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RESEARCH ARTICLE

Comparison of Ketamine Infusion Versus Conventional Therapy in Chronic Neuropathic Pain: A Prospective Randomized Controlled Study.

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Abstract: ***Background*** Chronic neuropathic pain is a persistent and debilitating condition arising from dysfunction of the somatosensory nervous system. Despite optimized conventional therapy using anticonvulsants, antidepressants, and opioids, many patients experience inadequate pain relief or adverse drug reactions. Intravenous ketamine, an NMDA receptor antagonist, has been proposed as an effective option for refractory neuropathic pain due to its action on central sensitization mechanisms. Aim: To compare the efficacy and safety of intravenous ketamine infusion versus conventional pharmacotherapy in patients with chronic neuropathic pain. Methods: A prospective randomized controlled study was onducted over 12 months in a tertiary care pain clinic. Sixty patients with chronic neuropathic pain (VAS ≥5 for >3 months) were randomized into two groups: Group K (ketamine infusion 0.3–0.5 mg/kg/hr for 4–6 hours under monitoring) and Group C (optimized conventional therapy including pregabalin/duloxetine/amitriptyline ± opioids). Pain intensity (VAS), opioid consumption, quality of life scores, and adverse effects were assessed at baseline, 1 week, 1 month, and 3 months. Continuous variables were analyzed using independent -test and repeated measures ANOVA; categorical variables were compared using Chi-square test. A p-value <0.05 was considered statistically significant. Results: The ketamine group demonstrated significantly greater reduction in pain scores compared to the conventional therapy group at 1 week (VAS reduction: 4.1 ± 1.2 vs 2.3 ± 1.1, p<0.001) and 1 month (3.5 ± 1.4 vs 1.9 ± 1.3, p=0.002). Sustained analgesic benefit at 3 months was observed in 53.3% of ketamine patients compared to 26.7% in the conventional group (p=0.03). Mean opioid consumption decreased significantly in the ketamine group (−38%) compared to the conventional group (−12%, p<0.001). Quality of life scores improved significantly in the ketamine arm (p=0.01). Transient adverse effects such as dizziness and mild psychomimetic symptoms were noted in 23.3% of ketamine patients but were self-limiting. Conclusion: Intravenous ketamine infusion provided superior short-term analgesia, significant opioid-sparing effect, and improved functional outcomes compared to conventional therapy in chronic neuropathic pain, with manageable adverse effects. Ketamine may be considered an effective option in treatment-resistant cases.

Keywords: Chronic neuropathic pain, Ketamine infusion, NMDA receptor antagonist, Opioid-sparingeffect, Randomized controlled study, Quality of life.

INTRODUCTION

Chronic neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system and persists beyond the expected period of tissue healing, typically lasting more than three

months [1]. It affects approximately 7–10% of the general population worldwide and is associated with substantial impairment in quality of life, sleep disturbance, depression, and functional disability [2]. In India, the burden of neuropathic pain is increasingly recognized, particularly in patients with diabetes, post-herpetic neuralgia, radiculopathy, and post-surgical neuropathies [3].

The pathophysiology of neuropathic pain involves peripheral and central sensitization, ectopic discharges, altered sodium channel expression, and enhanced excitatory neurotransmission mediated by N-methyl-D-aspartate (NMDA) receptor activation [4]. Persistent NMDA receptor activation plays a critical role in central sensitization and maintenance of chronic pain states [5]. Conventional pharmacological therapy includes gabapentinoids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioids; however, many patients experience inadequate relief or intolerable adverse effects [6].

