 50 mL normal saline through syringe pump over a period of 45 minutes. Pre and postinfusion 11 point Numerical Rating Scale (NRS) score was used to assess pain and World Health

Organisation Disability Assessment Schedule (WHODAS) 2.0 score to assess disability. Data are presented as mean and standard deviation. Statistical analysis was done by using the t-test for pre and post-treatment score, with a p-value<0.05 was considered statistically significant.

**Results:** The present study showed female predominance of 42 out of 60 patients (70%) compared to males 18 out of 60 (30%). Pretreatment average baseline NRS score was 8.8. The mean reduction in NRS scores after lignocaine-ketamine infusions at the end of one month was 1.40 and at sixth month 1.25 which was statistically significant (p-value=0.001). Pretreatment mean average disability score was 2.70 and at the end of sixth month it was 0.59 which was statistically significant (p-value=0.001). Three patients did not have reduction in NRS scores and reported mild to moderate side-effects in the form of dizziness, headache and raised blood pressure.

**Conclusion:** Combined infusions of lignocaine-ketamine resulted in significant reduction in pain and disability in patients with fibromyalgia. Higher and repeated doses seem to be more effective and resulted in longer pain relief. Long-term follow-up periods are needed to determine the effectiveness, dose response and safety of these infusions as a therapeutic modality for fibromyalgia.

**Keywords:** Chronic pain, Electrocardiogram, Numerical rating scale, Postinfusion

## INTRODUCTION

Fibromyalgia is a complex disorder that affects 1% to 5% of the population and can occur at any age. It presents as a widespread chronic musculoskeletal pain without physical or laboratory signs of any specific pathologic process. Chronicity is the rule and disability of the syndrome and depression increases with disease duration [1]. Treatment for fibromyalgia fall into several classes, that include; pharmacological, psychological, physical and complementary therapies [2]. Pharmacological interference with central pain processing can be achieved in two ways: one is by augmenting the action of inhibitory pain pathways or by inhibiting the action of pain pathways. Inhibitory pathway augmentation may be achieved by noradrenergic and serotonergic drugs or by opioids. Activity of the N-Methyl-D-Aspartate Receptor (NMDAR)-mediated glutamatergic synaptic transmission in the spinal cord and brain results in nociceptive hypersensitivity. Because ketamine, an NMDAR antagonist, it may reduce induction of synaptic plasticity and maintenance of states of chronic pain, the study of its use in i.v. form to treat fibromyalgia has increased considerably

[3]. Lidocaine acts by blocking sodium channels on the neuronal membrane that may play a role in the pathogenesis of inflammatory and neuropathic pain [4,5]. Escalating doses of lignocaine and ketamine provide analgesia by acting on different molecular pathways. Administering them together may produce synergistic effects which can allow for using lower dosage of each medication and thereby reducing the corresponding side-effects [6]. These infusions have been prescribed to the patients to alleviate pain in chronic pain syndromes like fibromyalgia for which standard anti-neuropathic medications have been ineffective or poorly tolerated by patients [6-8]. Fibromyalgia is often difficult to treat and different drug combinations are being tried for unresponsive patients or those who present side-effects with oral medications. Hence, the present study aimed to evaluate effectiveness of i.v. lignocaine-ketamine infusions in reducing pain and disability in fibromyalgia syndrome.

The primary objective was to evaluate effectiveness of escalating doses of i.v. lignocaine-ketamine infusions in reducing pain as assessed using 11 point NRS Scale and disability using World

Health Organisation Disability Assessment Schedule (WHODAS) 2.0 score as primary objective. The secondary objective was to study adverse effects of the drugs lignocaine and ketamine.

## MATERIALS AND METHODS

A prospective observational study was conducted at the Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India, between March 2021 and March 2022, on patients aged between 18-60 years diagnosed with fibromyalgia syndrome. Sixty patients were included in the study after obtaining ethical clearance from the Institutional Ethical Committee (BMCH/IEC/121/2021) and informed written consent was taken.

