General

Maintenance IV Ketamine Therapy in the Fibromyalgia Patient: A Case Report

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Introduction

Fibromyalgia is a complex disorder characterized by distributed and persistent pain often associated with fatigue and depression. The underlying causal agents of this dysfunction are not clear. Ketamine has been used to treat chronic pain in a variety of pain syndromes, including fibromyalgia, but the dosing protocols used are neither standardized nor consistent across cases. The current case presents an opportunity to contribute to a progression towards a consensus on ketamine dosing for fibromyalgia.

Case Presentation

A 60-year-old female presented with indications of fibromyalgia and was administered a 9-session IV ketamine treatment for pain. The initial dosing was 50 mg, with a concentration of 1.0 mg/ml at an infusion rate of 0.8 mg/kg/hr. This was increased to 200 mg and eventually to 240 mg, maintaining a ketamine concentration 4.0–4.8 mg/ml at an infusion rate of 1.5 mg/kg/hr.

Management and Outcomes

Following the first 9-session therapy, the patient reported >50% pain relief from pre-infusion levels and was placed on a maintenance regimen in perpetuity. This regimen involves two monthly IV ketamine infusions, one day apart for two hours at a maintenance rate of 4.8 mg/kg/hr.

Conclusion

Ketamine by IV is an effective option for pain management in patients with fibromyalgia. Compared to previous case studies, it is recommended that increased total dose, frequent administration, and longer duration of infusions all may be necessary for ketamine to maximize its beneficial effects.

INTRODUCTION

Fibromyalgia is a generalized pain disorder that affects approximately 1–5% of the US population.[1] People with fibromyalgia have a heightened sense of pain, and areas of their brain that process pain process it more intensely than people who do not have fibromyalgia. Symptoms can occur throughout the body and may include chronic musculoskeletal pain, generalized fatigue, disturbed sleep patterns, cognitive dysfunction, and depression.[2] The underlying mechanism of the disease is not well understood; certain conditions may be associated with it such as mental stress, certain viral conditions, and connective tissue disorders.[1]

Recent studies have focused on the efficacy of ketamine on chronic and refractory pain syndromes, *e.g.*, complex regional pain, neuropathic pain, and phantom limb pain.[3] Ketamine is a nonbarbiturate dissociative anesthetic that has

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been used safely as an anesthetic agent since the 1960s. Ketamine has several mechanisms of action but works primarily by noncompetitively antagonizing the *N*-methyl-D-aspartate (NMDA) receptor, the glutamate receptor and the HCN1 receptor. The mechanism by which it treats central sensitization appears to be by preventing the wind-up phenomenon (development of ongoing, worsening, or chronic pain), as well as altering 'pain memory.' Several different systems including the cholinergic, aminergic, and opioid systems appear to play a modulatory role in this process. Additionally, ketamine also reverses tolerance to opioids and has been used to decrease opioid usage.

The metabolism of this medication appears to be via the hepatic system by way of N-dealkylation, hydroxylation, conjugation, and dehydration. The half-life of ketamine is approximately 45 minutes.[4] Ketamine can be administered through several routes but has greatest bioavailability through IV and IM administration. These are also the preferred routes for administration as there is decreased risk of potential abuse in a monitored hospital or clinic setting. This is in contrast to oral and nasal formations that entail patient self-administration.[3]

The various studies reveal that ketamine is an effective means to treat pain syndromes and describe appropriate safety guidelines while disclaiming that its long-term effects remain unknown.[5] Despite this wealth of published data, clinical dose studies guiding providers on appropriate dose ranges in various pain syndromes, such as fibromyalgia, remain limited.[5,6] The few reports in the literature that exist, describe a wide range of dosing strategies when treating patients for pain with IV ketamine, ranging from a total of about 20 to 3000 mg, administered over a timeframe of a single dose to 10 days. Moreover, the rate of administration has spanned a 25-fold range, from 2.0 µg/kg/hr to 0.5 mg/kg/hr (*infra vide*). We report a case of a patient with fibromyalgia who received long-term ketamine infusion therapy in the outpatient setting with substantial benefit. Though there is ample literature on the efficacy of IV ketamine in chronic pain conditions such as fibromyalgia, little guidance exists on acceptable dose ranges.

