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# Intravenous patient-controlled analgesia with esketamine improves early depressive symptoms in patients with postherpetic neuralgia: a single-center retrospective cohort study

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## Abstract

**Objective** Patients with Postherpetic Neuralgia (PHN) often exhibit depressive-like symptoms, significantly impacting their quality of life. Esketamine, known for its analgesic properties, has also been recognized for its rapid antidepressant effects. However, its efficacy in the treatment of PHN requires further exploration. This study aims to evaluate the impact of intravenous patient-controlled analgesia(PICA) with esketamine on depressive mood in PHN patients.

**Methods** This retrospective study analyzed PHN patients hospitalized and treated at the affiliated hospital of Southwest Medical University from June 2021 to March 2023. Patients were divided into the esketamine group (E group) and the sufentanil group (S group) based on their treatment regimens. Primary outcomes included pain numerical rating scale(NRS), depression patient health questionaire-9(PHQ-9), and anxiety generalized anxiety disorder-7(GAD-7) scores measured before treatment, and at 3 days, 7 days, 1 month, 2 months, and 3 months post-treatment.

**Results** A total of 83 patients were included in the analysis. Before treatment, there were no statistically significant differences in pain NRS, depression PHQ-9, and anxiety GAD-7 scores between the two groups ($P > 0.05$). Compared to before treatment, significant reductions in pain NRS scores were observed at all post-treatment time points in both groups ($P < 0.05$), with no differences between groups ($P > 0.05$). The E group exhibited significantly lower depression PHQ-9 scores than the S group at 3 days and 7 days post-treatment ($P < 0.05$), but no significant differences were observed at 1 month, 2 months, and 3 months ($P > 0.05$). Anxiety GAD-7 scores were significantly lower in the E group compared to the S group at 3 days, 7 days post-treatment ($P < 0.05$), with no statistical differences at 1 month, 2 months, and 3 months post-treatment ($P > 0.05$).

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**Conclusion** Both PICA with esketamine and sufentanil alleviated pain equally in PHN patients. However, PICA with esketamine specifically improved early symptoms of anxiety and depression.

**Keywords** Esketamine, Postherpetic neuralgia, Depression

## Background

Postherpetic Neuralgia (PHN) is a persistent pain condition following herpes zoster infection and is one of the most severe complications of shingles. PHN causes constant pain and is associated with significant psychological disorders, such as anxiety and depression, which collectively reduce patients' quality of life and severely impact their personal and social functions [1–3]. Current treatment strategies for PHN include pharmacotherapy, minimally invasive interventions, and physical therapy. Among these, pulsed radiofrequency is widely used due to its minimal invasiveness, fewer complications, and non-destructive nature to nerves, effectively alleviating pain [4]. However, existing treatments have limited effects on relieving anxiety and depression in PHN patients, highlighting the importance of addressing psychological disorders in comprehensive PHN treatment.

In recent years, esketamine has gained attention for its dual functions of analgesia and rapid antidepressant effects [5–7]. As the S-enantiomer of ketamine, esketamine has a higher affinity for and selective inhibition of the NMDA receptor, especially the presynaptic NMDA receptors on the GluN2B subunit. It exerts antidepressant effects by inhibiting NMDA receptor-dependent neuronal burst firing and activating AMPA receptors [8]. The approval of esketamine nasal spray by the U.S. Food and Drug Administration (FDA) for treating treatment-resistant depression highlights its important role in mental health treatment [9].

This study aims to explore the effects of intravenous patient-controlled analgesia(PICA) with esketamine on pain, anxiety, and depression in PHN patients. It offers a new perspective and approach for the clinical treatment of neuropathic pain and provides a scientific basis for comprehensive treatment strategies for PHN patients.

## Methods

### Clinical data

This retrospective observational study included patients diagnosed with Postherpetic Neuralgia (PHN) at the Department of Pain Management of the Affiliated Hospital of Southwest Medical University from June 2021 to March 2023. The inclusion criteria were as follows: (1) a diagnosis of PHN according to the "Chinese Expert Consensus on Herpes Zoster" and the "Chinese Expert Consensus on Diagnosis and Treatment of Postherpetic Neuralgia"; (2) patients aged 18–80 years; (3) patients who provided informed consent for the relevant treatment; (4) patients who underwent pulsed radiofrequency treatment under ultrasound guidance, as this procedure is standard practice in our hospital for managing treatment-resistant PHN to enhance pain relief; (5) patients treated with either sufentanil or esketamine via PICA; (6) patients whose pain (NRS score), depression (PHQ-9 score), and anxiety (GAD-7 score) were routinely assessed as part of clinical care before treatment, and at 3 days, 7 days, 1 month, 2 months, and 3 months post-treatment. These assessments are part of our department's standard practice to monitor the psychological and physical well-being of patients with chronic pain conditions, such as PHN. The PHQ-9 and GAD-7 questionnaires, which are widely validated tools for assessing depression and anxiety respectively, were utilized (Kroenke et al., 2001; Spitzer et al., 2006) [10, 11].

Exclusion criteria included: (1) patients with a history of psychiatric disorders; (2) patients who declined participation during outpatient or telephone follow-up; (3) patients lost to follow-up; (4) patients who did not complete the NRS, PHQ-9, and GAD-7 assessments before and after treatment at the specified time points; (5) patients with contraindications to esketamine or sufentanil. To address potential bias, sensitivity analyses were conducted to evaluate differences between patients with complete and incomplete follow-up data.

