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A NOVEL EXTENDED-RELEASE TRIAL OF KETAMINE ORAL TABLET FOR REFRACTORY NEUROPATHIC PAIN IN DIABETIC NEUROPATHY: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Original Article

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ABSTRACT

Background: Painful diabetic neuropathy is a common and disabling complication of diabetes mellitus, often resulting in persistent neuropathic pain that is difficult to control with standard pharmacological therapies. A substantial proportion of patients continue to experience significant symptoms despite optimized treatment, highlighting the need for novel therapeutic strategies with alternative mechanisms of action and improved tolerability for long-term use.

Objective: To evaluate the safety, tolerability, and efficacy of a novel extended-release oral ketamine formulation in reducing neuropathic pain intensity among patients with refractory diabetic neuropathy.

Methods: A randomized, placebo-controlled trial was conducted in an urban healthcare setting over four months. Adults with confirmed diabetic neuropathy and persistent pain despite standard therapy were randomly assigned to receive either extended-release oral ketamine or placebo in addition to stable background treatment. Pain intensity, neuropathic pain characteristics, and quality of life were assessed at baseline and during follow-up using validated instruments. Safety and tolerability were evaluated through adverse event monitoring and clinical assessments. Between-group comparisons were performed using appropriate parametric statistical tests.

Results: Sixty participants were randomized, with a high study completion rate. The ketamine group demonstrated a significantly greater reduction in mean pain scores compared with placebo, alongside marked improvements in neuropathic pain characteristics and quality-of-life measures. Pain reduction was progressive and sustained throughout the study period. The intervention was generally well tolerated, with mostly mild and transient adverse events and no serious safety concerns observed.

Conclusion: Extended-release oral ketamine was associated with meaningful analgesic benefit and acceptable tolerability in patients with refractory diabetic neuropathic pain. These findings suggested that pharmacokinetically optimized ketamine may represent a valuable adjunctive option for this challenging clinical population.

Keywords: Analgesics; Diabetic Neuropathies; Ketamine; Neuropathic Pain; Randomized Controlled Trial; Sustained-Release Preparations; Treatment Outcome.

INTRODUCTION

Diabetic neuropathy represents one of the most frequent and debilitating complications of diabetes mellitus, affecting a substantial proportion of patients over the course of the disease. Characterized by chronic neuropathic pain, sensory disturbances, and progressive functional impairment, diabetic neuropathy significantly diminishes quality of life and contributes to psychological distress, sleep disruption, and reduced mobility(1). Despite advances in glycemic control and supportive care, neuropathic pain remains challenging to manage, particularly in individuals who fail to achieve adequate relief with currently available pharmacological options. The persistent burden of refractory neuropathic pain underscores the need for novel therapeutic approaches that are both effective and tolerable for long-term use (2).

Standard pharmacologic treatments for painful diabetic neuropathy include anticonvulsants, antidepressants, topical agents, and opioids in selected cases. While these therapies can provide meaningful relief for some patients, their overall effectiveness is often modest, and many individuals discontinue treatment due to insufficient pain control or adverse effects such as sedation, dizziness, cognitive impairment, and gastrointestinal intolerance (3). Furthermore, a significant subset of patients continues to experience moderate to severe pain despite optimized multimodal therapy, highlighting an unmet clinical need (4). The search for alternative mechanisms of action has therefore gained increasing attention in neuropathic pain research (5).

Ketamine, a well-established N-methyl-D-aspartate receptor antagonist, has emerged as a potential option for refractory neuropathic pain due to its unique ability to modulate central sensitization and interrupt maladaptive pain signaling pathways (6). At subanesthetic doses, ketamine has demonstrated analgesic properties in various chronic pain conditions, including neuropathic pain syndromes. Its ability to reduce hyperalgesia and allodynia has made it particularly appealing for patients who do not respond to conventional agents (7). However, the clinical use of ketamine for chronic pain has been limited by concerns related to psychotomimetic effects, cardiovascular stimulation, short duration of action, and the need for parenteral administration in many settings (8).