**Sample size calculation:** Sample size calculation formula:

$$N=4PQ/d^2$$

**p:** The prevalence of the condition, considering 30% pain reduction among 88% study population in above study [9],

**q:** (100-p)

**d (or l):** allowable error (10% of P),

$$\begin{aligned} &= \frac{4 \times 88 \times 12}{(8.8)^2} \\ &= 54 \sim (\text{approx}) = 60 \end{aligned}$$

**Inclusion criteria:** Patients diagnosed with fibromyalgia syndrome using Symptom Severity Index and Widespread pain Index Score [10] within the age group of 18-60 years of either sex were included in the study. Pain duration lasting >3 months, multifocal and non dermatomal neuropathic pain, those with failed medical management with atleast two neuromodulating agents (gabapentinoids, antidepressants) were included in the study.

**Exclusion criteria:** Patient's refusal to sign consent, allergic to lignocaine or ketamine, history of cardiovascular diseases, newly added analgesic or neuromodulating medications within 30 days, recently performed neuromodulating interventions within 90 days and previous lignocaine-ketamine infusions within six months were excluded from the study.

Sample size calculation: Sample size is 30 in each group.

### Study Procedure

During each treatment, patients were secured with 20 G i.v. cannula in the forearm, and their Electrocardiogram (ECG), Non Invasive Blood Pressure (NIBP), Heart Rate (HR), and Oxygen (O<sub>2</sub>) saturation were monitored by a registered nurse. Escalating doses of i.v. lignocaine of 5 mg/kg, 6 mg/kg and 7 mg/kg followed by escalating doses of i.v. Ketamine 0.4 mg/kg, 0.5 mg/kg and 0.6 mg/kg were administered on alternate days [6]. Infusions were given in 50 mL normal saline through syringe pump (BPL, Acura-S device) over a period of 45 minutes. The time interval between escalation of doses for both lignocaine and ketamine was 48 hours. Over a period of 12 days, total six infusions, three each of lignocaine and ketamine were given. Pre and postinfusion 11 point NRS score and WHODAS 2.0 score was noted. Eleven point NRS Scale was recorded serially at 1 hour, 2 hour and 3 hours postinfusion for both the drugs. Later patients were followed at weekly interval for four weeks postinfusion and monthly intervals upto three months to assess NRS and WHODAS 2.0 score. Repeat two-day bolus dose of i.v. lignocaine (7 mg/kg) and i.v. ketamine (0.5 mg/kg) was administered at the end of third month. Long-term analgesia was evaluated at follow-up visits done at monthly intervals up to six months. Side-effects of lignocaine such as oral numbness, dizziness, nausea, headache, brady and tachy arrhythmias, while that of ketamine like dizziness, confusion, nausea, euphoria, agitation, hallucinations were observed for patients with severe side-effects were excluded from the study. (As the side-effects in this study were very minimal, none of the study subjects were excluded from the study).

Pain was measured by using 11-point NRS (where 0 represents no pain and 10 represents maximal imaginable pain) [11]. WHODAS 2.0, a patient self-report assessment tool recommended by the DSM-5 disability study group was applied to measure the disability of the patient's pre and postdrug infusions. Postdrug infusions disability scoring was done at the end of first, second, third, fourth, fifth and sixth month. WHODAS 2.0 evaluates the patient's ability to perform activities in six domains of functioning over the previous 30 days, and uses these to calculate a score representing global disability [12,13]. These domains are:

- Understanding and communicating;
- Getting around (mobility);
- Self-care;
- Getting along with people (social and interpersonal functioning);
- Life activities (home, academic, and occupational functioning);
- Participation in society (participation in family, social, and community activities).

There are 36 items in WHODAS 2.0 and each is rated from 0-4. The total score is added and a mean value is obtained for 60 patients. This mean is divided by 36 to get mean of average Disability score which will range from 0-4 where,

0-0.49=none

0.5-1.49=mild

1.5-2.49=moderate

2.5-3.49=severe

3.5-4=extreme

## STATISTICAL ANALYSIS

Data are presented as mean and standard deviation. Statistical analysis was done by using the paired t-test for pre and post-treatment score, with a p-value <0.05 was considered statistically significant.

## RESULTS

The patient baseline characteristics: mean age (range)=40.20 years, with female predominance of 42 out of 60 patients (70%) while in males it was about 18 of 60 patients (30%). There was female (n=42, 70%) predominance than males (n=18, 30%) [Table/Fig-1].