### Rationale for choosing esketamine or sufentanil

Esketamine was chosen due to its dual analgesic and rapid antidepressant effects, which were beneficial for PHN patients who often experience both pain and depressive symptoms. Sufentanil, a potent opioid analgesic, was chosen as the comparator because it was commonly used in pain management for its strong analgesic properties. The comparison aimed to evaluate the additional benefits of esketamine's antidepressant effects beyond pain relief provided by sufentanil. The decision to use either sufentanil or esketamine for PICA was made by the treating clinician based on the patient's clinical presentation and history. Patients exhibiting more severe depressive symptoms or inadequate responses to previous opioid therapies were more likely to receive esketamine. This decision-making process was not standardized across the study period and was left to the discretion of the attending physicians.

### Sample size calculation

This cohort study's primary outcome, the NRS score, is a continuous variable. The sample size (N) was calculated using the formula $N = [(Z\alpha/2+Z\beta)^2 * \sigma^2 * (1+1/\kappa)] /$

δ^2, where σ is the pooled standard deviation, δ is the difference between the means, Z represents the standard normal distribution, α is the Type I error probability, and β is the Type II error probability. Based on previous literature [12, 13], the standard deviation (σ) was assumed to be 1.5, and the clinically meaningful difference (δ) was set at 1.0. These values are consistent with the findings from studies on related outcomes in anesthesia and analgesia [12, 13]. Using a Zα/2 of 1.96 (for a 5% Type I error) and Zβ of 0.84 (for 80% power), the calculated sample size was 40 cases per group, totaling 80 cases. These calculations were performed using PASS 2021 software. Considering the retrospective nature of the study and potential loss to follow-up, we included a total of 83 patients to ensure sufficient power.

#### Pulsed radiofrequency treatment

Targeting the affected nerve root under ultrasound guidance (Fig. 1), pulsed radiofrequency treatment was administered with specific parameters (70 V, 2 Hz, 20 ms, 42 °C for 6 min, 45 °C for 6 min).

#### Intravenous patient-controlled analgesia

Either sufentanil (100 μg in 100 ml saline) or esketamine (100 mg in 100 ml saline) was used for intravenous analgesia via a pump, set to a continuous infusion of 1 ml/h, with patient-controlled analgesia (PCA) of 0.5 ml per demand, and a lockout time of 30 min, continuously used for 3 days. If the pain NRS score exceeded 4, an additional intramuscular injection of 50 mg tramadol hydrochloride was given as a rescue analgesic measure. Intramuscular tramadol was chosen as it provides a rapid and reliable analgesic effect, which is important for breakthrough pain management. Increasing the bolus volume or the continuous background infusion was avoided to minimize the risk of potential side effects associated with higher doses of sufentanil or esketamine.

Data collection involved reviewing medical records for demographic information, medical history, PHN diagnosis details, NRS scores, and previous PHN treatment methods. Follow-up data collected during hospital stays, outpatient visits, or telephone follow-ups included pain (NRS score), depression (PHQ-9 score), anxiety (GAD-7 score), medication use, and any adverse events, all anonymized to protect patient privacy. Patients agreed to participate after being informed through outpatient services or telephone follow-ups, waiving the need for signed informed consent. NRS pain scores range from 0 to 10, with 0 indicating no pain, 1–3 light pain, 4–6 moderate pain, and 7–10 severe pain. PHQ-9 depression scores range from 0 to 4 for no depression, 5–9 for mild, 10–14 for moderate, 15–19 for moderately severe, and 20–27 for severe depression. GAD-7 anxiety scores range from 0 to 4 for no anxiety, 5–9 for mild, 10–14 for moderate, and 15–21 for severe anxiety.

#### Primary outcomes

Pain NRS, depression PHQ-9, and anxiety GAD-7 scores were assessed before treatment and at each specified time point after treatment (3 days, 7 days, 1 month, 2 months, and 3 months). These scores were collected through patient self-reports during hospital visits or telephone follow-ups.

#### Secondary outcomes

Patient demographic information, medical history, PHN diagnosis, previous PHN treatment methods, and adverse reactions were recorded from medical records. The PHQ-9 and GAD-7 questionnaires, validated for their reliability and validity in numerous studies (Kroenke et al., 2001; Spitzer et al., 2006), were used to assess depression and anxiety.

