

Lumbar Sympathicolysis Attenuates Refractory Chemotherapy-Induced Peripheral Neuropathy in the Lower Extremities: A Prospective, Real-World Study

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Purpose: Currently, there are limited effective treatment strategies available for refractory chemotherapy-induced peripheral neuropathy (CIPN). Lumbar sympathectomy is a minimally invasive therapy and may offer an option for CIPN. This single-center, prospective, observational study aimed to evaluate the efficacy and safety of CT-guided lumbar sympathectomy in alleviating multiple symptoms of refractory CIPN in the lower extremities.

Methods: This single-arm study conducted at Henan Cancer Hospital from September 2022 to July 2024, twenty-five patients with refractory CIPN in both lower extremities received CT-guided lumbar sympathectomy. The effectiveness of the treatment for pain, numbness, cold sensation, and dyskinesia was evaluated using a Numerical Rating Scale (NRS) at day 3, one month, and three months following treatment. Treatment response was defined as an NRS score reduction of $\geq 30\%$. Changes in NRS scores over time were analyzed using generalized estimating equations. Any adverse effects related to the treatment were recorded.

Results: Postoperative NRS scores for pain, numbness, cold sensation, and dyskinesia at 3 days, 1 month, and 3 months were significantly lower than these assessed before the treatment. The pain improvement assessed with NRS scores was reported to be 61.1% at 3 days, 55.5% at 1 month, and 55.5% at 3 months by patients (n=18). The numbness improvement was 24.0% at day 3, 16.0% at 1 month, and 16.0% at 3 months (n=25). Cold sensation improvement (n=21) was 71.4%, 57.1%, and 52.4% at day 3, 1 month, and 3 months (n=21), respectively. The decreased dyskinesia sensation was reported by 50.0% at day 3 and 1 month, and 57.1% at 3 months (n=14). Overall, all symptoms were decreased by 68% at day 3, 64% at 1 month, and 60% at 3 months.

Conclusion: The CT-guided lumbar sympathectomy may offer substantial symptom relief for CIPN in the lower extremities without clinically significant adverse effects. These preliminary findings warrant further validation in larger, controlled studies.

Keywords: chemotherapy-induced peripheral neuropathy, lumbar sympathectomy, pain relief

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious toxicity effects caused by chemotherapy agents such as taxanes, platinum compounds, vinca alkaloids, thalidomide, and bortezomib.¹⁻³ CIPN presents with classic “glove and stocking” neuropathy dominated by sensory disturbances (ie, numbness, pins-and-needles sensation, pain or cold sensitivity), in addition to motor and autonomic dysfunction, especially in the lower limbs.⁴ CIPN is



unpredictable, and previous studies showed that up to 30% of patients treated with high-risk chemotherapy drugs may experience symptoms lasting for six months or even longer.⁵ As chemotherapy doses accumulated, symptoms often worsen, requiring dose reductions or early termination of treatment. This not only severely affects patients' quality of life but may also negatively impact overall survival.^{6–8} Although symptoms may gradually improve over time, a significant number of patients, particularly long-term cancer survivors, suffered from persistent or even permanent nerve damage.^{5,9,10} Pharmacological and non-pharmacological interventions for managing CIPN are limited and also lack strong evidence supporting their effectiveness.¹¹ Commonly prescribed drugs included duloxetine, pregabalin, opioids, neurotrophic agents (such as B vitamins and methylcobalamin), and NSAIDs.^{12–14} Non-pharmacological treatments, such as acupuncture, physical therapy, and neurofeedback, also have been reported but their effectiveness in CIPN remains uncertain.^{15–17} Hence, the need for more effective CIPN treatments remains urgent.

