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Ambulatory Infusions of Lidocaine and Ketamine for Management of Chronic Pain: An Observational Prospective Cohort Study

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Abstract

Aim: The main purpose of this study was to examine the effect of lidocaine and ketamine infusion on pain relief in patients with neuropathic non-cancer pain and fibromyalgia, as well as on their quality of life, depression, and anxiety.

Method: 156 patients who had been diagnosed with neuropathic pain and/or fibromyalgia agreed to participate, and 7 standard questionnaires were used.

Results: The results of our investigation have proven that simultaneous IV lidocaine and ketamine infusion is a safe and effective intervention for any chronic neuropathic pain patient who did not respond at all to trials of conventional drug therapy (oral medications that are approved for the treatment of neuropathic pain), or when the obtained relief was not sufficient, or resulted in too many side effects.

Keywords: Lidocaine infusion • Ketamine infusion • Neuropathic pain • Fibromyalgia

Introduction

Chronic pain is defined as pain that persists past the normal time of healing, usually lasting or recurring for more than 3 to 6 months [1]. It is the leading cause of disability worldwide and is associated with the greatest economic cost among all psychiatric and neurologic disorders, given its impact on function which results in reduced productivity, lost wages and fewer hours worked in former productive adults, as well as the associated cost of care in the elderly [2]. It is estimated that 1 in 10 adults is diagnosed with chronic pain each year globally [3]. Common causes of chronic pain include cancer, rheumatoid and osteo-arthritis, operations and injuries, and spinal problems [4]. It is a debilitating condition that can impair daily functioning, sleep, and quality of life [5,6]. In the United States alone, the economic cost of pain to society, which comprises health care costs and lost productivity value, was estimated to be at least 560 billion dollars in 2010 [7]. To date, the available pharmacological treatments are accompanied with undesirable side effects and do not provide adequate pain relief for many patients [8]. Particularly, the use of prescription opioids has been controversial due to their long-term ineffectiveness, side effects including addiction, tolerance, immune modulation, and abnormal pain sensitivity, and the opioid overdose epidemic [9,10].

Neuropathic pain is a type of chronic pain that arises from a lesion or disease of the somatosensory nervous system, such as diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, and spinal cord injury [11]. It is estimated that the prevalence of pain with neuropathic characteristics lies between 6.9% and 10% [12]. Neuropathic pain is a difficult condition to manage due to its severity, chronicity, and resistance to simple analgesics [13]. Thus, as for other chronic pain conditions, there is always a demand for alternative therapeutic approaches.

The pathogenesis of neuropathic pain has been attributed to a number of different central and peripheral mechanisms [13]. Thus, a multimodal approach where different pharmacological treatments target different pathways may be best suited for neuropathic pain [14,15]. Not surprisingly, this is a common approach in treating chronic pain where low doses of medications are combined to increase analgesia with their additive or synergistic effects and to reduce the associated side effects [16].

The increased expression of the voltage-gated sodium channels in the neuropathic state is a well-established peripheral mechanism involved in neuropathic pain [17]. This increase would lead to the generation of inappropriate signals and uncontrolled neuronal firing in response to normal trivial inputs [17]. Lidocaine, a sodium channel blocker, exerts its effects by attenuating peripheral nociceptors sensitization and central hyperexcitability [17].

Increased N-Methyl-D-aspartate (NMDA) receptor activity is another mechanism that has been shown to play a role in neuropathic pain by contributing to central sensitization. These receptors, especially those localized in the dorsal horn of the spinal cord, are involved in nociceptive transmission and synaptic plasticity. Thus, NMDA antagonists such as ketamine have long been considered a treatment option for neuropathic pain patients [18]. NMDA antagonists, which are known to have a narrow therapeutic window, have been suggested to be administered in combination with other analgesics such as those with anticonvulsant activities (i.e. lidocaine) [18].

As lidocaine and ketamine provide analgesia by acting on different molecular pathways, administering them together may produce synergistic effects, which can allow for usage of a lower dose of each medication and thereby reducing the corresponding side effects. To our knowledge, despite the common practice of multimodal analgesia, lidocaine-ketamine infusions have never been studied prospectively in an out-of-hospital setting to treat neuropathic pain. The aim of the present study was to evaluate the effectiveness of the current routine practice of lidocaine-ketamine infusions conducted at Allevio Pain Management Clinic; a large outpatient community-based chronic pain management facility. IV Lidocaine-ketamine (IVLK) infusions are prescribed to patients that have pain that is considered to be neuropathic, for which standard anti-neuropathic medications have been ineffective or poorly tolerated.

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This study has been approved by VERITAS IRB Inc.

Study objectives

The primary objective of the study was to evaluate the effectiveness of lidocaine-ketamine infusions in reducing neuropathic pain, using the Revised Pain Quality Assessment Scale (PQAS-R).

- Secondary objectives were to evaluate the effectiveness of lidocaine-ketamine infusions on
- Pain score using the Short Form Brief Pain Inventory (BPI-SF)
- Pain relief using the Pain Catastrophizing Scale (PCS)
- Depression using the Beck Depression Inventory (BDI)
- Self-efficacy using the Pain Self-Efficacy Questionnaire (PSEQ)
- Treatment satisfaction using the Global Improvement and Satisfaction Score (GISS) questionnaire
- Pain-relief duration using the Patient Self-Reported Perceived Duration of Effect (PSPDE) questionnaire
- And to assess, analyze, and report treatment-related adverse events.

Methods

Study design

This was a single center observational prospective cohort study. The study was conducted at Allevio Pain Management Clinic, Toronto, Canada, from 2017 to 2020. For the duration of the study of 36 weeks, the subjects planned to receive a total of 6 infusions.

Subjects were assessed before and after completing the baseline questionnaires. The infusions were scheduled at every 8-week intervals. (Weeks #0, #8, #16, #24 and #32 +/- 1 week).

On each week of the infusion, before starting the treatment, subjects completed the questionnaires and reported the level of the pain.