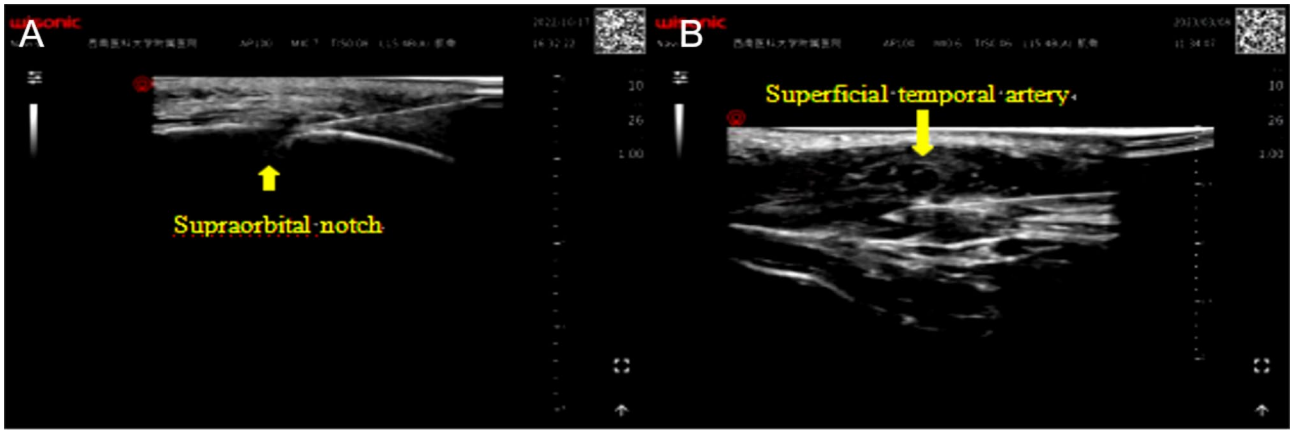


**Fig. 1** B-ultrasound image of radiofrequency needle puncture to the nerve. A shows the supraorbital nerve; B shows the ototemporal nerve

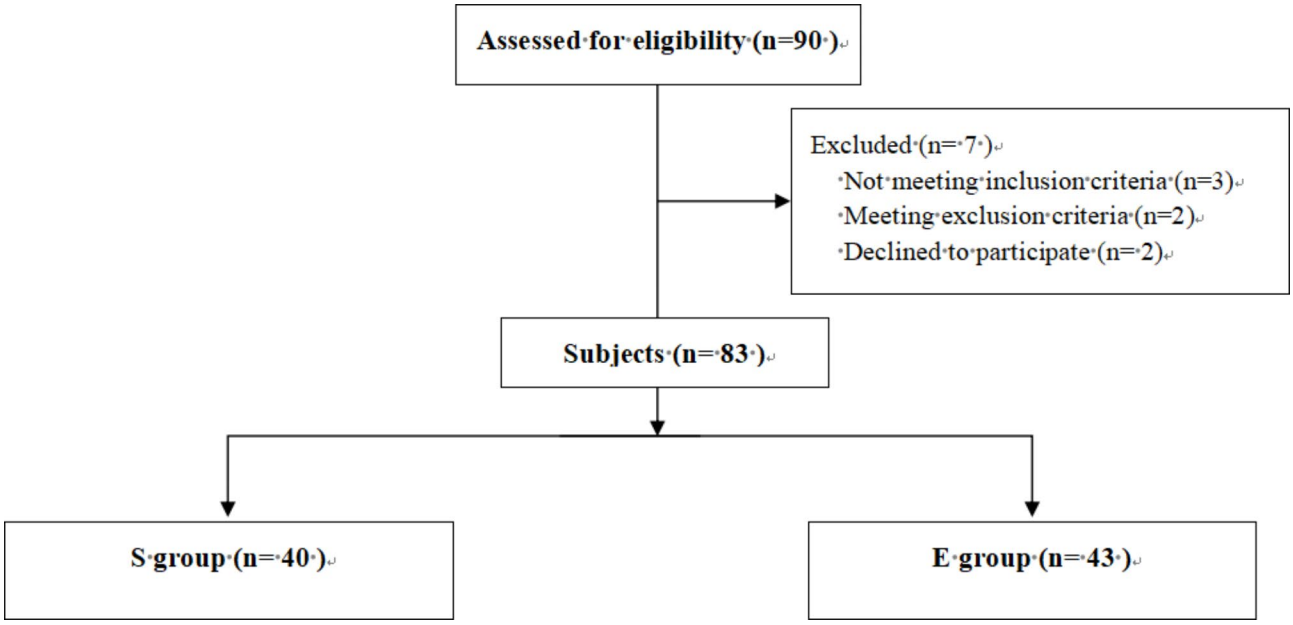


**Fig. 2** The study participants flow diagram

### Sensitivity analyses

Sensitivity analyses were performed to assess potential differences between patients who completed follow-up and those who did not. This analysis compared baseline characteristics such as age, gender, initial NRS scores, PHQ-9 scores, and GAD-7 scores between the two groups.

### Statistical analysis

Data processing and statistical analysis were performed using SPSS 26.0 and GraphPad Prism 9.0 software. Quantitative data following a normal distribution were presented as mean ± standard deviation and compared using t-tests or one-way ANOVA for inter-group comparisons, while non-normally distributed quantitative data were compared using the T-test or Mann-Whitney U test for inter-group comparisons, and the Friedman rank sum test for intra-group comparisons. Categorical data were compared using the Chi-square test. $P<0.05$ was considered statistically significant.

## Results

### Patient baseline characteristics

Between June 2021 and March 2023, a total of 90 patients diagnosed with PHN were initially included in this study. Of these, 3 patients were excluded due to loss of contact through outpatient visits or telephone, 2 patients refused to participate during telephone or outpatient follow-ups and were excluded, and 2 patients were excluded due to incomplete assessment information. Thus, the retrospective analysis ultimately included 83 patients, with 40 in the S group and 43 in the E group (Fig. 2). A comparison of general characteristics between the two groups showed no statistically significant differences (Table 1, $P>0.05$). Additionally, the results indicated no significant differences in baseline characteristics, including initial NRS scores, PHQ-9 scores, and GAD-7 scores, between the two groups (Figs. 3, 4 and 5, $P>0.05$). The sensitivity analyses also revealed no significant differences in baseline characteristics, including age, gender, initial NRS scores, PHQ-9 scores, and GAD-7 scores, between patients who completed follow-up and those who did not ($P>0.05$).