Ketamine, an NMDA receptor antagonist, has emerged as a potential therapeutic option for refractory neuropathic pain due to its ability to modulate central sensitization mechanisms [7]. Low-dose intravenous ketamine infusion has demonstrated analgesic efficacy in conditions such as complex regional pain syndrome, post-herpetic neuralgia, and diabetic neuropathy [8]. In addition to analgesia, ketamine may exert opioid-sparing effects and prevent development of opioid tolerance [9]. Several randomized controlled trials have reported short-term reduction in pain intensity following ketamine infusion compared to placebo or standard therapy [10]. However, variability exists in dosing protocols, duration of infusion, long-term benefit, and safety profiles,

necessitating further comparative studies in different clinical settings [11]. Furthermore, limited data are available from Indian tertiary care centers evaluating ketamine infusion against conventional pharmacotherapy in chronic neuropathic pain.

The present study aims to compare the efficacy and safety of ketamine infusion versus conventional therapy in patients with chronic neuropathic pain attending ESICMC & PGIMSR, Rajajinagar, with the objective of evaluating reduction in pain intensity, improvement in functional status, quality of life, opioid-sparing effect, and incidence of adverse events between the two treatment groups over a defined follow-up period. Chronic neuropathic pain remains a therapeutic challenge, with many patients demonstrating suboptimal response to standard pharmacological regimens such as antidepressants, anticonvulsants, and opioids; therefore, exploring the role of ketamine, an NMDA receptor antagonist with central sensitization-modulating properties, is clinically relevant. The justification for this study lies in the need for evidence-based alternatives for refractory neuropathic pain, particularly in tertiary care settings where disease burden and disability are

high, and long-term opioid dependence poses additional risks. By generating prospective randomized data from an Indian clinical setting, this study is expected to clarify whether ketamine infusion provides superior analgesia, faster onset of action, sustained pain relief, and acceptable tolerability compared to conventional therapy. The anticipated future outcomes include development of standardized treatment protocols, improved patient quality of life, reduction in chronic pain-related disability, and potential integration of ketamine infusion into multimodal pain management guidelines if proven effective and safe.

METHODOLOGY

The study was conducted as a prospective randomized controlled trial over a period of 12 months at a tertiary care pain clinic. Adult patients aged 18–70 years diagnosed with chronic neuropathic pain of more than 3 months' duration and having a baseline Visual Analog Scale (VAS) score ≥5 were screened for eligibility. Patients who had failed at least one standard conventional therapy were included after obtaining written informed consent. Exclusion criteria included severe psychiatric illness, uncontrolled hypertension, significant cardiac arrhythmias, raised intracranial pressure, and pregnancy. Eligible participants were randomized into two groups using a computer-generated random allocation sequence.

The sample size was calculated based on the expected mean difference in VAS reduction between groups. A previous randomized study evaluating ketamine infusion in chronic neuropathic pain reported an approximate 2-point greater reduction in VAS score in the ketamine group compared to conventional therapy at short-term follow-up [12]. Taking this mean difference ($\Delta = 2$), assuming a common standard deviation (σ) of 2.5, with 80% power ($Z\beta = 0.84$) and 5% level of significance ($Z\alpha/2 = 1.96$), the sample size was calculated using the formula for comparison of two independent means:

$n = 2 \times (Z\alpha/2 + Z\beta)^2 \times \sigma^2 / \Delta^2$ Substituting the values:

$n = 2 \times (1.96 + 0.84)^2 \times (2.5)^2 / (2)^2$

$n \approx 27$ per group

After accounting for an anticipated 10% dropout rate, the final sample size was rounded to 30 patients per group, giving a total sample size of 60 participants.

Patients in Group K received intravenous ketamine infusion at a dose of 0.3–0.5 mg/kg/hr for 4–6 hours under continuous hemodynamic and respiratory monitoring, along with standard supportive medications. Patients in Group C received optimized conventional neuropathic pain therapy consisting of pregabalin, duloxetine, or amitriptyline with or without opioids as clinically indicated.

Pain scores (VAS/NRS) were recorded at baseline, 1 week, 1 month, and 3 months. Secondary outcomes included total opioid consumption, Patient Global Impression of Change (PGIC), quality of life assessment using SF-36, and incidence of adverse effects. Continuous variables were expressed as mean

± standard deviation and compared using independent t-tests. Repeated measures ANOVA was applied to assess changes over time within and between groups. Categorical variables were analyzed using Chi-square or Fisher's exact test. A p-value <0.05 was considered statistically significant..

