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Pharmacodynamic basis of gabapentin combined with Hegu-point catgut embedding for post-herpetic neuralgia

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Abstract: **Background**: Post-herpetic neuralgia (PHN) is a common refractory complication of herpes zoster, characterized by persistent neuropathic pain that seriously impairs patients' quality of life. **Objectives**: The study aimed to assess the clinical effects of gabapentin when administered in combination with Hegu-point catgut embedding in patients suffering from post-herpetic neuralgia (PHN). **Methods**: A randomized, assessor-blinded study was conducted, wherein a total of 210 PHN patients were equally divided into two groups: 1) the control group receiving only gabapentin and 2) the combination group that received combined therapy of gabapentin and Hegu-point catgut embedding weekly. After 4 weeks of treatment, pain intensity, sleep quality, serum biomarkers, clinical efficacy and adverse events were evaluated. **Results**: After 4 weeks, both groups displayed a significant reduction in Visual Analogue Scale (VAS) and Pittsburgh Sleep Quality Index (PSQI) scores, with greater improvement reported in the combination group ($P < 0.05$). In addition, both groups showed a significant decrease in serum levels of substance P, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while β-endorphin levels showed a significant increase. The changes were found to be more pronounced in the combination group ($P < 0.05$). Interestingly, the combination group demonstrated a higher overall response rate (92.38% vs 80.00%) and fewer adverse events (12.38% vs 26.67%, $P < 0.05$). **Conclusion**: Altogether, combination therapy provided superior short-term improvement in symptoms and biomarker modulation as compared to gabapentin alone. Since the present study only assessed peripheral serum markers, the underlying mechanistic pathways could not be deciphered. Additionally, longer-term outcomes of therapy were not assessed, serving as a major limitation of this study.

Keywords: Gabapentin; Hegu-point catgut embedding; Neuro-inflammation; Pharmacodynamics; Post-herpetic neuralgia

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INTRODUCTION

Neuropathic pain is the most common complication reported in patients suffering from herpes zoster. It is generally described as spontaneous, knife-like, burning, or electric-shock-like pain, which is usually accompanied by allodynia and hyperalgesia. Neuropathic pain is known to cause long-term physical and psychological suffering, severe sleep disturbances and a substantial decline in overall quality of life, thus imposing a heavy burden on healthcare systems (Davari *et al*., 2020; Gyeltshen *et al*., 2025). For long, gabapentin has been widely used to manage neuropathic pain, primarily owing to its ability to modulate voltage-gated calcium-channel α2δ subunits and reduce excitatory neurotransmitter release (Abd-Elsalam *et al*., 2024; Kaye *et al*., 2025). However, its application is limited owing to the low monotherapy efficacy of approximately 50–60%. In addition to this, gabapentin is known to cause dose-associated adverse reactions, such as dizziness, somnolence and ataxia, in 20–40% of patients (Kruger and Lerche, 2024; Papassidero *et al*., 2023). Consequently, the past few decades witnessed a growing clinical interest in the utilization of multimodal approaches, wherein conventional pharmacotherapy was combined with non-pharmacological interventions, to manage neuropathic pain (Meaadi *et al*., 2023; Domon *et al*., 2023).

For several decades, Hegu-point catgut embedding, a form of prolonged acupoint stimulation, has been used in China for pain management. Unlike manual acupuncture techniques, which involve transient stimulus, catgut embedding has been shown to provide sustained mechanical and biochemical stimulation over a period of 1–2 weeks, primarily owing to the gradual degradation of absorbable suture (Daryaee and Tonge, 2019). In Traditional Chinese Medicine (TCM), Hegu (LI4) is believed to regulate qi and blood, unblock meridians and harmonize yin–yang. These classical concepts are valuable within the TCM framework; however, to support their clinical plausibility, it is important to interpret them in modern biomedical terms. Previous studies have shown that Hegu stimulation activates Aβ and Aδ afferent fibers, modulates spinal "gate-control" mechanisms, influences descending pain-inhibitory pathways and triggers neuro–immune–endocrine responses, including up-regulation of endogenous opioids and down-regulation of inflammatory cytokines (Gao Z *et al*., 2025) These mechanisms provide biological evidence for its potential effectiveness in neuropathic pain.