**Table 1** Clinical characteristics of the two groups (x ± SD)

| Group | S | E | *P* |
|---|---|---|---|
| Male/Female | 23/17 | 22/21 | 0.563 |
| Age(years) | 69.95 ± 11.9 | 68.63 ± 10.09 | 0.590 |
| Affected side(Left/Right) | 18/22 | 26/17 | 0.158 |
| Pathogenic segment | | | |
| Cephalic and Cervical segment | 14(35%) | 14(32.6%) | 0.814 |
| Thoracic segment | 24(60%) | 26(60.5%) | 0.965 |
| Lumbar segment | 2(5%) | 3(6.9%) | 0.705 |
| Comorbidity | 11/29 | 12/31 | 0.967 |
| Hypertension | 14 | 13 | 0.484 |
| Coronary Heart Disease | 2 | 5 | 0.167 |
| Diabetes | 11 | 10 | 0.657 |
| Time of onset(month) | 1.000[1.000,4.000] | 1.000[1.000,3.000] | 0.277 |

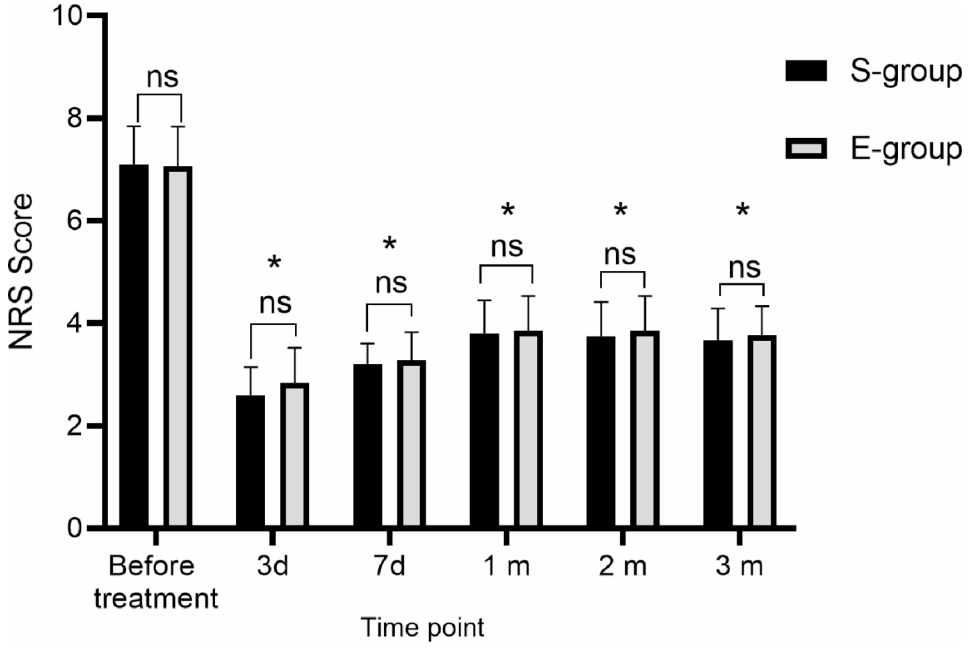


**Fig. 3** NRS scores of the two groups at different time points. NRS: Numerical Rating Scale, S: Sufentanil, E:Esketamine, d: day, m: month. Vs before treatment, $^{*}P < 0.05$, vs. S-group, $^{ns}P > 0.05$

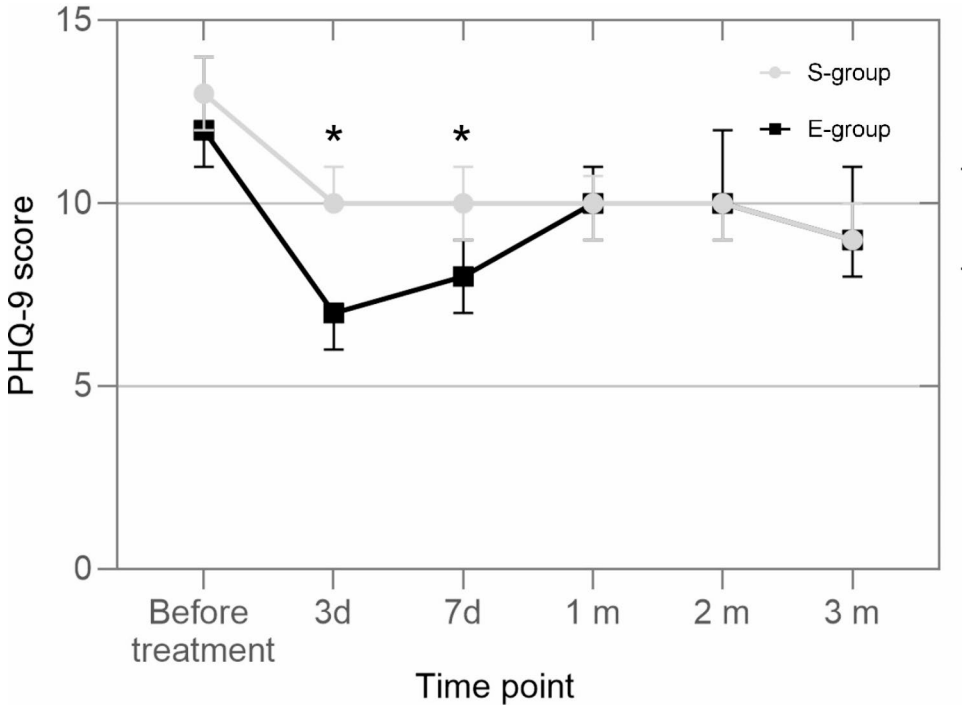


**Fig. 4** PHQ-9 scores of the two groups at different time points. PHQ-9: Patient Health Questionaire-9, S: Sufentanil, E: Esketamine, d: day, m: month. Vs S group, $^{*}P < 0.05$. Error bars represent the 95% confidence interval