In addition, participants completed study questionnaires in weeks # 4, #12, #20, #28, and #36.

The exit interview was scheduled to happen on the last week, #36, when the subjects completed the last set of questionnaires.

Research Ethics approvals were obtained from IRB. All study participants consented to the study. Patients were notified that they may withdraw their consent and terminate their participation at any stage without any consequences to their treatment at the clinic.

Study population

All consecutive patients with multifocal and/or non-dermatomal pain with neuropathic component seen at Allevio Pain Management Clinic were screened for the study. Patients were evaluated according to the following inclusion/exclusion criteria:

Inclusion criteria:

- Age 18-90.
- Pain duration >3 months.
- Multifocal and/or non-dermatomal neuropathic pain per Pain Diagram.
- Failed medical management with at least 2 neuromodulation agents (e.g., gabapentinoids, antidepressants, cannabinoids).
- Neuropathic component (S-LANSS score ≥ 12).

Exclusion criteria:

- Non-English speakers.
- Refusal to sign informed consent.
- Allergy to ketamine and/or lidocaine.

Known relative contraindications to ketamine including poorly controlled systemic illnesses: hypertension, hyperthyroidism, ischemic heart disease, heart failure, psychiatric comorbidities (e.g., psychosis, schizophrenia, and dissociative state), pregnancy, and breast feeding.

Known contraindication to lidocaine use including current symptomatic or clinically significant brady- or tachyarrhythmia, systolic blood pressure <90 or >180 mmHg.

Scheduled interventions targeting neuropathic pain: epidural injections, peripheral nerve blocks, Bier block, radiofrequency of dorsal root ganglia and peripheral nerves, additional lidocaine or ketamine infusions.

- Analgesic or neuromodulating medications added within the last 30 days.
- Neuromodulating interventions performed within the last 90 days.
- Previous lidocaine-ketamine, lidocaine, or ketamine infusion within the last 6 months.
- Acute intoxication or active illegal substance abuse.
- Infusion
- Patients had infusions administered under high standard of care and monitoring of blood pressure, heart rate, and oxygen level.
- The initial dose of lidocaine was 5.0 mg/kg +/- 1.0 mg/kg (based on actual weight, up to maximum dose 600 mg), followed by increase of 0.5 mg/kg per infusion based on tolerability of side effects, up to maximum 7 mg/kg or 600 mg.
- The initial dose of ketamine was 0.1 mg/kg (based on actual weight, rounded to the nearest 5 mg, up to maximum 15 mg), followed by increase of 0.1 mg/kg (rounded to the nearest 5 mg) per infusion based on tolerability of side effects.
- The infusion was initiated at 360 ml/hour for planned completion in 45 minutes. The infusion rate was adjusted if side effects developed. Total doses of medications were recorded in the medical record.

Study outcomes

Primary outcome: The primary outcome was the change in pain score from the baseline to end of the study, week 36, measured by the PQAS-R questionnaire [19].

Secondary outcomes:

- Changes in pain score evaluated by the Brief Pain Inventory (BPI)
- Changes in pain score evaluated by the Pain Catastrophizing Scale (PCS)
- Changes in depression score evaluated by the Beck Depression Inventory (BDI)
- Changes in self-efficacy score evaluated by the Pain Self-Efficacy Questionnaire (PSEQ)
- Changes in treatment satisfaction evaluated by the Global Improvement and Satisfaction Score (GISS) questionnaire
- Changes in pain-relief duration evaluated by the Patient Self-Reported Perceived Duration of Effect (PSPDE) questionnaire
- Safety, assessed by the number, severity, and duration of treatment-related adverse reactions.
- Changes in opioid usage evaluated in morphine milligram equivalents.
- The number of pain-related office/hospital visits during the study period.

Statistical analysis

Descriptive statistics were presented as counts and frequencies for categorical data, and means (with standard deviations) and medians (with interquartile range) for continuous data.

The analysis of the primary efficacy variable (PSEQ score) was performed using linear mixed models using random intercept. In these models, both the baseline and post-baseline PSEQ values were modelled as dependent variables; fixed effects were follow-up time, i.e., study week (treated as a factor), and random effects were the patients. The models were further adjusted for age and sex. The mean pain scores and 95% confidence intervals (CIs) were presented for the models. The secondary outcomes such as BPI, PCS, BDI and PSEQ scores were also analyzed using linear mixed models to test if there was a change in score over time. Statistical analysis was undertaken using R (version 3.3.0) and the "lme4" package. GISS satisfaction scores were presented descriptively.

Results

From 2017 to 2020, 162 patients were screened for this study. Out of those, six were excluded (five did not meet eligibility criteria and one did not provide consent). A total of 156 patients received at least one infusion and 156 responded to questionnaires at least once. Baseline characteristics of these 156 patients (114 females and 42 males) are presented in Table 1. The mean age was 48.5 (12.1), 125 (80%) were Caucasian, the reported median number of years of pain was 8.5 (IQR: 4-17), and the median number of pain-related visits within the last 2 months was 3 (IQR: 2-5). About a third of the patients (n=49; 31%) reported depression and 27 (17%) reported anxiety at the baseline (Table 1).

The median number of successfully completed infusions were 5 (IQR: 3-5) per patient. 156 patients (100%) successfully completed infusions at week 0; 143 (92%) – at week 8; 123 (79%) - at week 16; 102 (65%) – at week 24; and 86 (55%) – at week 32.

PQAS questionnaire

At the baseline (week 0), the mean pain score on the PQAS (range: 0 to 200) scale was 117 (95% CI: 112-123). During the study period, reported pain scores decreased. The mean pain relief computed as a difference from week 0 and week 36 was -37.9 (95% CI: -49.8; -25.9) points for males and -26.5 (95% CI: -33.3; -19.7) points for females on the PQAS questionnaire (Figure 1 and Table 2). The adjusted analysis showed that neither sex nor age had a significant impact on pain score in the adjusted model.

