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Original research article

Effectiveness of Escalating Intravenous Infusions of Lignocaine and Ketamine in Reducing Pain, Disability and Depression in Patients with Fibromyalgia Syndrome: A Prospective Observational Study

[1]Dr. Ashwini G S, [2]Dr. R S Deepak, [3]Dr. Anushree M, [4]Dr Suzanne Sonali Edwin, [5]Dr Aishwarya P Jog

[1]Associate Professor, Department of Anaesthesiology, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India

[2]Associate Professor, Department of Psychiatry, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India

[3]Senior Resident, Department of Ophthalmology, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India

[4]Junior Resident, Department of Anaesthesiology, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India

[5]Junior Resident, Department of Psychiatry, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India

Corresponding Author:

Dr. R S Deepak

Abstract

Background: Fibromyalgia is a chronic syndrome characterized by widespread musculoskeletal pain accompanied by fatigue, disability, sleep, memory and mood issues. People with fibromyalgia are more likely to develop major depressive disorder. A variety of medications have been tried to minimize symptoms and improve general health. This study was conducted to investigate the effectiveness of escalating doses of intravenous Lignocain-Ketamine infusions in reducing pain, disability and depression in fibromyalgia syndrome.

Aim:

1. To evaluate effectiveness of escalating doses of intravenous Lignocaine-Ketamine infusions in reducing pain, disability and depression.
2. To observe the adverse effects of lignocaine and ketamine.

Methods: The study was conducted on patients aged between 18 to 60 years diagnosed with fibromyalgia syndrome at a tertiary care center. 100 patients were included in the study. Escalating doses of intravenous Lignocaine of 5mg/kg, 6mg/kg and 7mg/kg followed by escalating doses of intravenous Ketamine of 0.4mg/kg, 0.5mg/kg and 0.6mg/kg were administered on alternate days. Infusions were given in 50ml normal saline through syringe pump over a period of 45 minutes. Pre and post infusion 11 point Numerical Rating Scale (NRS) score, WHODAS 2.0 score and MADRS score was noted.

Results: In our study there was female predominance of 42 out of 60 patients (70%). Pre-treatment 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=0.001). Pre-treatment mean average disability score was 2.70 and at the end of sixth month it was 0.59 which was statistically significant (P=0.001). There was statistically significant reduction in mean average MADRS Score from pre-treatment values of 48.25 to 16.76 at the end of sixth month. Three patients did not have reduction in NRS scores and reported mild to moderate side effects in the form of dizziness, headache, 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. Also repeated ketamine infusions showed greater antidepressant effects. 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: Fibromyalgia, lignocaine, ketamine, numerical rating scale, chronic pain, disability, depression

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;

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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. Pain pathway inhibition may be achieved by systemic administration of local anaesthetics by achieving inhibition of voltage-gated sodium channels [3]. 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. 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 [4, 5, 6]. Over the past decade ketamine has become a target of research for its antidepressant effects, and possible anti-suicidal effects. Several studies have suggested that repeated infusions beyond a single ketamine infusion increase antidepressant response and its durability [7]. The aim of this study was to evaluate effectiveness of escalating doses of intravenous Lignocaine-Ketamine infusions in reducing pain, disability and depression as assessed using 11 point NRS Scale, WHODAS 2.0 Score and MADRS Score respectively.

Methods

The study was conducted on patients aged between 18 to 60 years diagnosed with fibromyalgia syndrome at a tertiary care center between March 2021-March 2022. 100 patients were included in the study after obtaining ethical committee clearance and informed written consent was taken.

Study population:

Age group of 18-60 years of either sex were selected. Pain duration lasting >3months, multifocal and non dermatomal neuropathic pain, those with failed medical management with at least two neuromodulating agents (gabapentenoids, antidepressants) were included in the study. Patient's refusal to sign consent, allergy 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 6 months were excluded from the study. During each treatment, patients were secured with 20G IV cannula in the forearm, and their ECG, BP, HR and O_2 saturation were monitored by a registered nurse. Escalating doses of intravenous Lignocaine of 5mg/kg, 6mg/kg and 7mg/kg and intravenous Ketamine of 0.4mg/kg, 0.5mg/kg and 0.6mg/kg were administered on alternate days. Infusions were given in 50ml normal saline through syringe pump over a period of 45 minutes. Over a period of 12 days, total 6 infusions, 3 each of lignocaine and ketamine were given. Pre and post infusion 11point NRS score, WHODAS 2.0 score and MADRAS score was noted. 11 point NRS Scale was recorded serially at 1hr, 2hr and 3hrs post infusion for both the drugs. Patients were followed at weekly interval for 4 weeks post infusion and monthly intervals up to 3 months to assess WHODAS 2.0 score and MADRS score along with NRS. Repeat two-day bolus dose of IV Lignocaine (7mg/kg) and IV Ketamine (0.5mg/kg) was administered at the end of third month. Long term analgesia was evaluated at follow-up visits done at monthly intervals up to 6 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.