### Comparison of pain NRS, depression PHQ-9, and anxiety GAD-7 scores

Compared to before treatment, both groups showed a significant decrease in pain NRS scores at 3 days, 7 days, 1 month, 2 months, and 3 months after treatment, but there was no statistical difference between the groups at any time points after treatment ($P > 0.05$) (Fig. 3). The E group had significantly lower PHQ-9 scores than the S group at 3 days and 7 days post-treatment (Fig. 4, $P < 0.05$). There was no significant difference in PHQ-9

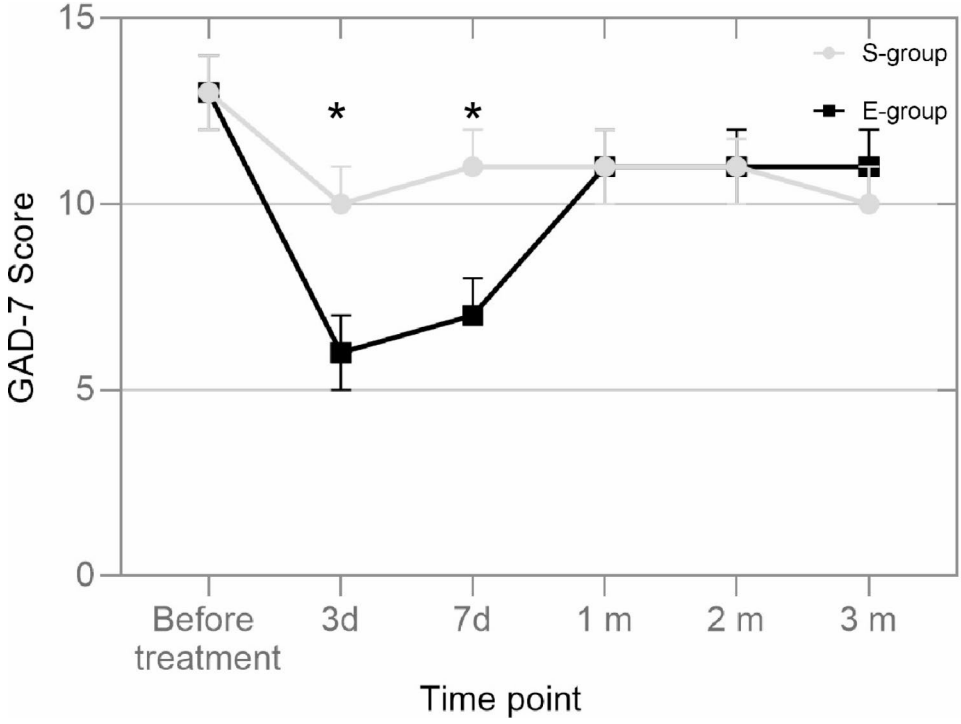


**Fig. 5** GAD-7 scores of the two groups at different time points. GAD-7: Generalized Anxiety Disorder-7, S: Sufentanil, E: Esketamine, d: day, m: month. Vs S group, *$P < 0.05$. Error bars represent the 95% confidence interval

scores between the groups at 1 month, 2 months, and 3 months after treatment (Fig. 4, $P > 0.05$). The E group showed significantly lower GAD-7 scores than the S group at 3 days and 7 days post-treatment (Fig. 5, $P < 0.05$). However, there was no significant difference in GAD-7 scores between the groups at 1 month, 2 months, and 3 months post-treatment (Fig. 5, $P > 0.05$).

### Comparison of daily oral doses of pregabalin, tramadol capsules, and adverse reactions between the groups

As depicted in Fig. 6, there were no statistically significant differences in the daily doses of pregabalin between the two groups at any time points before and after treatment (3 days, 7 days, 1 month, 2 months, and 3 months) ($P > 0.05$). Three patients in the S group and five in the E group required tramadol for pain relief, with no statistical difference observed ($P = 0.206$). Two instances of dizziness were reported in the S group, compared to three in the E group, with no statistical difference ($P = 0.705$) .

## Discussion

This retrospective observation found that all hospitalized patients receiving pulsed radiofrequency treatment in conjunction with either sufentanil or esketamine intravenous patient-controlled analgesia showed significant reductions in their pain NRS scores over a follow-up period of up to three months. This demonstrates the enduring analgesic effectiveness of combining pulsed radiofrequency with sufentanil or esketamine intravenous patient-controlled analgesia for PHN patients. Despite some patients experiencing mild pain recurrence 1–3 months post-treatment, the majority were satisfied with the treatment outcomes. The results of the sensitivity analyses suggested that the exclusion of patients who did not complete follow-up did not significantly bias our study findings. This added robustness to our conclusions, as the baseline characteristics between groups were comparable.