BPI questionnaire

At the baseline, the score on the BPI (range: 0 to 10) scale was 6.8 (95% CI: 6.5; 7.1) for pain severity and 7.1 (95% CI: 6.7; 7.4) for pain interference components. The mean pain relief computed as a difference from week 0 and week 36 was -1.76 (95% CI: -2.44; -1.08) points for males and -1.36 (95% CI: -1.68; -0.92) points for females on the BPI severity questionnaire (Figure 2 and Table 3). For the BPI interference questionnaire, the mean pain relief was

Table 1. Patients' baseline characteristics.

Parameters	Total n=156	Males n=42	Females n=114	p-value
Age, years (mean, SD)	48.5 (12.1)	50.1 (12.5)	47.9 (12.0)	0.341
Ethnicity, n (%)				
Caucasian	125 (80.2)	31 (73.8)	94 (82.5)	0.101
South Asian	6 (3.8)	2 (4.8)	4 (3.5)	-
Caribbean	6 (3.8)	2 (4.8)	4 (3.5)	-
Other	19 (12.2)	7 (16.7)	12 (10.5)	-
Marital status, n (%)				
Married/common-in-law	93 (59.6)	32 (76.2)	61 (53.5)	-
Single	36 (23.1)	5 (11.9)	31 (27.2)	0.157
Divorced/separated	22 (14.1)	5 (11.9)	17 (14.9)	-
Widowed	5 (3.2)	0 (0.0)	5 (4.4)	-
Income status, n (%)				
25,000 or less	44 (28.2)	8 (19.0)	36 (31.6)	-
25,000-50,000	29 (18.6)	8 (19.0)	26 (18.4)	-
50,000-80000	33 (21.2)	8 (19.0)	25 (21.9)	0.052
More than 80000	11 (7.1)	7 (16.7)	4 (3.5)	-
Not reported	39 (25.0)	11 (26.2)	28 (24.6)	-
Work status, n (%)				
Working	56 (35.9)	22 (52.4)	34 (29.8)	-
Unemployed	84 (53.8)	15 (35.7)	69 (60.5)	0.018
Retired	16 (10.3)	5 (11.9)	31 (27.2)	-
BMI, kg/m^2 (Median, iqr)	29.1 [25.7; 34.3]	28.8 [25.7; 31.8]	29.2 [25.7; 35.2]	0.449
Diagnosis, n (%)				
CWPS	56 (35.9)	14 (33.3)	42 (36.8)	-
Other	20 (12.8)	9 (21.4)	11 (9.6)	-
Missing	80 (51.3)	19 (45.2)	61 (53.5)	-
Comorbidities, n (%)				
Anxiety	27 (17.3)	6 (14.3)	21 (18.4)	0.714
Depression	49 (31.4)	9 (21.4)	40 (35.1)	0.151
PTSD	4 (2.6)	1 (2.4)	3 (2.6)	0.999
ADHD	4 (2.6)	0 (0.0)	4 (3.5)	0.151
Bipolar disorder	1 (0.6)	0 (0.0)	1 (0.9)	0.999
PD	0 (0.0)	0 (0.0)	0 (0.0)	-

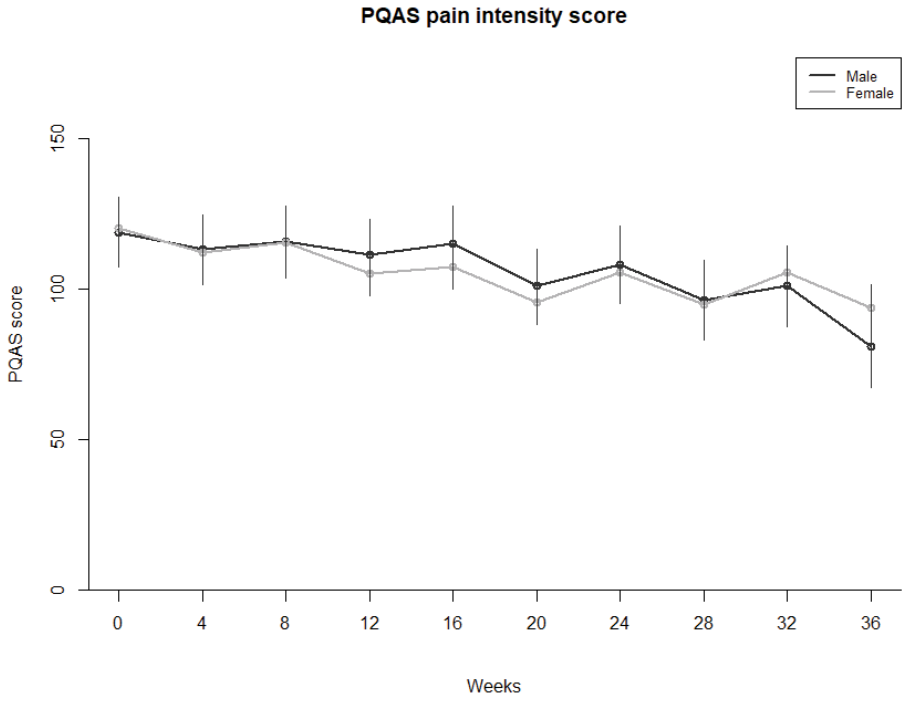

Figure 1. PQAS pain intensity score (score range: 0-200).

Table 2. Changes in PQAS scores by sex over the weeks.