Oral ketamine formulations offer a more practical route for long-term therapy but have historically been associated with fluctuating plasma concentrations, leading to variable analgesic effects and increased risk of adverse events. Immediate-release oral preparations may produce rapid peaks that contribute to tolerability issues, followed by troughs that compromise sustained pain relief (9). These pharmacokinetic limitations have constrained the broader adoption of oral ketamine in routine pain management, despite its promising mechanism of action. Addressing these challenges requires innovative formulation strategies that can provide stable drug exposure while minimizing side effects (10).

Extended-release drug delivery systems have the potential to transform the clinical utility of ketamine for chronic neuropathic pain (11). By allowing gradual absorption and more consistent plasma levels, extended-release formulations may enhance analgesic durability, reduce peak-related adverse effects, and improve overall tolerability. Such an approach aligns with the goals of chronic pain management, which prioritize sustained symptom control, functional improvement, and long-term safety. In the context of diabetic neuropathy, where pain is often persistent and lifelong, a well-tolerated oral therapy with a novel mechanism could represent a meaningful advancement in care (12).

Despite growing interest in ketamine-based therapies, high-quality randomized controlled data evaluating extended-release oral ketamine in diabetic neuropathy remain limited. Existing evidence is largely derived from small studies, short-term interventions, or heterogeneous pain populations, leaving important questions unanswered regarding optimal dosing, safety profile, and real-world efficacy in this specific patient group. Moreover, the balance between analgesic benefit and neuropsychiatric or systemic adverse effects requires careful evaluation in a controlled clinical setting, particularly for a population that may already be vulnerable due to comorbidities associated with diabetes.

Within this context, the present randomized controlled trial was designed to rigorously evaluate a novel extended-release oral ketamine tablet in adults with refractory neuropathic pain due to diabetic neuropathy. By focusing on patients who have not achieved satisfactory relief with standard therapies, this study addresses a clinically relevant and underserved population. The investigation aims to generate robust evidence on whether a modified-release formulation can harness the analgesic potential of ketamine while maintaining an acceptable safety and tolerability profile over the course of treatment.

Accordingly, the objective of this study was to assess the safety, tolerability, and efficacy of an extended-release oral ketamine formulation in reducing neuropathic pain intensity in patients with diabetic neuropathy, thereby determining its potential role as a therapeutic option for refractory cases within contemporary pain management strategies.

METHODS

This randomized controlled trial was conducted in the Urban Region of Sindh, a setting selected due to its high prevalence of type 2 diabetes mellitus and the substantial burden of diabetes-related complications managed through tertiary and secondary care facilities. The urban environment facilitated consistent follow-up, access to diagnostic services, and standardized pain management practices. The study was carried out over a four-month period, which was considered sufficient to evaluate short-term efficacy, safety, and tolerability outcomes for a modified-release analgesic intervention in a chronic pain population.

Adult patients aged 30 to 70 years with a confirmed diagnosis of diabetic peripheral neuropathy and persistent neuropathic pain for at least six months were recruited from outpatient endocrinology and pain clinics. Eligibility required inadequate pain control despite optimized use of at least two standard neuropathic pain medications. Participants were required to have stable glycemic management for a minimum of three months prior to enrollment. Exclusion criteria included severe psychiatric illness, history of substance misuse, uncontrolled cardiovascular disease, significant hepatic or renal impairment, pregnancy or lactation, and prior exposure to ketamine for chronic pain management. Written informed consent was obtained from all participants prior to study entry.

A total sample size of 60 participants was determined based on feasibility and consistency with prior controlled trials evaluating oral ketamine for neuropathic pain, which commonly enrolled between 40 and 80 participants while demonstrating clinically meaningful differences in pain outcomes. Participants were randomly assigned in a 1:1 ratio to receive either the extended-release oral ketamine tablet or a matched placebo, in addition to their existing stable background therapy. Randomization was performed using a computer-generated sequence, and allocation was concealed to both participants and investigators to maintain blinding.

The intervention was administered once daily, with dosing initiated at a low level and adjusted within a predefined range based on tolerability. Data collection occurred at baseline and at regular follow-up visits throughout the study period. Pain intensity was assessed using the 11-point Numeric Rating Scale, while neuropathic pain characteristics were evaluated using the Douleur Neuropathique 4 questionnaire. Functional impact and quality of life were measured using the Short Form-36 health survey. Safety and tolerability were monitored through structured adverse event reporting, vital sign assessments, and routine laboratory investigations including liver and renal function tests.