The intent of this case study is to form the basis of a much-needed conversation on IV ketamine dosing protocols such that further studies can be conducted on this topic.

CASE PRESENTATION

A 60-year-old female patient with fibromyalgia presented with complaints of right wrist pain and first carpometacarpal joint osteoarthritis with 8/10 pain intensity. On history, the patient also described generalized body pain, especially in the neck, hip, lower back, knee, and head regions.

She had mild benefit from acupuncture, chiropractic therapy, and physical therapy and minimal benefit from multiple platelet rich plasma (PRP) therapies and steroid injections. She had received epidurals and radiofrequency ablation of medial branches of her neck and lumbar spine, without benefit. She had injections into various joints including small joints of the hand, hips, and back, without lasting relief. Neuromodulation was not offered due to the widespread nature of the pain, making her a poor candidate. In terms of medications, gabapentinoids, duloxetine and NSAIDs had been tried in that past, without any benefit.

Upon physical exam, she had no acute distress. Respiratory, cardiovascular, musculoskeletal, and neurologic system evaluations were normal. Mental function examination showed normal thought content with no psychotic or suicidal thoughts. The patient's judgment was realistic, and her mental status included the correct time, place, and personal orientation as well as normal attention span, memory, and concentration ability. Her Mini-Cog test was also normal.

Ketamine was discussed as a treatment option as the patient had already tried conventional pharmacologic and other alternative therapies on numerous occasions with minimum effect. The patient consented to IV ketamine therapy. The initial protocol was planned for 10 initial infusions, 1 hour in duration every day for 10 days (with none on the weekends). There was no loading dose, and the initial infusion dose was 50 mg, with a concentration of 1.0 mg/ml at an infusion rate of 0.8 mg/kg/hr. Ondansetron 4 mg was administered at the start of the infusion for antiemetic prophylaxis. During the infusion, the patient remained visibly calm, vital signs were stable, and there were no signs of psychosis or change in mental status. The patient was monitored by a board-certified anesthesiologist and a registered nurse. Full ASA monitors, with the exception of a temperature probe, were applied to the patient prior to the start of every infusion.

The patient was interviewed after each infusion to assess for side effects (nausea, excessive drowsiness, headache, sleep disturbance, *etc*). Based on the presence (or absence) of adverse effects and whether any analgesic benefit was noted, the dose was titrated upward (or downward) accordingly. The patient elected to continue with the full course of IV ketamine therapy and the daily total dose was increased to 200 mg and eventually to 240 mg (ketamine concentration 4.0–4.8 mg/ml at an infusion rate of 1.5 mg/kg/hr). Varying amounts of midazolam and propofol were concurrently administered to treat mild anxiety caused by the increased ketamine dose. The patient had no complications, and she was evaluated at the conclusion of 9 sessions. The patient opted not to have a tenth infusion owing to significant analgesia after the ninth infusion. On a follow up visit one week later, she stated that the infusions resulted in >50% pain relief from pre-infusion levels. A decision was made to initiate a maintenance regimen.

Maintenance therapy consisted of 2 monthly infusions, one day apart for 2 hours at a maintenance rate of 4.8 mg/kg/hr. The patient continued to report >50% pain relief from pre-infusion levels as well as increased energy. Her PGIC at 1 month mark showed a score of 1. Frequent biweekly follow up appointments with a board-certified pain physician were done to assess for efficacy and side effects, and urine drug screen and blood work (BUN/Creatinine and LFTs) were done every 6 months to screen for any illicit substances and/or end organ damage, respectively. The pa-

tient decided to re-join the workforce and began working for a corporate firm that required traveling. Because long flights often worsened her fibromyalgia as a consequence of prolonged sitting, maintenance infusions were frequently scheduled prior to her flights, if possible. The patient continues to receive monthly infusions that are 2 hours in duration for 2 days for the next 2 years. Of note, her dosing has not deviated beyond 10% of the dose and she started her maintenance infusions on (4.8 mg/kg/hr). No further medical therapy has been needed. At her discretion, she had platelet rich plasma injections in her lumbar facets, wrist joint, and iliotibial (IT) band for added benefit.