Weeks	Male		Female	
	PQAS Score, Mean (95% CI)	PQAS Score, Mean Change (95% CI)	PQAS Score, Mean (95% CI)	PQAS Score Mean Change (95% CI)
Week 0	118.9 (107.3; 130.6)	Reference	120.2 (113.2; 127.1)	Reference
Week 4	113.1 (101.5; 124.8)	-5.8 (-15.2; 3.6)	112.3 (105.3; 119.3)	-7.9 (-13.5; -2.2)
Week 8	115.7 (103.9; 127.5)	-3.3 (-12.8; 6.3)	115.4 (108.3; 122.5)	-4.8 (-10.6; 1.1)
Week 12	111.5 (99.7; 123.4)	-7.4 (-17.0; 2.2)	105.0 (97.8; 112.3)	-15.1 (-21.1; -9.2)
Week 16	115.1 (102.7; 127.5)	-3.8 (-14.1; 6.4)	107.5 (100.2; 114.7)	-12.7 (-18.7; -6.7)
Week 20	101.0 (88.7; 113.3)	-17.9 (-28.1; -7.8)	95.6 (88.2; 102.9)	-24.6 (-30.8; -18.5)
Week 24	108.2 (95.4; 121.0)	-10.8 (-21.5; 0.0)	105.4 (97.8; 113.0)	-14.8 (-21.1; -8.4)
Week 28	96.4 (83.2; 109.5)	-22.6 (-33.8; -11.3)	94.7 (87.0; 102.5)	-25.4 (-32.0; -18.9)
Week 32	101.1 (87.6; 114.5)	-17.9 (-29.5; -6.3)	105.6 (97.6; 113.5)	-14.6 (-21.4; -7.8)
Week 36	81.1 (67.3; 94.9)	-37.9 (-49.8; -25.9)	93.7 (85.7; 101.6)	-26.5 (-33.3; -19.7)

Note: PQAS score ranges from 0-200, the higher the score the greater pain intensity.

-2.03 (95% CI: -2.78; -1.28) points for males and -1.08 (-1.51; -0.66) points for females (Figure 3 and Table 4).

PCS questionnaire

At the baseline, the score on the PCS (range: 0 to 52) scale was 30 (95% CI: 27.9; 32.2). The mean change in score computed as a difference from week 0 and week 36 was -10.69 (95% CI: -14.53; -6.86) for males and -9.12 (95% CI: -11.29; -6.96) for females (Figure 4 and Table 5).

BDI questionnaire

The BDI score gradually decreased over the study period and the mean reduction computed as a difference from week 0 and week 36 was -4.19 (95% CI: -7.21; -1.17) for males and -3.25 (95% CI: -4.96; -1.55) for females (Figure 5 and Table 6).

PSEQ questionnaire

Scores on the Pain Self-Efficacy Questionnaire (PSEQ) varied during study period with relatively lower scores observed on infusion weeks (Figure 6). The absolute scores for PSEQ questionnaire over time are displayed in Table 7.

Overall satisfaction

Overall satisfaction with the pain management strategy gradually improved over the weeks. At the end of the study 62.7% patients reported that they were satisfied/very satisfied with the pain-management offered at the clinic. Additionally, 69% people reported positive change in pain (somewhat better, better, or much better) at the end of the study (Figure 7).

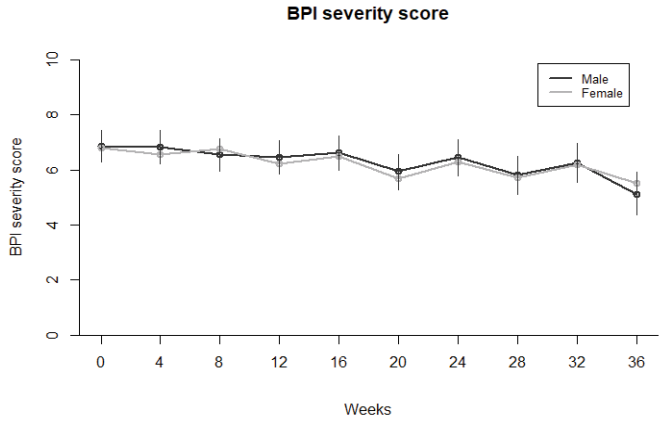

Figure 2. Scores of Brief Pain Inventory – Pain severity over study period (score range: 0-10).

Table 3. Changes in BPI severity scores by sex over the weeks.

Weeks	Male		Female	
	BPI Severity Score, Mean Score (95% CI)	BPI Severity, Mean Change (95% CI)	BPI Severity, Mean Score (95% CI)	BPI Severity Mean Change (95% CI)
Week 0	6.87 (6.27; 7.46)	Reference	6.8 (6.45; 7.16)	Reference
Week 4	6.85 (6.25; 7.44)	-0.02 (-0.56; 0.52)	6.58 (6.22; 6.94)	-0.23 (-0.55; 0.10)
Week 8	6.55 (5.94; 7.16)	-0.32 (-0.87; 0.23)	6.75 (6.39; 7.12)	-0.05 (-0.38; 0.28)
Week 12	6.45 (5.84; 7.07)	t-0.41 (-0.97; 0.14)	6.23 (5.86; 6.60)	-0.58 (-0.91; -0.24)
Week 16	6.62 (5.97; 7.26)	-0.25 (-0.84; 0.34)	6.48 (6.10; 6.86)	-0.32 (-0.67; 0.02)
Week 20	5.95 (5.31; 6.59)	-0.92 (-1.49; -0.34)	5.68 (5.30; 6.07)	-1.12 (-1.47; -0.78)
Week 24	6.46 (5.79; 7.13)	-0.41 (-1.02; 0.21)	6.29 (5.89; 6.69)	-0.51 (-0.88; -0.15)
Week 28	5.81 (5.12; 6.50)	-1.05 (-1.70; -0.41)	5.71 (5.31; 6.11)	-1.09 (-1.47; -0.73)
Week 32	6.25 (5.54; 6.96)	-0.62 (-1.28; 0.04)	6.19 (5.78; 6.61)	-0.61 (-1.00; -0.23)
Week 36	5.10 (4.37; 5.83)	-1.76 (-2.45; -1.08)	5.51 (5.09; 5.92)	-1.30 (-1.68; -0.92)

Note: BPI severity score ranges from 0-10, the higher the score the greater pain severity.