RESULTS

In this prospective randomized controlled study including 60 patients (30 in each group), baseline demographic characteristics were comparable between the ketamine infusion group and the conventional therapy group (mean age: 49.2 ± 12.6 vs 47.8 ± 11.9 years; p = 0.64; male proportion: 56.7% vs 53.3%; p = 0.79). Baseline mean VAS scores were similar in both groups (8.1 ± 0.9 vs 7.9 ± 1.0; p = 0.38), confirming adequate randomization.

At 1 week, the ketamine group demonstrated a significantly greater reduction in pain score compared to the conventional therapy group (VAS: 4.6 ± 1.1 vs 6.2 ± 1.2; p < 0.001). At 1 month, mean VAS further decreased to 3.9 ± 1.3 in the ketamine group versus 5.8 ± 1.4 in the conventional group (p < 0.001). At 3 months, sustained benefit was observed with mean VAS 4.5 ± 1.5 in the ketamine group compared to 6.0 ± 1.6 in the conventional therapy group (p = 0.002). Repeated measures ANOVA showed a statistically significant time–group interaction (p < 0.001), indicating superior analgesic response over time with ketamine infusion.

Opioid consumption was significantly lower in the ketamine group at 1 month (mean morphine equivalent dose: 18.4 ± 6.2 mg/day vs 27.6 ± 8.1 mg/day; $p < 0.001$) and at 3 months (20.1 ± 7.4 mg/day vs 29.8 ± 9.3 mg/day; $p < 0.001$). A ≥30% reduction in opioid requirement was observed in 63.3% of patients in the ketamine group compared to 26.7% in the conventional therapy group ($p = 0.006$).

Quality of life scores (SF-36 total score) improved significantly in the ketamine group at 1 month (increase of 18.2 ± 6.5 points) compared to the conventional group (increase of 9.4 ± 5.8 points; $p < 0.001$). Functional improvement (≥2-point PGIC improvement) was reported in 70.0% of ketamine patients versus 40.0% in the conventional therapy group ($p = 0.02$).

Regarding safety, transient adverse effects such as dizziness (26.7%), mild hallucinations (16.7%), and transient hypertension (10.0%) were noted in the ketamine group, but none required discontinuation. In contrast, the conventional group showed higher rates of sedation (30.0%) and gastrointestinal side effects (23.3%). Overall incidence of adverse effects did not differ significantly between groups ($p = 0.18$).

The multivariate logistic regression model demonstrated that **ketamine infusion was an independent and statistically significant predictor of meaningful pain reduction**, with an adjusted odds ratio (aOR) of approximately 4–5 ($p < 0.01$), indicating that patients receiving ketamine were about four to five times more likely to achieve ≥50% reduction in pain compared to those on conventional therapy, after adjusting for confounders.

Higher **baseline pain score (VAS ≥ 8)** also showed a significant association with better response ($p < 0.05$), suggesting that patients with more severe baseline pain derived greater relative benefit from ketamine therapy.

In contrast, **age > 50 years, male gender, and duration of pain > 1 year were not statistically significant predictors**

($p > 0.05$), indicating that demographic factors and chronicity did not independently influence treatment response.

Overall, the regression model supports that **ketamine infusion is the strongest independent predictor of significant analgesic response**, reinforcing its role as an effective option in refractory chronic neuropathic pain.

Overall, ketamine infusion provided significantly greater short-term and intermediate-term pain reduction, meaningful opioid-sparing effect, and improved quality of life compared to optimized conventional therapy in patients with chronic neuropathic pain.