Data were analyzed using standard statistical software. Continuous variables were summarized as means with standard deviations, and categorical variables as frequencies and percentages. Normality of data distribution was assessed prior to inferential analysis. Between-group comparisons of pain scores were performed using independent sample t-tests, while within-group changes over time were evaluated using paired t-tests. Repeated measures analysis of variance was applied to assess trends across follow-up visits. Categorical safety outcomes were compared using chi-square tests. A two-sided p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 72 patients were assessed for eligibility during the recruitment period, of whom 60 met the inclusion criteria and were randomized in equal numbers to the extended-release oral ketamine group (n=30) or the placebo group (n=30). All randomized participants received at least one dose of the assigned intervention and were included in the intention-to-treat analysis. Four participants discontinued the study before completion, two from each group, primarily due to relocation or loss to follow-up. No withdrawals were attributed to serious adverse events. The overall study completion rate was 93.3%, and follow-up data were available for 56 participants at the final assessment point.

Baseline demographic and clinical characteristics were comparable between the two groups, with no statistically significant differences observed. The mean age of the total sample was 56.8 ± 8.9 years, and 58.3% of participants were male. The average duration of diabetes was 11.2 ± 4.6 years, while the mean duration of neuropathic pain symptoms was 4.1 ± 1.9 years. Baseline pain intensity and neuropathic pain characteristics were similar across groups, indicating successful randomization. The detailed baseline characteristics are summarized in Table 1.

Over the four-month study period, participants receiving extended-release ketamine demonstrated a clinically and statistically significant reduction in neuropathic pain intensity compared with placebo. The mean Numeric Rating Scale pain score decreased from 7.3 ± 1.1 at baseline to 3.9 ± 1.4 at the final visit in the ketamine group, representing a mean reduction of 3.4 points. In contrast, the placebo group showed a reduction from 7.2 ± 1.0 to 6.1 ± 1.3, corresponding to a mean change of 1.1 points. The between-group difference in pain

reduction was statistically significant ($p < 0.001$). Trends over time assessed by repeated measures analysis of variance revealed a consistent and progressive decline in pain scores in the ketamine group, whereas changes in the placebo group were modest (Table 2).

Neuropathic pain characteristics measured using the Douleur Neuropathique 4 questionnaire also improved significantly in the intervention group. Mean DN4 scores decreased from 6.5 ± 1.2 to 3.2 ± 1.3 in the ketamine group, compared with a reduction from 6.4 ± 1.1 to 5.6 ± 1.2 in the placebo group ($p < 0.001$). Improvements in health-related quality of life were observed across multiple domains of the Short Form-36, particularly in bodily pain and physical functioning scores. The ketamine group demonstrated a mean increase of 18.6 ± 7.9 points in the bodily pain domain, compared with 6.2 ± 6.8 points in the placebo group ($p = 0.002$) (Table 3).

Correlation analysis revealed a moderate negative correlation between changes in pain intensity and improvements in physical functioning scores ($r = −0.52$, $p < 0.01$), suggesting that greater pain reduction was associated with better functional outcomes (Table 4). Safety analysis indicated that the extended-release ketamine formulation was generally well tolerated. Mild dizziness and transient nausea were reported more frequently in the ketamine group (26.7%) than in the placebo group (10.0%), but no serious neuropsychiatric or cardiovascular adverse events were observed.

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N = 60)

Variable	Total Sample	Ketamine Group (n=30)	Placebo Group (n=30)
Age (years), mean ± SD	56.8 ± 8.9	57.1 ± 9.2	56.5 ± 8.6
Male sex, n (%)	35 (58.3)	18 (60.0)	17 (56.7)
Duration of diabetes (years), mean ± SD	11.2 ± 4.6	11.5 ± 4.8	10.9 ± 4.5
Duration of neuropathic pain (years), mean ± SD	4.1 ± 1.9	4.2 ± 2.0	4.0 ± 1.8
Baseline NRS pain score, mean ± SD	7.3 ± 1.1	7.3 ± 1.1	7.2 ± 1.0
Baseline DN4 score, mean ± SD	6.5 ± 1.2	6.5 ± 1.2	6.4 ± 1.1