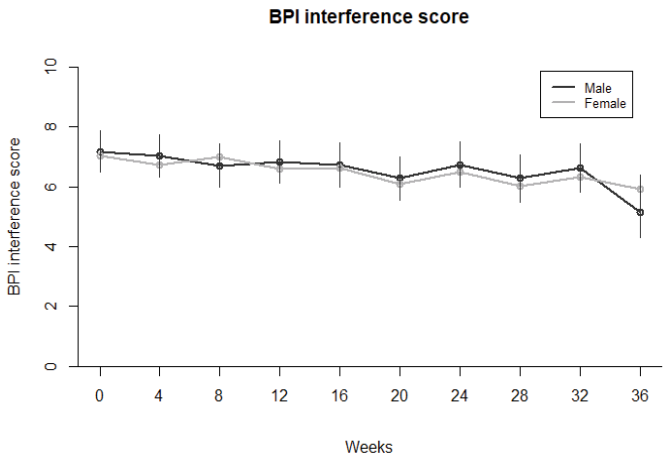

Figure 3. Scores of brief pain inventory – Pain interference over study period (score range: 0-10).

Table 4. Changes in BPI interference scores by sex over the weeks.

Weeks	Male		Female	
	BPI Interference Score, Mean Score (95% CI)	BPI Interference, Mean Change (95% CI)	BPI Interference, Mean Score (95% CI)	BPI Interference Mean Change (95% CI)
Week 0	7.18 (6.49; 7.86)	reference	7.02 (6.61; 7.43)	reference
Week 4	7.03 (6.35; 7.73)	-0.14 (-0.73; 0.45)	6.75 (6.32; 7.16)	-0.27 (-0.63; 0.08)
Week 8	6.70 (6.00; 7.40)	-0.48 (-1.08; 0.12)	7.00 (6.58; 7.43)	-0.01 (-0.38; 0.35)
Week 12	6.84 (6.14; 7.54)	-0.34 (-0.94; 0.26)	6.60 (6.17; 7.03)	-0.42 (-0.79; -0.05)
Week 16	6.74 (6.00; 7.47)	-0.44 (-1.09; 0.20)	6.62 (6.19; 7.06)	-0.40 (-0.78; -0.02)
Week 20	6.29 (5.56; 7.02)	-0.89 (-1.53; -0.26)	6.11 (5.66; 6.55)	-0.91 (-1.30; -0.53)
Week 24	6.75 (5.98; 7.51)	-0.43 (-1.11; 0.24)	6.50 (6.05; 6.95)	-0.52 (-0.92; -0.12)
Week 28	6.29 (5.50; 7.07)	-0.89 (-1.60; -0.19)	6.03 (5.57; 6.49)	-0.99 (-1.40; -0.58)
Week 32	6.62 (5.81; 7.43)	-0.56 (-1.28; 0.17)	6.34 (5.86; 6.81)	-0.68 (-1.11; -0.26)
Week 36	5.15 (4.32; 5.98)	-2.03 (-2.78; -1.28)	5.93 (5.46; 6.41)	-1.08 (-1.51; -0.66)

Note: BPI interference score ranges from 0-10, the higher the score the greater pain interference.

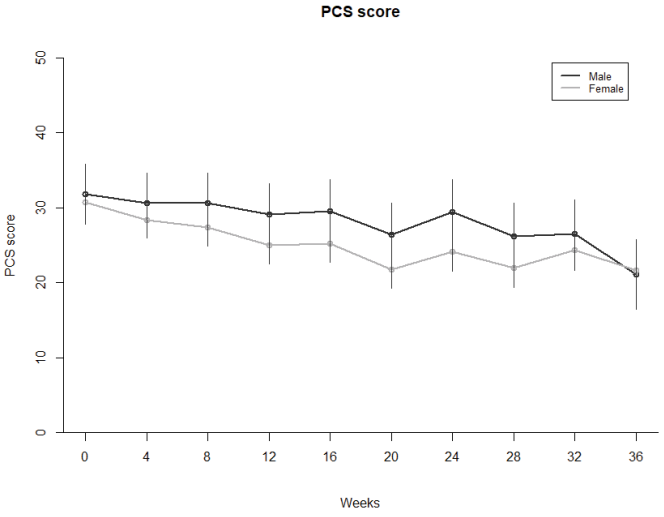

Figure 4. Scores of PCS questionnaire over study period (score range: 0-52).

Table 5. PCS scores by weeks.

Weeks	Male		Female	
	PCS, Mean Score (95% CI)	PCS Scores, Mean Change (95% CI)	PCS, Mean Score (95% CI)	PCS Scores, Mean Change (95% CI)
Week 0	31.8 (27.8; 35.8)	reference	30.7 (28.3; 33.1)	reference
Week 4	30.6 (26.6; 34.6)	-1.12 (-4.13; 1.89)	28.4 (26.0; 30.8)	-2.35 (-4.19; -0.52)
Week 8	30.6 (26.5; 34.6)	-1.19 (-4.25; 1.88)	27.3 (24.9; 29.8)	-3.39 (-5.25; -1.52)
Week 12	29.1 (25.1; 33.2)	-2.66 (-5.73; 0.41)	25.0 (22.5; 27.4)	-5.75 (-7.65; -3.85)
Week 16	29.6 (25.3; 33.7)	-2.25 (-5.53; 1.04)	25.2 (22.8; 27.8)	-5.48 (-7.41; -3.54)

Week 20	26.4 (22.2; 30.6)	-5.33 (-8.59; -2.08)	21.8 (19.2; 24.3)	-8.97 (-10.93; -7.00)
Week 24	29.4 (25.0; 33.7)	-2.40 (-5.84; 1.05)	24.1 (21.5; 26.7)	-6.62 (-8.66; -4.57)
Week 28	26.2 (21.7; 30.6)	-5.61 (-9.20; -2.02)	22.0 (19.4; 24.6)	-8.73 (-10.82; -6.64)
Week 32	26.5 (22.0; 31.1)	-5.22 (-8.93; -1.52)	24.3 (21.7; 27.1)	-6.37 (-8.54; -4.19)
Week 36	21.1 (16.4; 25.7)	-10.69 (-14.53; -6.86)	21.6 (18.9; 24.3)	-9.12 (-11.29; -6.96)

Note: PCS score ranges from 0-52, the higher the score the greater pain catastrophizing experience.