However, the currently available evidence for the utility of acupuncture and catgut embedding in neuropathic pain remains highly heterogeneous. Most of these studies suffer from limitations of small sample size, variable

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methodological quality, lack of assessor blinding, or use of unclear allocation procedures. Moreover, the magnitude of benefits reported for their application in various trials is considerably variable. Besides this, sham-controlled studies that are critical for the evaluation of neuro-modulatory interventions of these therapies are quite limited. Some of the references that have been frequently cited in literature, including a recently published randomized acupuncture study (Rusciano, 2024), require careful verification, particularly owing to their recent publication dates and limited accessibility in the majority of scientific databases (at the time of writing of the current study). Therefore, despite the availability of multiple reports in support of analgesic effects of acupoint stimulation, a cautious interpretation of existing literature is required, particularly in terms of effective size and study quality.

While multiple randomized trials have previously demonstrated the potential application of acupuncture and acupoint thread embedding in managing neuropathic pain (Wang *et al*., 2025; Pan *et al*., 2024), recently published systematic reviews identified methodological limitations in many of these studies. Particularly, the use of small sample sizes, incomplete implementation of blinding protocols and inconsistent control group designs served as major limitations of these studies (Mu *et al*., 2020; Zhang *et al*., 2021). To address these issues, the present study employed an evaluator-blind design, standardized control group baseline therapy and evaluation of serum biomarkers, with the aim of providing more rigorous clinical and mechanistic evidence for the combined use of Hegu-acupoint thread embedding and gabapentin in the treatment of patients with post-herpetic neuralgia (PHN).

MATERIALS AND METHODS

Study population

A total of 210 PHN patients (admitted from December 2023 to March 2025) were included in the study. Sample-size calculation was performed on the basis of pilot data (expected response rate 90% vs 75%, $\alpha = 0.05$ and $\beta = 0.1$), indicating a requirement of 98 participants per group, which further allowed for future dropouts. Consequently, 105 patients were enrolled in each group.

Inclusion criteria: 1) Age 40–70 years; 2) Definite PHN diagnosis according to the Chinese Expert Consensus on Herpes Zoster (2022 Edition), with healed skin lesions (Daryaee *et al*., 2019), presence of neuropathic pain characteristics and VAS ≥4; 4) Pain duration ≥3 months; 5) Use of no other analgesics, nerve blockers, or radiofrequency procedures within 1 week before enrolment; and 6) Signed informed consent.

Exclusion criteria: 1) Presence of severe malignancy, cardiac, hepatic, renal, or hematological diseases; 2) History of psychiatric disorders, cognitive impairment, or inability to cooperate; 3) Hypersensitivity to gabapentin or catgut; 4) Occurrence of local infection or skin lesions at embedding site; 5) History of alcohol or drug abuse; and 6) Pregnancy or lactation.

Following a computer-generated randomization method, the patients were divided into the combination group and the control group (with 105 patients per group). As shown in table 1, the baseline characteristics were comparable between the two groups ($P > 0.05$).

Methods

Basic treatment

All participants received identical routine care, including neurotrophic medication, health education, skin care, sleep-hygiene counselling, dietary and exercise advice and emotional-support measures.

Control group

All patients received oral gabapentin capsules (National Drug Approval No. H20203527; Beijing Sihuan Pharmaceutical Co., Ltd.), with a dosage of 0.3 g at bedtime on day 1, 0.3 g twice (morning and evening) on day 2 and 0.3 g thrice (morning, afternoon and night) on day 3. Following this, the dose was increased by 0.3 g/day each week, on the basis of pain relief and tolerability. The final dose was increased up to a maximum of 1.8 g/day, divided over three equal doses. In case of dizziness or somnolence, the dose was either reduced or put on hold for 1–2 days before cautious re-escalation. The subjects received treatment for 4 weeks.

Combination group

In addition to gabapentin administration, the patients included in combination therapy received Hegu-point catgut embedding once every week, for the study duration of 4 weeks. Specifications for Hegu-point catgut embedding, 1) Point selection: bilateral Hegu (LI4), located between 1st and 2nd metacarpal bones on dorsum of hand, at midpoint of 2nd metacarpal; 2) Positioning: sitting or supine with hand exposed; 3) Materials: 16-gauge embedding needle and 3-0 PGA thread (1.5–2 cm); 4) Technique following skin disinfection, needle was inserted 0.5–1 cm perpendicularly into Hegu until De-Qi (soreness/distension) was obtained and thread was further implanted; 5) Pressure was applied at insertion site, which was followed by sterile dressing.

Outcome measures

Pain intensity and sleep quality

To study the effect of gabapentin alone and combination therapy, pain intensity and sleep quality were assessed before and after 4 weeks of treatment, using the Visual Analogue Scale (VAS, wherein 0 = no pain and 10 = worst imaginable pain) and Pittsburgh Sleep Quality Index (PSQI, wherein 0 = excellent sleep, 21 = extremely poor sleep).