Gender	n (%)
Males	18 (30)
Females	42 (70)

[Table/Fig-1]: Sex distribution.

### Numerical Rating Score (NRS)

Pretreatment average baseline NRS score was 8.8. The mean reduction in NRS scores after lignocaine-ketamine infusions at the end of one month was 1.40 which was statistically significant (p-value=0.001). However, there was slight raise in NRS at the end of second and third month which was not statistically significant. After two days repeat infusions of lignocaine and ketamine the mean NRS was 1.25 which was statistically significant. Three patients did not have reduction in NRS scores and reported mild to moderate side-effects in the form of dizziness, headache, raised BP [Table/Fig-2].

Shows the mean average disability score at different intervals. Pretreatment mean average disability score was 2.70 and at the end of sixth month it was 0.59 which was statistically significant (p-value=0.001) [Table/Fig-3].

With respect to complications observed during the study, patients those who received lignocaine did not complain of any side-effects postinfusion.

Time interval	Mean NRS score	Standard deviation	p-value
Pretreatment	8.80	3.22	-
At the end of 1 <sup>st</sup> hour	5.33	1.54	<b>0.001</b>
2 <sup>nd</sup> hour	4.44	1.32	<b>0.001</b>
3 <sup>rd</sup> hour	4.44	1.32	<b>0.001</b>
1 <sup>st</sup> week	3.88	0.95	<b>0.001</b>
2 <sup>nd</sup> week	3.28	0.58	<b>0.001</b>
3 <sup>rd</sup> week	2.55	0.64	<b>0.001</b>
4 <sup>th</sup> week	1.40	0.78	<b>0.001</b>
2 <sup>nd</sup> month	2.55	0.58	<b>0.001</b>
3 <sup>rd</sup> month	3.88	0.65	<b>0.001</b>
4 <sup>th</sup> month	1.40	0.90	<b>0.001</b>
5 <sup>th</sup> month	1.40	0.80	<b>0.001</b>
6 <sup>th</sup> month	1.25	0.70	<b>0.001</b>

**[Table/Fig-2]:** The mean NRS score at different time intervals. p-value is calculated using the t-test; p-value in bold font indicates statistically significant values

Duration	Mean of average disability score	Standard deviation	p-value
Pretreatment	2.70	0.16	-
4 weeks	1.52	0.13	<b>0.001</b>
2 <sup>nd</sup> month	1.50	0.06	<b>0.001</b>
3 <sup>rd</sup> month	1.29	0.07	<b>0.001</b>
4 <sup>th</sup> month	1.03	0.05	<b>0.001</b>
5 <sup>th</sup> month	0.79	0.05	<b>0.001</b>
6 <sup>th</sup> month	0.59	0.04	<b>0.001</b>

**[Table/Fig-3]:** Showing the mean disability score at different time intervals. The significance level, or p-value, is calculated using the t-test.

Post ketamine infusion patients complained of minimal side-effects like, hallucinations (n=5), nausea/vomiting (n=2), and there were no complaints of agitation, memory defects, cardiovascular effects and hepatotoxicity. The findings were not statistically significant.

## DISCUSSION

Fibromyalgia is a chronic syndrome with a variety of symptoms that include, widespread musculoskeletal pain, tender points, disturbed sleep, fatigue and is frequently associated with disability, reduced quality of life and depression [14].

Systemic local anaesthetics are primarily prescribed for their anti-arrhythmic actions. Short-term analgesia with i.v. lignocaine in a variety of neuropathic pain conditions, such as diabetic neuropathy and postherpetic neuralgia was well tolerated by these patients and had prolonged relief from these treatments [15-17]

i.v. ketamine infusions have been used extensively to treat refractory neuropathic pain conditions. Low dose ketamine produces strong analgesia in chronic pain states, presumably by inhibition of NMDAR. Other mechanisms include enhancement of descending inhibition and anti-inflammatory effects at central sites. Also, they are known to have additional effects on mu opioid and dopamine receptors [1]. In the present study of 60 patients, it showed that lignocaine-ketamine infusions safely and effectively reduced pain and disability in a significant number of patients diagnosed with fibromyalgia.

Vlainich R et al., discussed the long-term effect of lignocaine analgesia and suggested that a reduction in medullary sensitisation is responsible for the extended duration of pain relief [18].