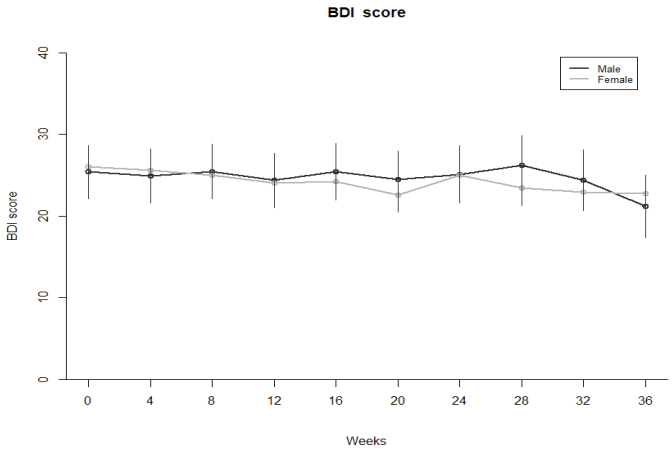

Figure 5. Scores of BDI questionnaire over study period (score range: 0-63).

Table 6. BDI scores by weeks.

Weeks	Male		Female	
	BDI, Mean Score (95% CI)	BDI Scores, Mean Change (95% CI)	BDI, Mean Score (95% CI)	BDI Scores, Mean Change (95% CI)
Week 0	25.4 (22.1; 28.7)	reference	26.0 (24.1; 28.0)	reference
Week 4	24.9 (21.6; 28.2)	-0.51 (-2.88; 1.86)	25.7 (23.7; 27.6)	-0.36 (-1.80; 1.07)
Week 8	25.5 (22.1; 28.8)	0.06 (-2.36; 2.47)	25.0 (23.0; 27.0)	-0.98 (-2.45; 0.49)
Week 12	24.4 (21.1; 27.7)	-1.03 (-3.44; 1.39)	24.1 (22.1; 26.1)	-1.93 (-3.42; -0.43)
Week 16	25.4 (22.0; 28.9)	0.04 (-2.54; 2.63)	24.3 (22.8; 26.3)	-1.76 (-3.27; -0.25)
Week 20	24.5 (21.1; 27.9)	-0.88 (-3.44; 1.68)	22.6 (20.5; 24.7)	-3.41 (-4.95; -1.86)
Week 24	25.1 (21.6; 28.7)	-0.27 (-2.98; 2.44)	25.0 (22.9; 27.1)	-1.00 (-2.62; 0.60)
Week 28	26.2 (22.6; 29.9)	0.84 (-1.98; 3.66)	23.4 (21.3; 25.6)	-2.57 (-4.21; -0.93)
Week 32	24.4 (20.7; 28.1)	-0.99 (-3.92; 1.91)	22.9 (20.7; 25.1)	-3.12 (-4.83; -1.41)
Week 36	21.2 (17.4; 25.0)	-4.19 (-7.21; -1.17)	22.8 (20.6; 24.9)	-3.25 (-4.96; -1.55)

Note: PCS score ranges from 0-63, the higher the score more severe reported depressive disorder

On average, patients reported that they need infusions every 5 weeks to achieve adequate management of their pain.

Adverse events

Six patients developed one, and three patients developed two adverse events during the study period. None of the events were classified as serious adverse events or led to hospitalization.

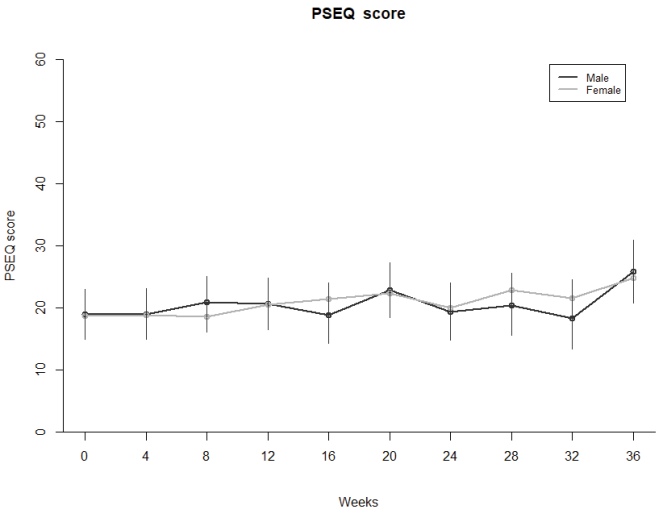

Figure 6. Scores of PSEQ questionnaire over study period (score range: 0-63).

Table 7. PSEQ scores by weeks.

Weeks	Male		Female	
	PSEQ, Mean Score (95% CI)	PSEQ Scores, Mean Change (95% CI)	PSEQ, Mean Score (95% CI)	PSEQ Scores, Mean Change (95% CI)
Week 0	18.9 (14.9; 23.0)	reference	18.7 (16.3; 21.1)	reference
Week 4	19.0 (14.9; 23.1)	0.08 (-3.76; 3.92)	18.9 (16.4; 21.3)	0.20 (-2.13; 2.54)
Week 8	20.9 (16.7; 25.1)	1.96 (-1.94; 5.86)	18.6 (16.1; 21.1)	-0.06 (-2.43; 2.31)
Week 12	20.7 (16.5; 24.9)	1.76 (-2.14; 5.67)	20.5 (17.9; 23.0)	1.78 (-0.62; 4.19)
Week 16	18.8 (14.3; 23.2)	-0.17 (-4.35; 4.00)	21.4 (18.8; 23.9)	2.68 (0.22; 5.14)
Week 20	22.8 (18.4; 27.2)	3.88 (-0.25; 8.02)	22.3 (19.7; 25.0)	3.63 (1.14; 6.14)
Week 24	19.4 (14.8; 24.0)	0.46 (-3.92; 4.84)	20.0 (17.3; 22.7)	1.30 (-1.30; 3.92)
Week 28	20.4 (15.6; 25.2)	1.42 (-3.14; 5.99)	22.9 (20.1; 25.6)	4.17 (1.52; 6.82)
Week 32	18.2 (13.3; 23.2)	-0.70 (-5.41; 4.00)	21.6 (18.7; 24.4)	2.88 (0.11; 5.66)
Week 36	25.8 (20.7; 30.9)	6.89 (2.01; 11.76)	24.9 (22.0; 27.1)	6.17 (3.42; 8.92)