Pain was measured by using 11-point numerical rating scale (where 0 represents no pain and 10 represents maximal imaginable pain).

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 post drug infusions. Post drug 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.

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.

The Montgomery-Åsberg Depression Rating Scale (MADRS) is often used in clinical trials to select patients and to assess depressive symptomology and treatment efficacy. The scale is clinician-rated and consists of 10 items; each item is rated on a 0-6 scale, resulting in a maximum total score of 60 points, with higher scores indicative of greater depressive symptomology. The MADRS scoring instructions indicate that a total score ranging from 0 to 6 indicates that the patient is in the normal range (no depression), a score ranging from 7 to 19 indicates "mild depression," 20 to 34 indicates "moderate depression," a score of 35 and greater indicates "severe depression" and a total score of 60 or greater

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indicates “very severe depression”. There is evidence that an improvement of two points or more on the MADRS is considered clinically relevant.

Statistical analysis

Data are presented as mean and statistical analysis was done by using the Chi-squared test for pre and post treatment score, with a $p<0.05$ was considered statistically significant.

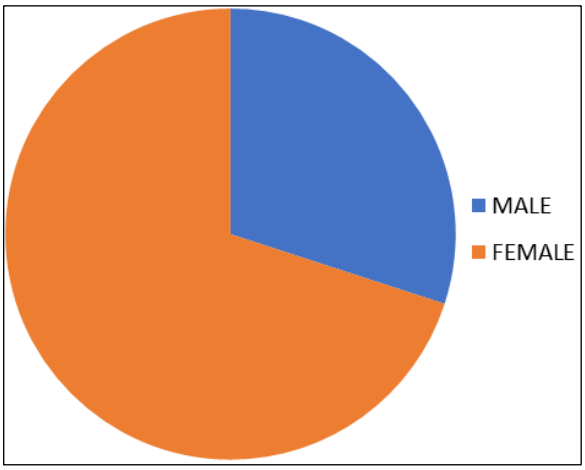
Results

In this prospective observational study, 60 patients with fibromyalgia syndrome were studied with 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%).

Sex distribution

Table 1: Sex Distribution

No. of male patients	No. of female patients
18 (30%)	42 (70%)



Graph 1: Sex Distribution

The above pie chart shows fibromyalgia incidence with female predominance of 42 out of 60 patients (70%). In males it is about 18 of 60 patients (30%).

Numerical Rating Score

Table 2: Showing the mean NRS score at different time intervals

Time Interval	Mean NRS Score
At the end of 1st hour	5.33
2nd hour	4.44
3rd hour	4.44
1st week	3.88
2nd week	3.28
3rd week	2.55
4th week	1.40
2nd month	2.55
3rd month	3.88
4th month	1.40
5th month	1.40
6th month	1.25

Pre-treatment 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=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.

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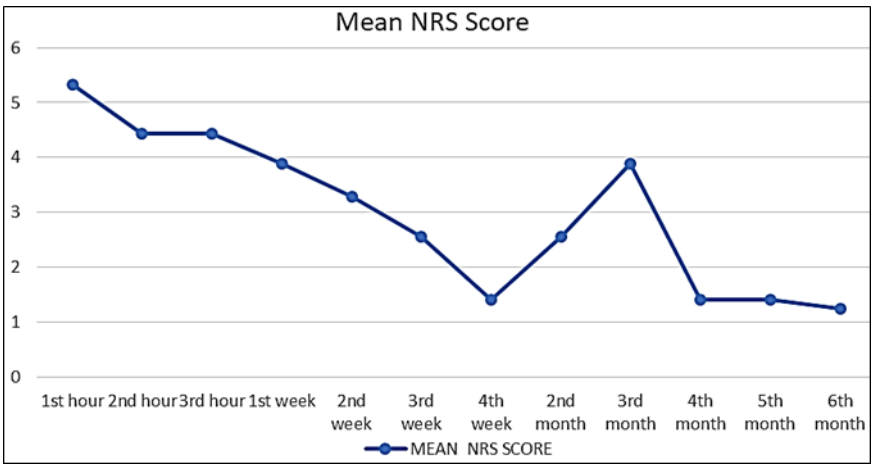

*NRS: Numerical Rating Scale.