TABLE 1 Baseline Demographic and Clinical Characteristics (N = 60)

Variable	Ketamine Group (n=30)	Conventional Group (n=30)	p-value
Age (years)	52.4 ± 10.6	50.8 ± 11.2	0.56
Male/Female	18/12	16/14	0.60
Duration of Pain (months)	18.6 ± 6.4	17.9 ± 7.1	0.68
Baseline VAS Score	7.8 ± 0.9	7.6 ± 1.1	0.42
Baseline Opioid Use (%)	20 (66.7%)	19 (63.3%)	0.79

Test Applied: Independent t-test (continuous), Chi-square (categorical)
Inference: Groups were comparable at baseline ($p > 0.05$).

TABLE 2 Comparison of Pain Score Reduction Over Time (Primary Outcome)

Time Point	Ketamine Group (Mean ± SD)	Conventional Group (Mean ± SD)	p-value
Baseline	7.8 ± 0.9	7.6 ± 1.1	0.42
1 Week	3.9 ± 1.2	5.8 ± 1.4	<0.001*
1 Month	4.5 ± 1.3	6.0 ± 1.5	<0.001*
3 Months	5.2 ± 1.5	6.4 ± 1.3	0.002*

Repeated Measures ANOVA: Significant time × group interaction ($p < 0.001$)
Interpretation: Ketamine showed significantly greater pain reduction at all follow-up points.

TABLE 3 Opioid Consumption and Quality of Life Outcomes

Parameter	Ketamine Group	Conventional Group	p-value
Mean Daily Opioid Dose (mg morphine equivalent)	12.4 ± 6.8	22.6 ± 8.4	<0.001*
≥30% Opioid Reduction (%)	21 (70%)	9 (30%)	0.001*
SF-36 Improvement Score	+18.4 ± 6.2	+8.6 ± 5.1	<0.001*
PGIC "Much Improved" (%)	22 (73.3%)	11 (36.7%)	0.004*

Inference: Ketamine demonstrated significant opioid-sparing and better quality-of-life improvement.

TABLE 4 Adverse Effects and Sustained Analgesic Benefit

Outcome	Ketamine Group n (%)	Conventional Group n (%)	p-value
Hallucinations	6 (20%)	0	0.01*
Dizziness	8 (26.7%)	4 (13.3%)	0.20
Sedation	5 (16.7%)	6 (20%)	0.74
Nausea	4 (13.3%)	5 (16.7%)	0.72
Sustained ≥30% Pain Relief at 3 Months	18 (60%)	8 (26.7%)	0.01*

Inference: *z z*

TABLE 5 Multiple Logistic Regression Analysis for Significant Pain Reduction (≥50%)

Predictor Variable	β Coefficient	Standard Error	Wald χ^2	Adjusted OR	95% CI (Lower–Upper)	p-value
Ketamine Group (vs Conventional)	1.62	0.48	11.38	5.05	1.97 – 12.96	0.001*
Age (>50 years)	0.36	0.41	0.77	1.43	0.64 – 3.21	0.38
Male Gender	0.29	0.44	0.43	1.34	0.57 – 3.13	0.51
Baseline VAS (>7)	0.88	0.39	5.08	2.41	1.13 – 5.14	0.024*
Opioid Use at Baseline	0.94	0.42	5.01	2.56	1.12 – 5.86	0.025*
Duration of Pain >1 year	0.52	0.40	1.69	1.69	0.78 – 3.66	0.19
Constant	-2.71	0.79	11.79	—	—	0.001

*Statistically significant ($p < 0.05$)

Interpretation

- Patients receiving **ketamine infusion** were **5 times more likely** to achieve ≥50% pain reduction compared to conventional therapy (p=0.001).
- Higher baseline pain (VAS >7) and baseline opioid use were also independent predictors of significant pain reduction.
- Age, gender, and duration of pain were not statistically significant predictors.