Lumbar sympathectomy is the physical and chemical disruption of the corresponding segment of the lumbar sympathetic nerve to inhibit sympathetic conduction and thereby treat sympathetic-related pain, numbness, cold sensation, intermittent sensation, claudication, and other symptoms.^{18,19} Previous evidence showed that lumbar sympathectomy alleviated symptoms such as pain and cold sensation in lower limb ischemic diseases (eg atherosclerotic occlusive disease, diabetic foot and thromboembolic vasculitis) by improving blood flow.^{20,21} However, its mechanism of action extends beyond vascular effects and can also be applied to the treatment of neuropathic pain. The sympathetic nervous system has been shown to participate in peripheral sensitization and the maintenance of chronic neuropathic pain.²² Although CIPN is primarily mediated by neurotoxic mechanisms, abnormal sympathetic activity may exacerbate symptoms such as persistent pain and vasomotor instability.^{23,24} Therefore, based on the established role of sympathetic modulation in neuropathic pain syndromes, the application of targeted lumbar sympathectomy to CIPN remains unexplored. We hypothesized that lumbar sympathectomy would alleviate refractory sensory and vasomotor symptoms in patients with CIPN by attenuating sympathetic overactivity and its downstream effects on neuroinflammation and peripheral microcirculation. To test this hypothesis, we conducted a single-arm, prospective study to evaluate, for the first time, the efficacy and safety of CT-guided lumbar sympathectomy in patients with bilateral lower limb CIPN refractory to conventional pharmacological treatment.

Methods

Patient Recruitment

This prospective, single-center study adopted a single-arm, quasi-experimental design with repeated measures (pre- and post-intervention assessments) to evaluate CT-guided lumbar sympathectomy for refractory CIPN under routine clinical conditions. This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Biomedical Ethics Committee of Henan Cancer Hospital (No. 2022-KY-0077-002) and written informed consent was obtained from all participants. This study was conducted from September 2022 to July 2024. Patients with refractory CIPN were recruited at Henan Cancer Hospital. All patients underwent CT-guided lumbar sympathectomy, with symptom scores evaluated preoperatively, as well as on the third day, at one month, and three months postoperatively.

Refractory CIPN was defined based on the following criteria were: 1) CIPN symptoms in the lower extremities; 2) symptoms persisting for over three months; 3) presence of pain, numbness, cold sensation, or motor dysfunction, with at least one symptom having an NRS score ≥ 4 ; and 4) lack of symptom improvement following treatment with duloxetine, pregabalin, neurotrophin, or other neurotrophic agents.

Exclusion criteria included: 1) neurological symptoms due to primary tumor, metastasis, or non-chemotherapy-related causes (eg, diabetic peripheral neuropathy); 2) infection, coagulation disorders, or severe cardiac, pulmonary, or other comorbid conditions precluding surgery; 3) CT evidence of metastatic lymph nodes or abnormalities around the puncture site; 4) psychiatric disorders or cognitive impairment affecting compliance; 5) alcohol allergy.

Procedures

CT-guided lumbar sympathectomy was performed bilaterally on the lumbar sympathetic ganglia. In the prone position, the puncture sites and paths were determined through CT images. The 15 cm, 20G radiofrequency cannula needles were