Graph 2: Showing the mean NRS score at different time intervals

Table 3: Showing the mean Disability score at different time intervals

Duration	Mean of Average Disability Score
Pre-treatment	2.70
4 weeks	1.52
2nd month	1.50
3rd month	1.29
4th month	1.03
5th month	0.79
6th month	0.59

Table 3 shows the mean average disability score at different intervals. Pre-treatment mean average disability score was 2.70 and at the end of sixth month it was 0.59 which was statistically significant (P=0.001)

Table 4: Showing the mean of Average MADRS score at different time intervals

Duration	Mean of Average Madras Score
Pre-treatment	48.25
At the end of 1st week	34.06
2nd week	28.76
4th week	24.04
2nd month	25.91
3rd month	26.62
4th month	23.34
5th month	20.26
6th month	16.76

Table 4 shows the mean of average MADRS score at different intervals. Pre-treatment mean average MADRAS score was 48.25 and at the end of sixth month it was 16.76 which was statistically significant (P=0.001)

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 [7].

Systemic local anaesthetics are primarily prescribed for their anti-arrhythmic actions. Short term analgesia with intravenous lignocaine in a variety of neuropathic pain conditions, such as diabetic neuropathy and post-herpetic neuralgia was well tolerated by these patients and had prolonged relief from these treatments [8, 9, 10].

Intravenous 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 N-methyl-D-aspartate receptor. 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 our study of 60 patients it showed that lignocaine-ketamine infusions safely and effectively reduced pain, disability and depression in a significant number of patients diagnosed with fibromyalgia.

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Prolonged analgesic effect following IV lignocaine-ketamine has been previously reported in a number of studies.

Vlainich *et al*. discussed the long-term effect of lignocaine analgesia and suggested that a reduction in medullary sensitization is responsible for the extended duration of pain relief [11].

Schafranski *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 lignocaine and 30 days after their fifth infusion [12].

They also stated that for each 1mg increase in lignocaine, the odds of achieving 30% pain relief benchmark increased by 0.2%. Similarly, every 10mg 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 IV 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 *et al*. presented a retrospective chart review of 74 patients diagnosed with Fibromyalgia who underwent at least three escalating doses of intravenous (IV) lignocaine infusions (5mg/kg of body weight, 7.5mg/kg, and 7.5mg/kg of lignocaine + 2.5g of magnesium sulfate) and demonstrated that escalating doses of IV lignocaine to 7.5mg/kg safely and effectively reduced the pain with prolonged effect in a significant number of patients diagnosed with fibromyalgia [13].

Hanna and Smith *et al*. in 2016 presented a case report of VAS 7/10 pre-treatment which reduced to VAS 0/10 post IV ketamine infusion and remained same for >1 year [1].

In a study conducted by Noppers *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 [14]. Hence the need for repeated infusions is substantiated in our study for long term pain relief.

In a study conducted by Schwartzman *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 [15].

Raphael *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 IV lignocaine up to 550 mg over six hours [3].

In our study the length of pain relief was relatively sustained in duration. We also experienced mild side effects which were short lived and subsided within 1 hour of post infusion.

Multiple studies have found WHODAS 2.0 to be reliable, responsive to change, and applicable across geographic regions. As a standardized 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 etiology [16, 17]. Hence it was adopted in our study and post treatment disability scores were significantly reduced.

There is compelling evidence to link fibromyalgia and depression. They co-occur, they share similar pathophysiology and the pharmacological treatment of each includes (but is not limited to) the same dual serotoninergic and noradrenergic agonists such as amitriptyline, duloxetine and milnacipran. These similarities support the concept that depression and FM are "differential symptom presentations of a single underlying condition" [18].

The majority of the literature indicates that patients with pain and depression experience reduced physical, mental, and social functioning as opposed to patients with only depression or only pain. In addition, ketamine, psychotropic and cognitive-behavioral therapies present promising options for treating both pain and depression [19]. Ketamine, administered in sub-anesthetic doses, is an effective off-label treatment for severe and even treatment-refractory depression [20]. Studies have repeatedly found the MADRS to have greater sensitivity to treatment-related change compared with the HAM-D.

Maurizio Fava *et al*., conducted a study in resistant depressive patients and concluded intravenous ketamine in dosages of 0.5mg/kg and 1.0mg/kg were effective in the treatment of depressive symptoms [21].