Esketamine's significant reduction in PHQ-9 scores at 3 and 7 days post-treatment, with no significant change from 1 to 3 months, indicates its rapid antidepressant-like action, providing a marked therapeutic effect on early depressive states in PHN patients. This rapid onset of antidepressant effects is consistent with the known pharmacodynamics of esketamine, which targets NMDA receptors to exert its effects quickly [14, 15]. However, the transient nature of these effects highlights the need for further research into sustained treatment strategies. Compared to other treatments, such as traditional antidepressants which often take weeks to show effects, esketamine offers a significant advantage in terms of rapid relief. However, the comparison over a longer period indicates that while esketamine provides quick initial relief, the maintenance of its antidepressant effects may require additional or ongoing treatments. Traditional antidepressants like SSRIs and SNRIs, although

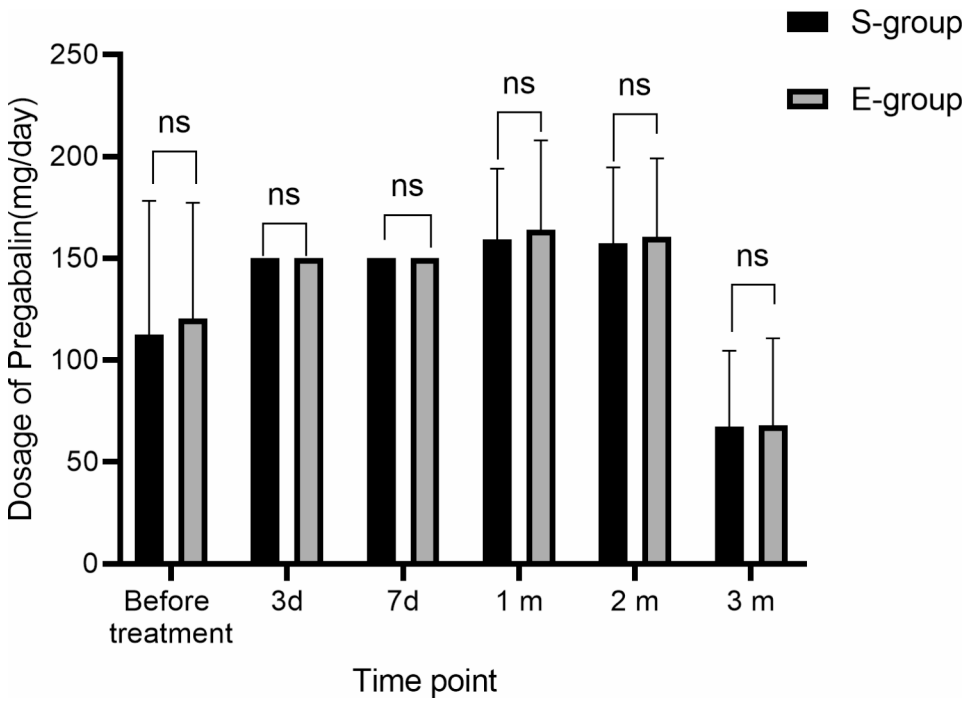


**Fig. 6** Daily use of pregabalin in the two groups at different time points. S: Sufentanil, E: Esketamine, d: day, m: month. Vs S-group, $^{ns}P > 0.05$

slower to act, have a more prolonged effect on depressive symptoms over time [16, 17]. Future studies should explore combination therapies, where esketamine is used for rapid symptom control, followed by traditional antidepressants for long-term maintenance.

Furthermore, our study noted significant reductions in GAD-7 scores at 3 days and 7 days post-treatment, suggesting esketamine's potential short-term anti-anxiety effects. However, this effect was not sustained at 1 month, 2 months, or 3 months post-treatment. This dual benefit on both anxiety and depression adds to its therapeutic value. However, the variations in its efficacy over time underline the importance of a nuanced treatment approach tailored to individual patient needs, potentially incorporating both esketamine and traditional long-term treatments to maximize therapeutic outcomes [18–20].

Recent literature has suggested several mechanisms that may underlie esketamine's rapid antidepressant effects in patients with postherpetic neuralgia (PHN). Esketamine, the S-enantiomer of ketamine, primarily functions as an N-methyl-D-aspartate (NMDA) receptor antagonist. By inhibiting NMDA receptors, particularly those containing the GluN2B subunit, esketamine enhances synaptic plasticity and increases the release of brain-derived neurotrophic factor (BDNF) [21–24]. This process facilitates the formation of new synaptic connections, which is crucial for mood regulation. Additionally, esketamine's interaction with the mammalian target of rapamycin (mTOR) pathway plays a significant role in its antidepressant effects. Activation of the mTOR pathway leads to increased protein synthesis and synaptogenesis, which are essential for the rapid onset of antidepressant action [25]. Furthermore, esketamine's ability to increase gamma-aminobutyric acid (GABA) transmission and reduce the excitotoxic effects of glutamate contributes to its efficacy in alleviating depressive symptoms [26, 27]. Studies have also highlighted the importance of esketamine's effects on the lateral habenula, a brain region involved in processing negative emotions and stress. By inhibiting hyperactivity in the lateral habenula, esketamine helps to reduce depressive and anxiety-like behaviors [28]. These mechanisms collectively explain the rapid antidepressant effects observed with esketamine treatment in PHN patients, offering valuable insights into its therapeutic potential beyond traditional analgesic properties.