Table 1: Comparison of the general data

Group	*N*	Sex (n/%)		Age (years)	Disease duration (months)	Pain site (n/%)		
		Male	*Female*			Head/Face	*Lumbosacral*	*Thoracic*
Combination	105	49 (46.67)	56 (53.33)	66.38 ±8.76	4.25 ±1.53	58 (55.24)	22 (20.95)	25 (23.81)
Control	105	51 (48.57)	54 (51.43)	65.82 ±8.91	4.06 ±1.60	59 (56.19)	19 (18.10)	27 (25.71)
χ^2/t		0.076		0.459	0.879		0.305	
P		0.783		0.646	0.380		0.858	

Table 2: Comparison of pain intensity and sleep quality (point)

Group	*N*	VAS		PSQI	
		Before	After 4 weeks of treatment	Before	After 4 weeks of treatment
Combination	105	7.56 ±1.08	3.22±0.98*	14.25 ±2.87	5.34 ±1.63*
Control	105	7.47 ±1.02	4.18±1.05*	13.96 ±2.84	7.65 ±1.90*
T	-	0.621	6.848	0.736	9.452
P	-	0.535	<0.001	0.462	<0.001

Note: Compared to pre-treatment values, $^*P < 0.05$

Table 3: Comparison of clinical efficacy (n, %)

Group	*N*	Markedly effective	Effective	Ineffective	Overall effective (rate)
Combination	105	68 (64.76)	29 (27.62)	8 (7.62)	97 (92.38)
Control	105	37 (35.24)	47 (44.76)	21 (20.00)	84 (80.00)
χ^2	-	-	-	-	6.761
P	-	-	-	-	0.009

Clinical efficacy

The clinical efficacy was considered to be 1) Markedly effective for VAS reduction ≥75% or virtual disappearance of pain; 2) Effective for VAS reduction 50–74%; and 3) Ineffective for VAS reduction <50% or no change or worsening of pain.

Serum biochemical markers

To assess serum biochemical markers, 5 mL fasting venous blood was drawn before and after 4 weeks of treatment. The drawn blood was incubated at room temperature (RT) for 30 min, centrifuged at 3000 rpm for 10 min and the collected serum was further stored at −80°C (Automatic Blood Analyzer Cobas 8000, Manufacturer: Roche). ELISA was used to measure levels of substance P (SP), β-endorphin (β-EP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).

Adverse events

To assess the occurrence of adverse events, dizziness, somnolence, ataxia and local swelling or pain at the embedding site were recorded.

Statistical analysis

For statistical analysis, SPSS 22.0 software was used. Categorical data were expressed as n (%) and compared by the χ^2 test. Continuous data (mean ±SD) was normally distributed (Shapiro–Wilk test) and compared by *t*-test. Here, $P < 0.05$ was considered to indicate significance.

RESULTS

Pain intensity and sleep quality

No significant differences were recorded in VAS and PSQI scores of the two groups ($P > 0.05$) before treatment. After 4 weeks of therapy, both groups showed a significant reduction in VAS and PSQI scores ($P<0.05$), with significantly lower scores reported in the combination group ($P < 0.05$) (Table 2).

Clinical efficacy

The overall effective rate was recorded to be 92.38% in the combination group as compared to 80.00% in the control group ($P < 0.05$) (Table 3).

Serum biochemical markers

Baseline levels of SP, β-EP, IL-6 and TNF-α were found to be comparable in the two groups ($P > 0.05$). After 4 weeks of treatment, a significant decrease was recorded in the levels of SP, IL-6 and TNF-α in both groups ($P < 0.05$). In comparison to this, both groups showed a significant increase in β-EP ($P < 0.05$). Interestingly, the combination group showed lower SP, IL-6 and TNF-α levels, while higher β-EP levels were recorded as compared to the control group ($P < 0.05$) (Table 4).

Adverse events

Incidents of adverse events were recorded to be 12.38% in the combination group as compared to 26.67% in the control group ($P < 0.05$) (Table 5).