Note: PSEQ score ranges from 0-60, the higher the score more confident to function with pain

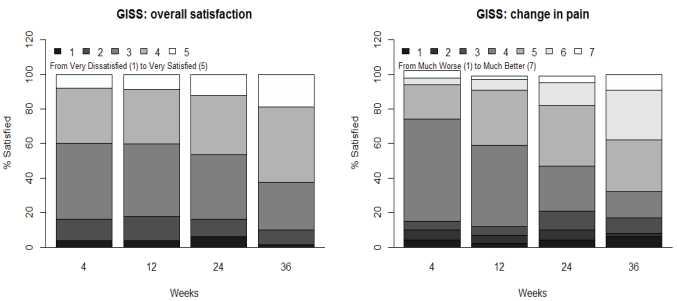

Figure 7. Global improvement and satisfaction score over study period.

MEQ and concomitant procedures

At exit interview only 64 patients reported the MEQ; most of the patients did not use opioids (n=51) or used <20MEQ (n=9), and only 4 patients reported

the usage >20MEQ. The usage of concomitant injections (n=2), acupuncture (n=1), or physiotherapy (n=1) were rare.

The reported usage of concomitant medication (NSAIDs, antidepressants, benzodiazepines, antiepileptic, and "other" medications) was also less frequent at the end of the study compared to the baseline.

Discussion

For many years, we have provided intravenous lidocaine and ketamine infusions (IVLK) for patients with neuropathic pain. After 37071 IV infusions during nine years of practice, we had an extensive list of appreciations from our patients.

One could argue that anecdotally, only people who responded well to the treatment would come back for more infusions and assume that for each satisfied person, there could be several others who did not gain any benefit from IVLK infusions. To understand the limitations of retrospective assessment of any form of intervention, an unbiased and prospective study has been designed. The results of this large study helped us understand the value of this modality as a helpful intervention to be offered to patients.

Although retrospectively, an extremely low rate of serious side effects revealed that IVLK infusion is a very safe intervention, even in the elderly and people with other health issues such as hypertension.

The P values less than 0.0001 in many areas that have been investigated made the results deserving of the attention of all chronic pain management communities. It is important to note that all patients were new patients, and there was no previous doctor-patient relationship with the subjects. People providing care to chronic pain patients are aware that the strong bond between caregivers and this vulnerable group of society can cause a significant bias in retrospective investigations. To prevent this bias, we decided to design the study prospectively in a way so that every subject would be a new patient. The assessment of subjects, as well as addressing their concerns and questions were conducted as formally as possible. At the end of the trial, a meeting was held, and more bonding with the subjects were allowed.

The author will go over the results of the investigation one at a time, which will serve as proof that IVLK infusion is a safe and effective intervention for any chronic neuropathic pain patient who did not respond at all to trials of conventional drug therapy (approved oral medications for the treatment of neuropathic pain), or when the relief was not sufficient, or resulted in too many side effects. The author acknowledges that IVLK infusion, even when effective, cannot be the sole intervention for management of neuropathic pain, and that the effect is unfortunately not very long-lasting. Moreover, the study has shown that IVLK infusion provides more than just pain relief. This modality, despite its shortcoming in the duration of its effect, could increase the quality of life; IVLK infusion has affected many other aspects of the patients' lives in a positive way.

There are also additional new findings. Given the prospective observational nature of this study, any patient who was indicated to have the infusion, regardless of gender, age, or type of pain, have been evaluated for participation. Therefore, due to the broad spectrum of different people's lives, unexpected findings have been captured, and collectively, these new results could be very influential in treating chronic pain.

- Half of all patients were diagnosed with chronic widespread pain syndrome (CWPS) based on the diagnostic criteria of Fibromyalgia, since there are no better criteria available for the diagnosis of CWPS. The author acknowledge that fibromyalgia is only one aspect of CWPS, and we cannot come to a conclusion that every patient with this central neuropathic pain responds in the same manner to intravenous lidocaine and ketamine infusion. The dominant diagnosis of CWPS in our observational study was not surprising, as the prevalence of CWPS is much higher than any other neuropathic condition. This result represents the estimation and statistical information of Canada.
- Anecdotally, many patients have explained their pain is less in the warmer months of the year, or when they travel to the warmer climates (For example, when in the south of the United State of America). Considering this information, perhaps the higher number of CWPS compared to other chronic neuropathic pain conditions in our practice is not applicable to every part of the world. Again, having a multicentric observational study is necessary to answer the question about the effect of weather on the incidence of CWPS (resistance to standard treatment options) and the ratio of this diagnosis compared to other diagnosis of neuropathic pain. One of the main challenges while interpreting the raw data was establishing their statistical significance on the efficacy of the infusion on different genders, and across different age groups. After adjusted analysis, the results showed that neither sex nor age significantly impacted pain score reduction in the adjusted model.
- Even though we investigated pain scores that were reported and documented, the author will not comment on the findings. The report of the intensity of pain is subjective; therefore, a study with a larger sample size, and preferably homogenous groups in terms of age, education, ethnicity, and general health (perhaps The American Society of Anesthesiologists (ASA) Physical Status Classification System could be used) can be utilized to determine whether the pain score in response to intravenous infusions that we have observed is in fact accurate. Reporting the pain score in different ethnicities, cultures, and levels of education could be significantly different. Another unexpected observation happened at week 16. When the dose of the infusion for lidocaine was 5.5 mg/kg and the ketamine was 0.3 mg/kg, a significant effect on the PQAS score was found. The PQAS score includes a general score for any form of pain, and not only neuropathic pain. Therefore, the PQAS served as a more valuable tool, providing further in-depth knowledge of every kind of pain, including burning, sharp, and numbing pain.
- After the first data analysis, the interpretations of data suggested that at least in this study's population, the ideal dose of ketamine infusion that effectively help all patients, regardless of the diagnosis, has been found (Figure 1 - PQAS pain intensity score). The numbers in this figure indicate ketamine dosage, based on mg/kg, when the drug is administered IV in one hour or less.