Regarding the safety of esketamine's clinical application, this retrospective observation reported only two cases of dizziness in the esketamine group compared to three in the sufentanil group, with no significant difference in adverse effects between the groups. This suggests the safety and feasibility of using esketamine intravenous patient-controlled analgesia in treating PHN. In comparison with existing literature, the safety profile observed in our study aligns with the findings reported to the FDA's adverse event reporting system within one year of the market release of esketamine nasal spray. Common adverse effects reported include nausea, vomiting, dizziness, and elevated blood pressure [29]. In our study, dizziness was the most common adverse event,

consistent with the literature where dizziness accounted for 389 out of 2274 esketamine-related adverse events reported by 962 patients [21–24]. Furthermore, no cases of drug addiction were observed during administration or after cessation of treatment in our study, which is in line with the existing reports that suggest a low potential for addiction with esketamine when used under medical supervision [25]. These findings support the safety profile of esketamine in the context of its use for PHN, indicating that while some mild adverse effects may occur, they are manageable and consistent with previously reported data. Future studies should continue to monitor safety outcomes, particularly with long-term use, to further substantiate these findings.

This study has several limitations. First, the relatively small sample size of 83 patients may limit the generalizability of our findings. Although the sample size was calculated based on previous literature and statistical formulas, future studies should include larger cohorts to enhance the reliability of the results. Second, the non-randomized assignment of patients to the sufentanil or esketamine groups, based on clinical judgment, introduces a potential source of selection bias. Clinicians may have chosen esketamine for patients with more severe depressive symptoms or those unresponsive to prior opioid treatments, which could have influenced the study outcomes. To mitigate this bias, future research should consider a randomized controlled trial design. Third, the inclusion of only patients who underwent pulsed radiofrequency treatment may limit the generalizability of the findings, as this procedure is standard practice in our hospital for treatment-resistant PHN cases to enhance pain relief. This selection criterion may not be applicable to all clinical settings. Future research should consider including a broader patient population to improve the generalizability of the results. Fourth, the exclusion of patients who did not complete follow-up could introduce bias, as these patients might differ from those who completed the study. Although our sensitivity analyses indicated no significant differences in baseline characteristics, including age, gender, initial NRS scores, PHQ-9 scores, and GAD-7 scores, between the groups, suggesting that this exclusion likely did not introduce significant bias into the study results. Lastly, the retrospective design and the short follow-up period of this study cannot comprehensively assess the long-term efficacy and safety of esketamine in patients with postherpetic neuralgia (PHN). Extending the follow-up duration would provide a better understanding of the long-term effects of esketamine. Additionally, this study primarily relied on subjective scales such as the NRS for pain, PHQ-9 for depression, and GAD-7 for anxiety, which may introduce bias. The absence of objective metrics limits the depth of our understanding. Future research should employ objective measurement tools, such as biomarkers and neuroimaging, to reduce subjective bias and provide a more comprehensive assessment of esketamine's effects. Furthermore, exploring the underlying mechanisms of esketamine's therapeutic effects on PHN would offer valuable insights into its biological impact and potential pathways. This will help in understanding the full scope of esketamine's efficacy and safety in this patient population.

In summary, this study, as an exploratory analysis, reveals that intravenous patient-controlled analgesia with esketamine combined with pulsed radiofrequency can alleviate pain and improve early symptoms of anxiety and depression in PHN patients. However, these findings need to be further validated through large-scale, multicenter, prospective randomized controlled trials, and should incorporate objective measurement tools and mechanism studies to provide deeper insights.

#### Author contributions

Xiaobin Wang designed the study. Ling Qiu, and Xuhui Chen analyzed the data and drafted the manuscript participated in the critical discussion and revision of the article. Fu Jia, and Chen Xingqu collected the data. All authors contributed to the article and approved the submitted version.

#### Funding

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#### Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. All data were stored and analyzed using secure, password-protected systems to ensure confidentiality.

## Declarations

#### Ethics approval and consent to participate

The application of intravenous analgesia with esketamine (KY2021299) and this retrospective study (KY2023001) were both approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University, in accordance with the Declaration of Helsinki. All participants were informed about their participation in this study through outpatient services or telephone follow-up, and the requirement for signed informed consent was waived for this retrospective study. This research was also registered with the China Clinical Trial Registry (ChiCTR2300069263) on March 10, 2023.

#### Consent for publication

All authors have given their consent for publication.

#### Competing interests

The authors declare no competing interests.