Schafrański MD 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 i.v. lignocaine and 30 days after their fifth infusion [19]. NRS scale is widely used in clinical settings because it is easy to administer and score. Whereas in VAS, the patient is asked for visualisation of his pain as a point on 10 cm line presented on paper. Although many studies have shown a high

correlation between VAS and NRS, NRS shows greater compliance and ease of use compared to VAS [20]. They also stated that for each 1 mg increase in lignocaine, the odds of achieving 30% pain relief benchmark increased by 0.2%. Similarly, every 10 mg increase in the ketamine dose was associated with a 21% increase in the odds of achieving a 30% reduction in pain scores. Thus, the analgesic effect of i.v. infusions of lignocaine is significantly longer than the biological half-life of lignocaine (approximately 120 minutes) as well as the biological half-life of its active metabolites (up to 12 hours).

Wilderman I et al., presented a retrospective chart review of 74 patients diagnosed with Fibromyalgia who underwent at least three escalating doses of i.v. lignocaine infusions (5 mg/kg of body weight, 7.5 mg/kg, and 7.5 mg/kg of lignocaine+2.5 g of magnesium sulfate) and demonstrated that escalating doses of i.v. lignocaine to 7.5 mg/kg safely and effectively reduced the pain with prolonged effect in a significant number of patients diagnosed with fibromyalgia [5].

Hanna AF et al., presented a case report of VAS 7/10 pretreatment which reduced to VAS 0/10 post i.v. ketamine infusion and remained same for >1 year [1]. In a study conducted by Noppers I et al., with 0.5 mg/kg ketamine infusion in 24 subjects diagnosed with fibromyalgia showed that VAS scores were lower in Ketamine group at 15 minutes after infusion, but there was no difference between groups beyond that time point [21]. Hence, the need for repeated infusions is substantiated in the present study for long-term pain relief.

In a study conducted by Becerra L et al., using ketamine infusion in 19 subjects with neuropathic pain showed that ketamine-treated group demonstrated greater decreases in pain scores that lasted for 12 weeks post-treatment evaluation period [22].

Sigtermans MJ et al., studied 60 CRPS-1 patients with severe pain in a double-blind randomised placebo-controlled parallel-group trial. Patients were given a 4.2-day intravenous infusion of low-dose ketamine using an individualised stepwise tailoring of dosage based on effect and side effects. The primary outcome of the study was the pain score during the 12-week study period and they concluded lowest pain relief at the end of first week. Also, treatment with ketamine was safe with psychomimetic side effects that were acceptable to most patients [23].

Raphael J et al., reported that 42% of Fibromyalgia patients had adverse effects, of which two were serious during six consecutive daily infusions of escalating doses of i.v. lignocaine up to 550 mg over six hours [4].

In the present study, the length of pain relief was relatively sustained in duration. None of the subjects experienced major side-effects. Minimal side-effects such as hallucinations to ketamine was noticed postinfusion which was short lived and subsided within one hour. After lignocaine infusions the patients did not encounter any side-effects.

Multiple studies have found WHODAS 2.0 to be reliable, responsive to change, and applicable across geographic regions. As a standardised cross-cultural measurement of health status, it has been demonstrated to have robust psychometric properties across a wide variety of psychiatric and physical disorders without regard to aetiology [11,12]. Hence, it was adopted in the present study and post-treatment disability scores were significantly reduced.

## Limitation(s)

The study was conducted only in patients belonging to American Society of Anaesthesiologists (ASA) Class I and II physical status. Therefore, effects of lignocaine and ketamine for fibromyalgia in geriatric population and those having associated comorbidities are yet to be studied. The study was conducted with a sample size of 60 patients, 30 in each study group, results obtained cannot be generalised for entire population. Randomised, placebo-controlled clinical trials with different infusion protocols should be conducted to apply these results to a larger population. Long-term

follow-up periods are needed to determine the effectiveness, dose response and safety of these infusions as a therapeutic modality for fibromyalgia.

## CONCLUSION(S)

In conclusion, combined infusions of lignocaine-ketamine resulted in significant reduction in fibromyalgia syndrome symptoms. Higher and repeated doses seem to be more effective and resulted in longer pain relief and improving disability.

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