DISCUSSION

Fibromyalgia is a complex disorder that currently affects a significant fraction of the US population. Patients suffering from this disease state present with widespread chronic musculoskeletal pain without physical, radiological or laboratory signs of any specific pathologic process. The mainstay of conventional treatment involves a multidisciplinary approach that encompasses pharmacologic (NSAIDs, opioids, SNRIs, and gabapentinoids) and alternative therapy options (physical therapy, occupational therapy, counseling).[7]

There is recent interest in the use of ketamine for indications including treatment resistant pain and depression.[4] In March 2019, the *S*(+)-enantiomer of ketamine (*i.e.*, esketamine) was approved as a nasal spray (Spravato) for treatment resistant depression (cf. DEA Drug Fact Sheet 2020). A large body of evidence also supports its usefulness in treating severe discomfort such as that induced by trauma or fractures or by flank, low back, neuropathic, and extremity pain.[4,8] Ketamine has gained acceptance in its role in treating pain because it reduces opioid requirements and opioid-induced side effects.[9] Ketamine's effects also far outlast its drug levels and patients enjoy its benefits well past administration.[1]

Though the exact mechanism still needs to be determined, the current data suggests central sensitization and disordered pain regulation at the spinal cord and supraspinal levels, with a resulting imbalance between excitation and inhibition that may alter central nervous system nociceptive processing. Because ketamine may reduce the induction of synaptic plasticity and the resulting maintenance of chronic pain states, the study of its use in intravenous infusion form to treat fibromyalgia has increased.

Various protocols and RCTs on the use of IV ketamine infusion have been published (Table 1). These protocols differ in dosages, duration, frequency, indications, and follow up. This heterogeneity makes it almost impossible to draw any definitive conclusions as to what a proper dosing regimen for the fibromyalgia patient ought to be.

We used a protocol that was a modification of the Schwartzman *et al.* (2009) protocol.[16] Our initial dosing was higher than Schwartzman *et al.*,[16] *i.e.*, 1.0 mg/kg/hr *vs*. 0.5 mg/kg/hr in the latter, but the frequency of infusions was daily (with a break for the weekend) and the duration was 1 hour instead of 4 hours as in Schwartzman *et al*.[16] The reason for the departure was that whereas the Schwartzman *et al.* protocol was for complex regional pain syndrome (CRPS),[16] our patient was suffering from an entirely different disease state, and, unlike CRPS, there is not a clear downward progression of fibromyalgia if not rapidly treated. Additionally, being in an outpatient clinic limited our ability to administer long infusions because of personnel issues.

Using our protocol, and adjusting every subsequent dose based on the feedback from the previous 24 hours, allowed us to achieve the optimal concentration and duration for the patient. After 9 infusions, the patient reported >50% pain relief and improved ambulation, and thus we concluded the treatment session.

The issue of whether ketamine infusions should be continued as potentially lifelong maintenance therapy is a matter of controversy. Because ketamine is a "disease modifying" agent, it is believed that once the pathways responsible for pain have been successfully re-aligned by ketamine, subsequent doses are no longer necessary. As a result, those requiring re-dosing are labeled as "non-responders" and other treatments are considered. However, to date there is no pharmacokinetic study that establishes that ketamine infusions, if given over a small period of time, can irreversibly and permanently re-align the complex NMDA-glutamatergic pathway. Furthermore, there is no pain therapy, including epidural, ablations, joint injections, or analgesic medications (opioid or nonopioid), that is limited to just an initial treatment without any maintenance option. Thus, we felt that offering a maintenance regimen consisting of 1–2 ketamine infusions per month in perpetuity was in keeping with best practices when considered through the lens of wider pain management protocols.

Lastly, while the specifics of ketamine infusion therapy may yet need to be established, safety protocols for IV ketamine have been described by the ASA and ASRA.[6] According to these guidelines, ketamine should be administered with frequent blood pressure monitoring, trained personnel (RN or higher), with emergency airway and cardiovascular equipment available. Our protocol followed these guidelines.