Conclusion

In conclusion, combined infusions of lignocaine-ketamine resulted in significant reduction in NRS, disability and depression scores. 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. Randomised, placebo-controlled clinical trials with different infusion protocols should be conducted to apply these results to a larger population.

References

1. Ashraf F Hanna, Bishoy Abraham, Andrew Hanna, Micheal McKenna, Adam J Smith. Intravenous ketamine produces long term pain relief in a patient with fibromyalgia. Journal of Medical Cases.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 02, 2023

2016;9(5):142-144.
2. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum. 1986 Nov;29(11):1371-7. Doi: 10.1002/art.1780291110. PMID: 3535811.
3. Raphael J, Southall J, Treharne G, *et al*. Efficacy and adverse effects of intravenous lignocaine therapy in fibromyalgia syndrome. BMC Musculoskelet Disord. 2002;3:21.
4. Kvarnstrom A, Karlsten R, Quiding H, Emanuelsson BM, Gordh T. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand. 2003;47:868-877.
5. Orhurhu V, *et al*. Ketamine infusions for chronic pain: A systematic review and meta-analysis of randomised controlled trials. Anesthesia & Analgesia. 2019 July;129:241-254.
6. Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. Expert Opin Pharmacother. 2010;11:2417-2429.
7. Ledingham J, Doherty S, Doherty M. Primary fibromyalgia syndrome-an outcome study. Br J Rheumatol. 1993 Feb;32(2):139-42. Doi: 10.1093/rheumatology/32.2.139. PMID: 8428227.
8. Kastrup J, Petersen P, Dejgård A, Angelo HR, Hilsted J. Intravenous lidocaine infusion-a new treatment of chronic painful diabetic neuropathy? Pain. 1987 Jan;28(1):69-75. Doi: 10.1016/0304-3959(87)91061-X. PMID: 3822496.
9. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. Neurology. 1991 Jul;41(7):1024-8. Doi: 10.1212/wnl.41.7.1024. PMID: 1712433.
10. Edwards WT, Habib F, Burney RG, Begin G. Intravenous lidocaine in the management of various chronic pain states: a review of 211 cases. Regional Anaesthesia. 1985;10:1-6.
11. Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. Clin J Pain. 2011 May;27(4):285-8. Doi: 10.1097/AJP.0b013e3181ffbfde. PMID: 21178598.
12. Schafranski MD, Malucelli T, Machado F, Takeshi H, Kaiber F, Schmidt C, *et al*. Intravenous lidocaine for fibromyalgia syndrome: An open trial. Clin Rheumatol. 2009 Jul;28(7):853-5. Doi: 10.1007/s10067-009-1137-8. Epub 2009 Mar 5. PMID: 19263182.
13. Wilderman I, Pugacheva O, Perelman VS, Wansbrough MCT, Voznyak Y, Zolnierczyk L. Repeated Intravenous Lidocaine Infusions for Patients with Fibromyalgia: Higher Doses of Lidocaine Have a Stronger and Longer-Lasting Effect on Pain Reduction. Pain Med. 2020 Jun;21(6):1230-1239. Doi: 10.1093/pm/pnz251. PMID: 31621870.
14. Noppers I, Niesters M, Swartjes M, *et al*. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur. J Pain. 2011;15(9):942-9.
15. Becerra L, Schwartzman RJ, Kiefer RT, Rohr P, Moulton EA, Wallin D, *et al*. CNS measures of pain responses pre- and post-anesthetic ketamine in a patient with complex regional pain syndrome. Pain Med; c2009.
16. Gold LH. DSM-5 and the assessment of functioning: The World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0). Journal of the American Academy of Psychiatry and the Law Online. 2014 Jun;42(2):173-81.
17. Üstün TB, Kostanjsek N, Chatterji S, Rehm J. Measuring health and disability: Manual for WHO disability assessment schedule WHODAS 2.0. World Health Organization; c2010.
18. Maletic V, Raison CL. Neurobiology of depression, fibromyalgia and neuropathic pain, Frontiers in Bioscience. 2009;14:5291-5338.
19. IsHak WW, Wen RY, Naghdechi L, Vanle B, Dang J, Knosp M, *et al*. Pain and depression: a systematic review. Harvard review of psychiatry. 2018 Nov;26(6):352-63.
20. Andrade C. Ketamine for depression, 4: in what dose, at what rate, by what route, for how long, and at what frequency? The Journal of clinical psychiatry. 2017 Aug;78(7):101-06.
21. Maurizio Fava, Marlene P. Freeman, George I. Papakostas. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression. Molecular Psychiatry. 2020;25:1592-1603.