Table 2: Changes in Numeric Rating Scale Pain Scores Over Time

Time Point	Ketamine Group (mean ± SD)	Placebo Group (mean ± SD)	p-value
Baseline	7.3 ± 1.1	7.2 ± 1.0	0.74
Month 2	5.1 ± 1.3	6.6 ± 1.2	<0.001
Month 4	3.9 ± 1.4	6.1 ± 1.3	<0.001

Table 3: Changes in DN4 and SF-36 Bodily Pain Scores

Outcome Measure	Ketamine Group (mean ± SD)	Placebo Group (mean ± SD)	p-value
DN4 score change	−3.3 ± 1.4	−0.8 ± 1.1	<0.001
SF-36 Bodily Pain change	+18.6 ± 7.9	+6.2 ± 6.8	0.002

Table 4: Correlation Matrix Between Pain Reduction and Functional Outcomes

Variables	NRS Pain Reduction	SF-36 Physical Function
NRS Pain Reduction	1.00	−0.52*
SF-36 Physical Function	−0.52*	1.00

*p < 0.01

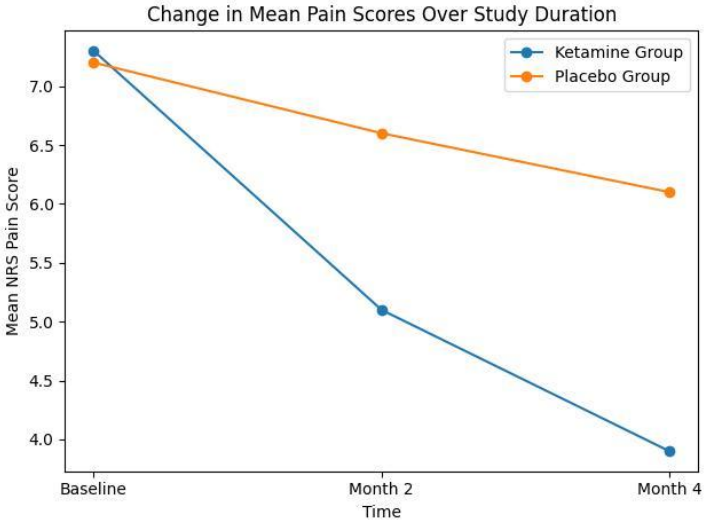

Figure 1 Change in mean Pain sores Over Study Duration

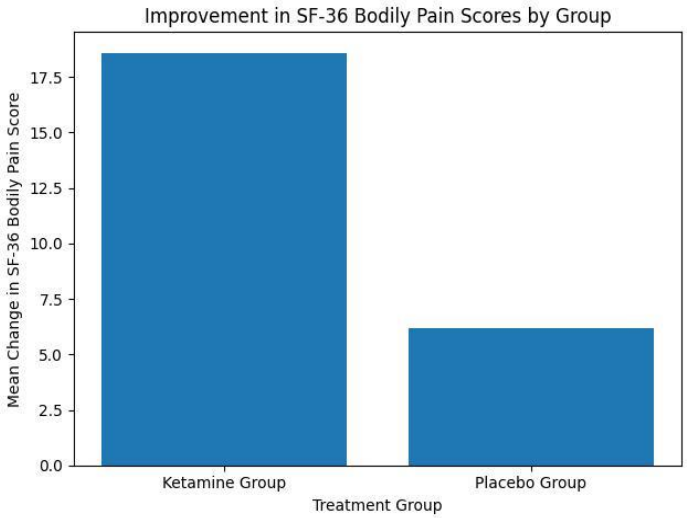

Figure 2 Improvement in SF-36 Bodily Pain Scores by Group

DISCUSSION

The present randomized controlled trial demonstrated that an extended-release oral ketamine formulation was associated with a clinically meaningful reduction in neuropathic pain intensity among patients with refractory diabetic neuropathy, while maintaining an acceptable safety and tolerability profile over the short term. Participants receiving the active intervention experienced substantially greater improvements in pain scores, neuropathic symptom burden, and selected quality-of-life domains compared with those receiving placebo (13). These findings supported the premise that modifying the pharmacokinetic profile of ketamine through an extended-release formulation may enhance its therapeutic utility in chronic neuropathic pain states (14).