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**References**

1. Lerman SF, Rudich Z, Brill S, Shalev H, Shahar G. Longitudinal associations between Depression, anxiety, Pain, and Pain-Related disability in Chronic Pain patients. Psychosom Med. 2015;77:333–41.
2. Drolet M, Brisson M, Schmader KE, et al. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. Can Med Assoc J. 2010;182:1731–6.
3. Zhu X, Hu P, Fan Z, et al. Effects of Mindfulness-based stress reduction on Depression, anxiety, and Pain in patients with postherpetic Neuralgia. J Nerv Ment Dis. 2019;207:482–6.
4. Xu L, Zhang Y, Huang Y. Advances in the Treatment of Neuropathic Pain. In: Ma C, Huang Y, editors. Translational Research in Pain and Itch Dordrecht: Springer Netherlands; 2016 [cited 2023 Jul 7]. pp. 117–29 http://link.springer.com/https://doi.org/10.1007/978-94-017-7537-3_9
5. Martinotti G, Dell'Osso B, Di Lorenzo G, et al. Treating bipolar depression with esketamine: safety and effectiveness data from a naturalistic multicentric study on esketamine in bipolar versus unipolar treatment-resistant depression. Bipolar Disord. 2023;25:233–44.
6. Chen X, Hou X, Bai D, et al. Efficacy and safety of flexibly dosed esketamine nasal spray plus a newly initiated oral antidepressant in adult patients with treatment-resistant depression: a Randomized, Double-Blind, Multicenter, active-controlled study conducted in China and USA. NDT. 2023;19:693–707.
7. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant Major Depression: a two-site Randomized Controlled Trial. AJP. 2013;170:1134–42.
8. Nasir M, Trujillo D, Levine J, Dwyer JB, Rupp ZW, Bloch MH. Glutamate systems in DSM-5 anxiety disorders: their role and a review of glutamate and GABA psychopharmacology. Front Psychiatry. 2020;11:548505.
9. Del Sant LC, Sarin LM, Lucchese AC, et al. Impact of repeated doses of Subcutaneous Esketamine on Acute dissociative symptoms in treatment-resistant depression. Pharmaceuticals. 2022;16:31.
10. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.
11. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092–7. https://doi.org/10.1001/archinte.166.10.1092.
12. LI X, QIAO RENB, LU Y, CUI X, Y., MIAO, C., ZHANG Z. (2022). Efficacy of esketamine for PCIA in elderly patients undergoing modified radical mastectomy for breast cancer. Chin J Anesthesiology, 181–5.
13. Ohnesorge H, Alpes A, Baron R, Gierthmühlen J. Influence of intraoperative remifentanil and sufentanil on sensory perception: a randomized trial. Curr Med Res Opin. 2016;32(11):1797–805.
14. Swartjes M, Niesters M, Heij L et al. TJ Price editor 2013 Ketamine does not produce relief of Neuropathic Pain in mice lacking the β-Common receptor (CD131). PLoS ONE 8 e71326.
15. Johnson RW, Rice ASC. Postherpetic Neuralgia. Solomon CG, editorN Engl J Med. 2014;371:1526–33.
16. Swiatek KM, Jordan K, Coffman J. New use for an old drug: oral ketamine for treatment-resistant depression. BMJ case Rep. 2016;2016:bcr2016216088.
17. Grunebaum MF, Galfalvy HC, Choo TH, Keilp JG, Moitra VK, Parris MS, Marver JE, Burke AK, Milak MS, Sublette ME, Oquendo MA, Mann JJ. Ketamine for Rapid reduction of suicidal thoughts in Major Depression: a midazolam-controlled Randomized Clinical Trial. Am J Psychiatry. 2018;175(4):327–35.
18. Yang C, Shirayama Y, Zhang JC, Ren Q, Yao W, Ma M, Dong C, Hashimoto K. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Translational Psychiatry, 2015;5(9):e632.
19. US Food and Drug Administration. FDA approves new nasal spray medication for treatment- resistant depression; available only at certified doctor's office or clinic[EB/OL]. (2019-03-05) [2021-01-19].
20. Canady VA. FDA approves esketamine treatment for MDD, suicidal ideation[J]. Mental Health Wkly. 2020;30:6–7.
21. Turner EH. Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval. Lancet Psychiatry. 2019;6(12):977–9.
22. Wajs E, Aluisio L, Holder R, Daly EJ, Lane R, Lim P, George JE, Morrison RL, Sanacora G, Young AH, Kasper S, Sulaiman AH, Li CT, Paik JW, Manji H, Hough D, Grunfeld J, Jeon HJ, Wilkinson ST, Drevets WC, Singh JB. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: Assessment of Long-Term Safety in a phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry. 2020;81(3):19m12891.
23. Gastaldon C, Raschi E, Kane JM, Barbui C, Schoretsanitis G. Post-marketing safety concerns with Esketamine: a disproportionality analysis of spontaneous reports submitted to the FDA adverse event reporting system. Psychother Psychosom. 2021;90(1):41–8.
24. Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, Thase ME, Winokur A, Van Nueten L, Manji H, Drevets WC. Efficacy and Safety of Intranasal Esketamine Adjunctive to oral antidepressant therapy in treatment-resistant depression: a Randomized Clinical Trial. JAMA Psychiatry. 2018;75(2):139–48.
25. Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sánchez E, Gutiérrez-Rojas L, Meana JJ. Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. CNS Drugs. 2018;32(5):411–20.
26. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. Mol Psychiatry. 2018;23(4):801–11. https://doi.org/10.1038/mp.2017.255.
27. Duman RS, Aghajanian GK. Synaptic dysfunction in depression: potential therapeutic targets. Science. 2012;338(6103):68–72. https://doi.org/10.1126/science.1222939.
28. Fuchikami M, Thomas A, Liu R, et al. Optogenetic stimulation of infralimbic PFC reproduces ketamine's rapid and sustained antidepressant actions. Proc Natl Acad Sci U S A. 2015;112(26):8106–11. https://doi.org/10.1073/pnas.1414728112.
29. Yang Y, Cui Y, Sang K, et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. Nature. 2018;554(7692):317–22. https://doi.org/10.1038/nature25509.

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