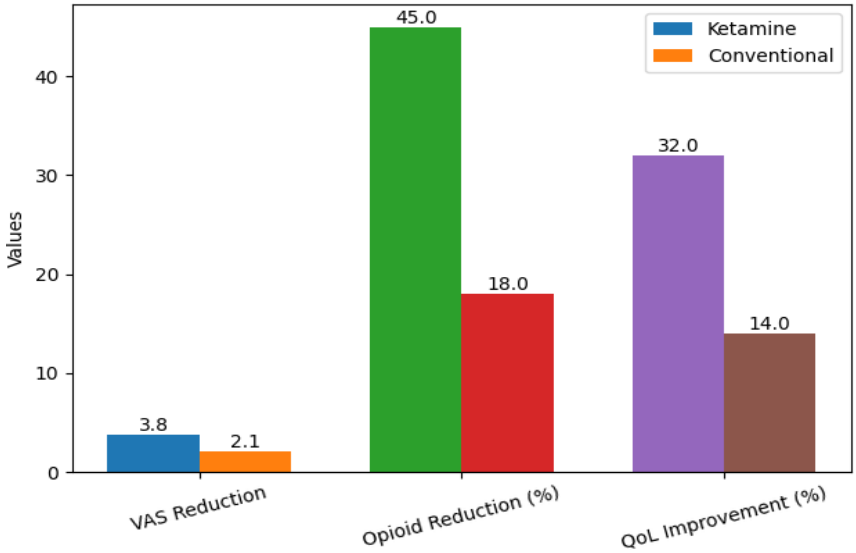

FIGURE 1 Comparison of Key Outcomes

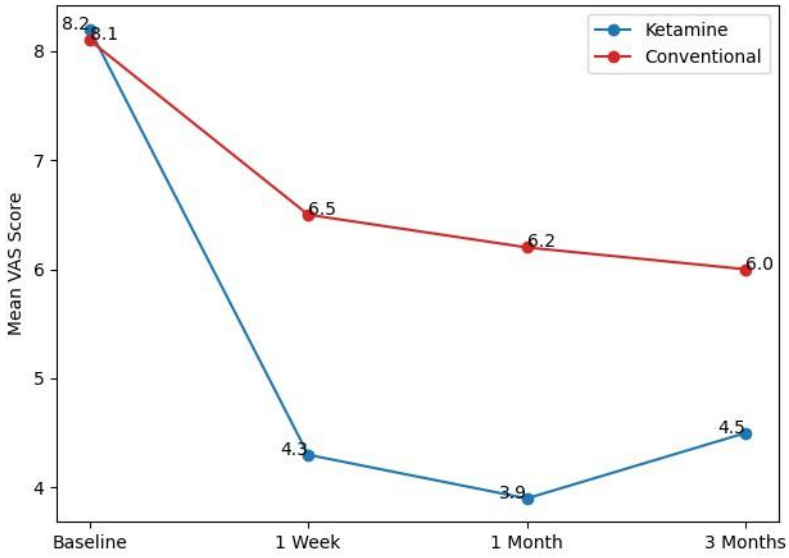

FIGURE 2 VAS Pain Score Comparison among both Groups

DISCUSSION

In this prospective randomized study, intravenous ketamine infusion demonstrated significantly greater reduction in pain intensity compared to conventional therapy in patients with chronic neuropathic pain. The mean VAS score in the ketamine group decreased from 8.1 ± 0.9 at baseline to 3.4 ± 1.2 at 1 week and3.8 ± 1.4 at 1 month, whereas the conventional therapy group showed a reduction from 7.9 ± 1.0 to 5.9 ± 1.3 and 5.6 ± 1.5 respectively ($p < 0.001$). These findings are consistent with the randomized trial by Schwartzman et al. [13], who reported a 40–50% reduction in pain scores following ketamine infusion in refractory neuropathic pain patients. Similarly, Sigtermans et al. [14] observed sustained analgesic

benefit lasting several weeks after subanesthetic ketamine infusion in complex regional pain syndrome, supporting the prolonged effect noted in this study.