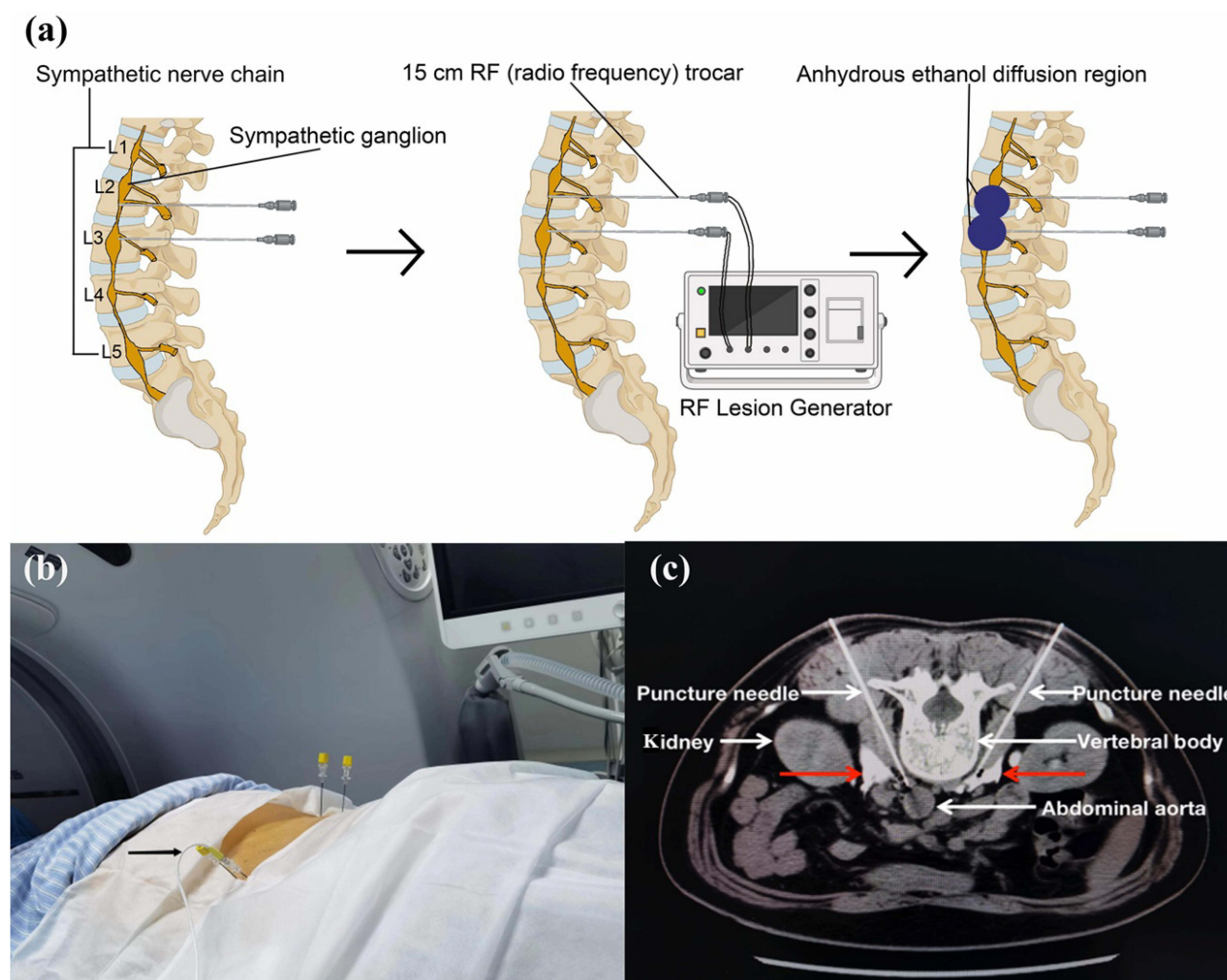


Figure 1 Schematic diagram of CT-guided lumbar sympathicotomy in patients with refractory chemotherapy-induced peripheral neuropathy in the lower extremities. (a) Schematic illustration of the procedure. (b) After four puncture needles were inserted into place under CT-guidance, radiofrequency electrodes (black arrow) were disposed of from the core of the puncture needles for sensory-motor testing and subsequent continuous operation with physical radiofrequency. (c) A CT scan in the case of both-sided lumbar sympathicotomy: intercavovertebral positioning of the puncture needle and distribution of the sympatholytic agent. Red arrows highlight the distribution area of the agent around the lumbar sympathetic chain.

inserted, with the tips positioned at the anterolateral third of the L2 vertebra and the upper third of the L3 vertebra, to minimize the risk of injury to the aorta or mesenteric artery. Following confirmation of needle placement, sensory and motor function assessments were conducted using radiofrequency electrodes (Figure 1a and b), and 1–2 mL of a mixture of 1% lidocaine and 10% iodinated contrast agent was injected. CT confirmed the appropriate spread of the contrast agent along the prevertebral fascial plane without abnormal diffusion.