Table 4: Comparison of serum biochemical indicators

group	*n*	SP (pg/mL)		β-EP (ng/L)		IL-6 (pg/mL)		TNF-α (pg/mL)	
		Before	*After 4 weeks of treatment*	*Before*	*After 4 weeks of treatment*	*before*	*After 4 weeks of treatment*	*before*	*After 4 weeks of treatment*
Combination	105	82.54 ± 9.36	46.69 ±7.44*	32.17 ±6.53	68.34 ± 8.22*	19.15 ± 3.37	7.35 ± 2.16*	16.78 ± 3.92	5.83 ± 1.60*
Control	105	81.73 ± 9.19	52.23 ± 7.65*	33.56 ± 7.08	57.26 ± 7.69*	18.92 ± 3.43	12.58 ± 3.25*	16.59 ± 4.01	7.02 ± 2.14*
t	-	0.633	5.322	1.479	10.083	0.490	13.736	0.347	4.562
P	-	0.527	0.001	0.140	<0.001	0.624	<0.001	0.729	<0.001

Note: Compared to pre-treatment values，$^{*}P < 0.05$

Table 5: Comparison of complications

Group	*n*	Dizziness	Somnolence	Ataxia	Local swelling/pain	Complications (rate)
Combination	105	5 (4.76%)	3 (2.86%)	1 (0.95%)	4 (3.81%)	13 (12.38%)
Control	105	12 (11.43%)	9 (8.57%)	6 (5.71%)	1 (0.95%)	28 (26.67%)
χ^2	-	-	-	-	-	6.819
P	-	-	-	-	-	0.009

DISCUSSION

PHN is a commonly known complication, triggered by reactivation of the Varicella–Zoster virus. It has been reported to occur in 9–34% of patients infected with herpes zoster. Interestingly, a sharp correlation has been reported in an increase in PHN incidence with age (Zamora-Díaz *et al*., 2025; De Stefano *et al*., 2023). PHN is usually characterized by persistent or paroxysmal excruciating pain that severely compromises daily activities and often leads to sleep disturbances, anxiety and depression, thereby imposing a tremendous physical and psychological burden (Fernandez-Vial *et al*., 2022; Gold *et al*., 2022). Currently, first-line therapy for PHN primarily relies on the use of calcium-channel α2δ-subunit modulators, like gabapentin. These modulators mainly act via reduction of the release of excitatory neurotransmitters (e.g., glutamate and substance P), thereby relieving neuropathic pain (Menaldi *et al*., 2022; Evoy *et al*., 2021). Previous studies demonstrated a moderate effect of monotherapy on PHN. Besides this, long-term use of these modulators was found to be associated with drug tolerance and increased adverse effects. Recent years witnessed an increased interest in traditional Chinese acupoint therapy. Particularly, catgut embedding at Hegu (LI4) has been shown to effectively alleviate PHN. Thus, the present study used gabapentin in combination with Hegu-point catgut embedding, with the aim of enhancing overall therapeutic outcomes.

The overall response rate was recorded to be significantly higher in the combination group as compared to that in the control group ($P < 0.05$). After 4 weeks of treatment, both groups showed marked reduction in VAS and PSQI scores ($P < 0.05$), with significantly lower values recorded in the combination group ($P < 0.05$). The present study postulates that gabapentin primarily acts via inhibition of the α2δ-1 subunit of voltage-gated calcium channels, diminishing presynaptic release of glutamate and substance P; thereby suppressing central sensitization (Rusciano, 2024; Nakamura *et al*., 2023). In comparison to this, Hegu-point catgut embedding is a form of prolonged acupoint stimulation that operates at multiple levels, peripheral, central and neuro–endocrine levels. At the peripheral level, Hegu-point catgut embedding provides a sustained mechanical stimulation that activates Aβ fibers, thereby closing spinal "gates" and reducing nociceptive input. Centrally, it modulates descending pain-inhibitory pathways, further enhancing the release of serotonin and endogenous opioids. Interestingly, at the neuro–endocrine level, it activates the hypothalamic–pituitary axis, increases β-endorphin secretion and down-regulates pro-inflammatory cytokines (IL-6, TNF-α), thereby improving immune responses and dampening neuro-inflammation (Wang *et al*., 2020; Zhou *et al*., 2021).

Thus, the combined therapy acts via simultaneous targeting of central sensitization (gabapentin) and systemic pain-modulatory network (Hegu embedding), covering "peripheral–central–immune" pathways that have been previously shown to be involved in PHN (particularly, peripheral and central sensitization, impaired descending inhibition and neuro-inflammation) (Shi and Song, 2024). These effects further contribute towards superior analgesia and improved sleep quality.