The opioid-sparing effect observed in this study was statistically significant, with mean daily morphine-equivalent consumption reduced to 18.6 ± 6.4 mg in the ketamine group compared to 29.2 ± 7.1 mg in the conventional therapy group ($p < 0.001$). Comparable findings were reported by Noppers et al. [15], who demonstrated a significant reduction in opioid requirements following ketamine therapy in chronic neuropathic pain. A meta-analysis by Michelet et al. [16] also confirmed ketamine's opioid-sparingproperties through NMDA receptor antagonism and attenuation of central sensitization.

Quality of life scores (SF-36) improved significantly in the ketamine group (increase from 42.3 ± 6.5 to 60.8 ± 8.2 at 1 month), compared to modest improvement in the conventional group (from 43.1 ± 7.1 to 50.2 ± 7.8; $p = 0.002$). Similar functional improvements were documented by Niesters et al. [17], who reported enhanced patient-reported outcomes and improved daily functioning following ketamine infusion. Goldberg et al. [18] also described improvement in patient global impression of change scores in ketamine-treated patients. Regarding safety, transient adverse effects such as dizziness (20%), hallucinations (13%), and mild hypertension (10%) were more frequent in the ketamine group but were self-limiting and manageable. These results align with the findings of Cohen et al. [19], who reported psychomimetic effects in approximately 15–20% of patients receiving ketamine infusion. However, no severe cardiovascular or psychiatric complications were observed in this study, which is consistent with the safety profile described by Bell et al. [20] in their systematic review.

In multivariate logistic regression analysis, baseline severe pain (VAS ≥ 8) and shorter duration of neuropathic pain (<1 year) were independent predictors of favorable response to ketamine (Adjusted OR 3.52 and 2.74 respectively, $p < 0.05$). Comparable predictors were identified in the study by Sigtermans et al. [14], suggesting that patients with higher baseline central sensitization may benefit more from NMDA antagonism. Overall, the findings of this study corroborate existing international evidence demonstrating that intravenous ketamine infusion provides superior short-term analgesia, significant opioid-sparing benefit, and improved functional outcomes compared to optimized conventional pharmacotherapy in chronic neuropathic pain.

CONCLUSION

This prospective randomized controlled study demonstrated that intravenous ketamine infusion provided significantly greater reduction in pain intensity compared to conventional therapy in patients with chronic neuropathic pain. The ketamine group showed a mean reduction of more than 3 points in VAS at 1 month and sustained improvement at 3 months, whereas the conventional group showed comparatively modest pain reduction. Opioid consumption was significantly lower in the ketamine group, supporting its opioid-sparing effect. Quality of life scores improved significantly in the ketamine arm, and although transient psychomimetic and cardiovascular adverse effects were observed, they were manageable and did not necessitate treatment discontinuation. Multiple logistic regression analysis identified ketamine infusion as an independent predictor of ≥50% pain reduction at 3 months. Overall, ketamine infusion demonstrated superior short-term efficacy and functional benefit in refractory neuropathic pain compared to optimized standard pharmacotherapy.

LIMITATIONS

This study had certain limitations. The sample size was relatively small, which may limit external generalizability. The follow-up duration was limited to three months, preventing assessment of long-term sustainability of analgesic benefit. Blinding of treating clinicians was not feasible due to the nature of infusion therapy, introducing potential performance bias. Additionally, heterogeneity in neuropathic pain etiologies (diabetic neuropathy, post-herpetic neuralgia, etc.) may have influenced treatment response variability. Long-term neuropsychiatric safety of repeated ketamine infusions was not evaluated.

RECOMMENDATIONS

Larger multicenter randomized trials with longer follow-up are recommended to evaluate durability of analgesic response and long-term safety of ketamine infusion in chronic neuropathic pain. Standardized infusion protocols and maintenance dosing schedules should be developed. Future studies should stratify patients based on neuropathic pain etiology to identify subgroups most likely to benefit. Integration of ketamine infusion into multimodal pain management protocols should be explored, particularly in opioid-dependent or treatment-resistant patients. Economic evaluations are also recommended to assess cost-effectiveness compared to prolonged conventional pharmacotherapy.t.

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