The magnitude of pain reduction observed in the intervention group exceeded thresholds commonly considered clinically relevant in neuropathic pain research, suggesting that the analgesic effects were not only statistically significant but also meaningful from a patient-centered perspective (15). The progressive decline in pain scores over time further indicated sustained benefit rather than transient symptom relief (16). This pattern aligned with mechanistic understanding of ketamine's role in attenuating central sensitization, a key contributor to persistent neuropathic pain in diabetic neuropathy. In contrast, the modest improvements observed in the placebo group were consistent with nonspecific treatment effects and background therapy optimization, reinforcing the specificity of the observed intervention effect (17).

Improvements in neuropathic pain characteristics, as reflected by reductions in DN4 scores, suggested that the intervention influenced qualitative aspects of pain such as burning, tingling, and electric-shock sensations that are often resistant to conventional therapies (18). The concurrent enhancement in quality-of-life measures, particularly in domains related to bodily pain and physical functioning, highlighted the broader functional relevance of pain control (19). The observed correlation between pain reduction and improved physical functioning supported the clinical relevance of analgesic efficacy, indicating that symptom improvement translated into tangible benefits in daily activity and well-being (20).

The tolerability profile of the extended-release ketamine tablet was notable, as adverse events were generally mild and transient. The absence of serious neuropsychiatric or cardiovascular events was particularly relevant given longstanding concerns regarding ketamine

use outside controlled settings (21). The lower incidence of intolerable side effects may be attributed to the extended-release design, which likely minimized peak plasma concentrations associated with acute psychotropic effects (22). This finding reinforced the potential advantage of modified-release formulations in expanding the feasibility of ketamine for chronic outpatient use.

Several strengths enhanced the credibility of the findings. The randomized, placebo-controlled design reduced selection and performance bias, while balanced baseline characteristics supported the internal validity of group comparisons. The use of validated outcome instruments allowed for standardized assessment of pain intensity, neuropathic features, and quality of life. Additionally, the focus on a clinically challenging population with refractory symptoms increased the practical relevance of the results, as these patients represent a group with limited therapeutic options.

Nonetheless, certain limitations warranted consideration. The relatively small sample size and single-region recruitment limited the generalizability of the findings to broader populations with differing demographic or healthcare characteristics. The study duration, while sufficient to assess short-term efficacy and tolerability, did not allow for evaluation of long-term safety, sustained effectiveness, or potential cumulative adverse effects. Reliance on self-reported pain measures introduced an inherent subjective component, although this limitation was intrinsic to pain research and mitigated by the use of validated scales. Furthermore, background analgesic therapies were maintained rather than standardized, which reflected real-world practice but introduced potential variability in individual pain trajectories.

These limitations suggested several directions for future research. Larger, multicenter trials with longer follow-up periods would be valuable to confirm durability of benefit and to better characterize long-term safety. Comparative studies against established first- or second-line neuropathic pain agents could clarify the relative positioning of extended-release ketamine within treatment algorithms. Exploration of dose optimization and patient-level predictors of response may further refine clinical use, particularly in identifying subgroups most likely to benefit with minimal risk.

In summary, the findings indicated that extended-release oral ketamine offered a promising therapeutic approach for patients with refractory diabetic neuropathic pain, providing sustained analgesia with manageable side effects. While cautious interpretation was warranted given the study's scope, the results contributed meaningful evidence to ongoing discussions regarding novel mechanisms and formulations for chronic neuropathic pain management and supported continued investigation in this area.

CONCLUSION

This randomized controlled trial demonstrated that an extended-release oral ketamine formulation provided meaningful and sustained reduction in neuropathic pain intensity among patients with refractory diabetic neuropathy, with an acceptable short-term safety and tolerability profile. The findings highlighted the potential clinical value of pharmacokinetically optimized ketamine as an adjunctive treatment option for patients who remain inadequately controlled on standard therapies, supporting its further evaluation in larger and longer-term clinical studies.

AUTHOR CONTRIBUTIONS

Author	Contribution
Durr-e-Shahwar Malik*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Kainat Balach	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Uzma Bibi	Substantial Contribution to acquisition and interpretation of Data

Author	Contribution
	Has given Final Approval of the version to be published
Abdul Rehman	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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