More findings have been discovered:

- The PQAS score (pain score) was almost the same across all participants, regardless of the sex (118/200 in males and 120/200 in females).
- All subjects (male and female) expressed minimal catastrophizing score. This According to the findings, female patients expressed the same minimum score as male subjects.

The author chooses not to explore the reasons behind these findings, nor try to make any conclusion. One must understand that:

- The participants of the study are not a representative sample of society in general, nor the proportion of chronic pain patients in society. This study's participants represent a small group of people with chronic neuropathic pain who had tried other modalities for the treatment of chronic pain and referred to Allevio Pain Management, that were seen and chosen to have IV lidocaine and ketamine infusion as another modality.

The author suggests involvement of a psychiatrist in the design of similar studies in the future. Two completely different patterns of pain reporting (PQAS scores) have been found in the weeks of infusion, compared to the weeks between the treatments.

- In the weeks between the infusions (Weeks #4, #12, #20, #28 and #36), subjects reported almost identical pain scores.
- However, in the weeks of the infusions (#8, #16, #24, #32), when they have been asked to score the pain right before start of the infusion, the reported values were very different. Almost constantly, participants

reported a higher score before the infusion. This observation was true for each individual, as well as in general across all groups.

- During the treatment, each patient showed a gradual reduction of pain.

Invariably, all patients reported a considerable reduction of pain at the end of infusion (consistently), regardless of the gender of participant. The effect of the infusion on mood was analyzed, even though management of depression was not one of the goals of the treatment, nor was the patients chosen based on their mood. It has been demonstrated that:

- The effect of lidocaine and ketamine on depression was temporary. In conclusion, based on incomplete data gathered in this regard, the effect had lasted less than 4 weeks.
- All participants, regardless of age, gender, or pain score, reported almost the same score in week #4 compared to the time of the infusion.
- The effect on mood was dose dependent, and the effect was meaningful when the dose of the drug was gradually increased to: Lidocaine 6.5 mg/kg and 7 mg/kg, and Ketamine 0.4 mg/kg and 0.5 mg/kg.

The author concluded that findings corroborate with general knowledge that a higher dose of ketamine could be effective for the treatment of depression.

The author would like to suggest the confirmation of the minimum effective dose of ketamine that could be considered, when the treatment of depression is the primary goal:

- Our data suggests that the starting dose of ketamine should be higher or equal to 0.5 mg/kg per hour.
- Another suggestion is the attention of drug distribution of IV ketamine when the main target is the central nervous system, namely the brain. One must remember that with a faster administration of an IV drug, a higher drug serum level could be anticipated. The blood level of the drug indicates how much of the substance will be available at the blood-brain barrier. There will always be a trend toward maintaining a balance across BBB. Therefore, when one considers the same dose of ketamine, a faster administration could result in a larger amount of the drug penetrating the CNS. Again, it highlights the importance of calculating the dose of ketamine based on mg/kg/h when the goal is achieving higher CSF level and aiming to reach the brain receptors.
- The observation for mood was started before the first infusion and the score remained almost unchanged until week #28 of the study. In weeks #28 and #36, a significantly lower score in both genders have been observed. The score was reduced from 101 to 81-96.4 in men, and from 95.6 to 93.7-94.7 in women. The positive effect on mood was much more prominent in men. This sample size was probably too small for a clinical conclusion, as this designed study and calculated the number of subjects to assess the intervention on chronic pain.
- Overall, in both genders, higher levels of lidocaine and ketamine were equal to a meaningful reduction of the score.

The author has an alternative theory to explain the effects of infusion on mood:

- The most statistically meaningful reduction of the score (increase in mood) was observed between weeks #32 and #36.
- Only 50% of the subjects completed the online questionnaire at week #36.
- The author's speculation for the reason is due to the design of the study (design bias) and not the effect of higher dose of ketamine.

At the end of the study, only subjects who had a significant positive effect on their pain had completed the online questionnaires. Therefore, this score does not represent every subject in the study regarding the reduction of pain and satisfaction.

- 69% of patients agreed that the infusion had significantly helped them to manage their pain.
- Some of the "non-responsive" subjects (based on the questionnaires' responses) had reported a significant reduction of pain and agreed to continue the IVLK treatment after the study as they had believed it was helping with pain control.
- Interestingly, the responsive patients (people who finished the study) and those who quit in the middle of the study had shown similar results in each subgroup.
- In both the responsive and non-responsive patients, pain reduction was significant 5-6 weeks after start of the infusion.

After contacting all participants that dropped out of study and asking them the reason for dropping out, a wide variety of reasons were gathered. Unfortunately, almost none of the subjects gave a warning about the possibility of dropping out. was only found out when the participant did not show up 8 weeks after the previous treatment.

Problems with memory are a well-known complication of chronic pain. Therefore, asking the participants questions about specific reasons for not completing the study was unreliable and inaccurate. Not all "non-responders" answered the questions and had communicated. Lastly, when the responsive patients had been asked, in their opinion, what the ideal infusion interval is, they indicated that they need the infusion every five weeks.

Conclusion

Simultaneous Lidocaine and Ketamine infusion is an effective treatment to control neuropathic pain and fibromyalgia, as well as in improving the quality of life.

Supplemental Analysis

In a subgroup of patients with CWPS diagnosis (n=53, number of observations 268, with on average 5 observations per patient), the trend in the PQAS score (primary outcome) decline was similar to that of the total sample.

Even though we observed 24.3 (-51.2; 2.5) points reduction in PQAS scores between the baseline and 36th week, it did not reach statistical significance, likely because of the small sub-sample and hence, lack of statistical power.

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