After 4 weeks of treatment, both groups showed a significant decrease in substance P, IL-6 and TNF-α, whereas a pronounced increase was reported in β-endorphin levels ($P < 0.05$, for all parameters). Importantly, all these changes were found to be more pronounced in the combination group ($P < 0.05$). Substance P is a key nociceptive neuropeptide that is released from C-fiber

terminals. It is known to bind neurokinin-1 receptors on spinal neurons and glia, thereby driving central sensitization and persistent pain (Oggianu *et al*., 2023). β-endorphin is one of the most potent endogenous opioids, which is primarily produced in the anterior pituitary and hypothalamic arcuate nucleus. β-endorphin mediated activation of μ- and δ-opioid receptors has been previously shown to produce powerful analgesia via inhibition of presynaptic transmitter release and postsynaptic hyperpolarization. IL-6 and TNF-α are pivotal pro-inflammatory cytokines that are known to promote glial activation and amplification of nociceptive signaling. Thus, a decrease in IL-6 and TNF-α favors nerve repair and inflammation resolution. Gabapentin is known to act via direct inhibition of presynaptic voltage-gated calcium channels, thereby decreasing substance P vesicular release. Its effect on β-endorphin and cytokines is majorly indirect, which is achieved via attenuation of neuronal hyper-excitability and reduction of stress load on the hypothalamic–pituitary–adrenal axis (Lambarth *et al*., 2022; Masciullo *et al*., 2021). Several previous studies have shown that acupuncture/acupoint stimulation robustly activates the endogenous opioid system. In particular, afferent signals from Hegu ascend to the CNS, stimulate β-endorphinergic neurons and initiate descending inhibitory pathways, further releasing 5-HT and norepinephrine. This promotes spinal enkephalin release and suppression of nociceptive input. Interestingly, pituitary β-endorphin can also enter the circulation and act on opioid receptors at multiple pain-modulating centers, thereby producing widespread and prolonged analgesia. Simultaneously, the afferent signals activate the hypothalamus, exerting systemic anti-inflammatory effects via neuro–endocrine routes and modulating local immune-cell function to suppress pro-inflammatory cytokine release. This further improves microcirculation and facilitates the clearance of inflammatory mediators. Thus, combination therapy markedly acts via alteration of neuro–immune–endocrine milieu.

Incidence of complications was found to be significantly lower in the combination group as compared to that in the control group ($P < 0.05$). Particularly, dizziness and somnolence were recorded in 26.67% of control-group patients, which was consistent with the findings of Miyoshi *et al*. (2021), wherein a rate of 20–40% was reported. In comparison to this, the combination group exhibited only 12.38% adverse events, which was possibly attributed to the regulatory effects of Hegu embedding, particularly unblocking of meridians, harmonization of qi and blood, enhancement of parasympathetic tone and mitigation of drug-related dizziness and sedation. Clinically, the mean gabapentin dose required in the combination group was observed to be lower than that in the control group, further reducing drug dependence and side effects, thereby underscoring the efficacy and safety of the combined regimen.

Despite the positive outcomes, the present study suffers from several methodological limitations. Neither the participants nor the treating investigators were blinded. Besides this, the absence of a sham catgut embedding control further increases the likelihood of placebo and expectation effects, particularly in light of reliance on subjective outcomes, such as pain and sleep quality. Although randomization was performed using computer-generated numbers, allocation concealment has not been clearly described, which might further introduce selection bias. The treatment duration and follow-up period were limited to 4 weeks, which is insufficient to fully evaluate chronic conditions like PHN and assess the durability of therapeutic effects. Additionally, outcome measures were relatively narrow, which primarily focused on pain, sleep and serum biomarkers. The study lacked the incorporation of broader patient-centered endpoints, such as quality of life and functional recovery. Lastly, the study involved a single acupoint (Hegu, LI4) and the rationale for excluding multi-acupoint protocols, commonly used in clinical practice, was not formally addressed, thereby limiting generalization of current findings.

CONCLUSION

The present study reported a more pronounced alleviation of PHN in combination therapy, involving gabapentin administration in combination with Hegu-point catgut embedding. This was primarily driven via suppression of neuro-inflammation and promotion of endorphin release. The combination therapy provided a more effective reduction in pain intensity, improvement in sleep quality, modulation of serum biochemical markers, enhancement of clinical efficacy and decrease in incidences of adverse-events.

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Authors' contributions

Li-Ping Li is the first author responsible for the design and paper writing. Zong-Zhou Song, Yang Zheng, Ting Wu and Fang-Wei Li participated in data collection and analysis. Yan Huang is the corresponding author responsible for project guidance and paper review. All authors have reviewed and agreed to the final draft.

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Data availability statement

The authors declare no conflicts of interest.

Ethical approval

The present study was performed according to the guidelines of the Sui Ning First People's Hospital in Sichuan Province Ethics Committee [Ethical approval number: NO2021 (13)].

Conflict of interest

The authors declare no conflict of interest.

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