Based on the efficacy of IV ketamine on the patient in our case study, we believe that a longer duration of ketamine infusion (*i.e.*, 2 hours) than initially thought, increases in total dose, and provision of more frequent infusions are all required for ketamine to be an effective treatment option for chronic pain. IV Ketamine should also be continued for maintenance therapy so that the patient continues to experience relief. While it may not always be economically feasible to continue IV therapy, switching the patient to oral or nasal ketamine formulations simply increases abuse potential and a possible return to the use of opioids for pain management.

CONCLUSION

We conclude that IV ketamine is an effective means to address treatment resistant pain conditions, such as fibromyalgia. Although the long-term effects of IV ketamine

Table 1. Published ketamine IV administration protocols. All studies referenced here were randomized clinical trials.

Year/citation	Patient population	Protocol	Total ketamine hours	Total ketamine (mg)	# of infusions	Results	Follow up
2008: Eichenberger *et al.*[10]	20 patients with phantom limb pain	**0.4 mg/kg over 1 hr with a minimum of 48 hr between infusions**	4	112	unknown	Ketamine is more effective than calcitonin.	48 hr
2000: Graven-Nielsen *et al.*[11]	fibromyalgia	**0.3 mg/kg over 30 min**	1	21	unknown	unknown	
2019: Kugler *et al.*[12]	patients ≥ 65 with rib fractures	**2.0 µg/kg/min for 48 hr**	48	403.2	1	Low-dose ketamine failed to affect pain score or Oral Morphine Equivalent within the overall cohort, but a decrease in oral morphine equivalent was observed after 12 and 24 hours in severely injured patients.	
2010: Noppers *et al.*[13]	24 patients with fibromyalgia	**0.5 mg/kg over 30 min**	0.5	unknown	unknown	Ketamine is more effective than placebo up to three hours.	8 weeks
1998: Persson *et al.*[14]	8 patients with resting pain	**sub-dissociative doses of 0.15, 0.30, or 0.45 mg/kg for 4 days (racemic ketamine)**	0.083	42, 84, or 126	1	Ketamine has a strong, dose-dependent pain-relieving effect in patients with ischemic pain. However, due to a limited effective dose range, the best use of ketamine for pain relief is in combination with other pain medications.	unknown
2020: Pickering *et al.*[15]	20 patients with neuropathic pain	**0.5 mg/kg/hr for 2 hr**	2	70	1	Many patients responded positively to ketamine but the study results in total find no pain or cognitive-emotional benefit when compared to placebo. Researchers acknowledge that the limited effect may be due to the use of a low dose.	35 days
2009: Schwartzman *et al.*[16]	19 patients with CRPS	**100 mg over 4 hr for 10 days**	40	400	unknown	Ketamine is better than placebo.	9–12 weeks
2009: Sigtermans *et al.*[17]	60 patients with CRPS	**0.43 mg/kg/hr continuously for 4.2 days**	100	3010	unknown	Ketamine provided more significant pain relief compared to placebo up to 11 weeks.	
1997: Sörensen *et al.*[18]	18 patients with fibromyalgia	**0.3 mg/kg**	unknown	unknown	unknown	FM diagnosed according to the American College of Rheumatology criteria seems to include patients with different pain processing mechanisms. A pharmacological pain analysis with subdivision into responders and non-responders might be considered before instituting therapeutic interventions or research.	

are still not understood, increased total dose, frequent administration, and longer duration of infusions are all necessary for ketamine to continue to have its beneficial effects. Further studies are required to develop appropriate dosing protocols and guideline for the administration IV ketamine.

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AUTHORS' CONTRIBUTIONS

Both R.G. and S.B. contributed equally to the research design, implementation, case study evaluation, writing, and editing of the manuscript.

CONFLICT OF INTEREST DISCLOSURE STATEMENT

The Authors claim no conflicts of interest.

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VALIDATED PATIENT REPORTED OUTCOME MEASURES

PGIC scores.

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