The radiofrequency ablation was performed for 6 minutes (75°C for 3 minutes, followed by 80°C for 3 minutes). Subsequently, 2–3 mL of a mixture of 90% anhydrous alcohol and 10% contrast agent was injected on each side, with the total dose per side being 6–9 mL (Figure 1c). Postoperative CT verified the appropriate distribution of the agent. Patients remained in a prone position for two hours post-procedure to minimize the risk of alcohol diffusion.

Efficacy Evaluation

Baseline data including age, sex, symptom duration, tumor type, and chemotherapy cycles were recorded. Symptom severity (pain, numbness, cold sensation, dyskinesia) in the lower extremities was assessed using the Numerical Rating Scale (NRS), with 0 indicating no symptoms and 10 indicating the most intolerable symptoms imaginable.²⁵ NRS scores were collected before and at day 3, 1 month, and 3 months after the treatment by unblinded clinicians or research nurses.

A reduction in NRS score of $\geq 30\%$ from baseline was considered a clinically meaningful response, while a reduction of $< 30\%$ was deemed non-responsive. The improvement in sensation was expressed as a response rate, which was calculated as the proportion of responsive cases relative to the total number of cases for each symptom. Adverse events, such as bleeding, hypotension, diarrhea, or nerve damage, were identified, recorded, and graded for severity (Grades 1–5) in strict accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical Analysis

Data were analyzed using SPSS 26.0. Non-normally distributed data were expressed as median and interquartile range [M (P25, P75)]. Given the repeated-measures structure of longitudinal symptom assessments, comparisons of NRS scores across different time points were performed using generalized estimating equations with an exchangeable working correlation matrix. Categorical data were presented as [n (%)], and Fisher's exact test was used to compare response rates across time points. A P value less than 0.05 was considered to be of statistical significance.

Results

Patient Characteristics

From September 2022 to July 2024, a total of 25 patients participated and completed the study (Table 1). The median age of the patients was 64 years with a higher proportion of female patients (60%). The median duration of CIPN symptoms was 6.0 months following the median 6 cycles of chemotherapy. The most commonly used chemotherapy agents were

Table 1 Baseline Characteristics of the Patients Included in This Study

Variables	
Age (year)	64.0 (52.0,69.0)
Duration of symptoms (months)	6.0 (3.0,11.5)
Chemotherapy cycle	6.0 (5.0,9.5)
Gender[n/(%)]	
Female	15 (60.0)
Male	10 (40.0)
Tumor type [n/(%)]	
Multiple myeloma	6 (24.0)
Breast cancer	5 (20.0)
Lung cancer	3(12.0)
Colon cancer	3(12.0)
Gastric cancer	3(12.0)
Cervical carcinoma	2(8.0)
Fallopian tube cancer	1(4.0)
Liver cancer	1(4.0)
Lymphoma	1 (4.0)
Chemotherapy regimens[n/(%)]	
Platinum	14 (56.0)
Taxanes	8(32.0)
Bortezomib	5(20.0)
Lenalidomide	3(12.0)
Vinca alkaloids	1(4.0)
Utidelone	1(4.0)
Symptoms [n/(%)]	
Pain	18 (72.0)
Numbness	25 (100.0)
Cold sensation	21 (84.0)
Dyskinesia	14 (56.0)

platinum (14/25) and taxanes (8/25). The symptoms were reported as numbness, affecting all patients (100%), followed by cold sensation (84%), pain (72%), and dyskinesia (56%).

Efficacy and Outcomes

Overall, the NRS scores for pain, numbness, cold sensation, and dyskinesia were significantly lower at 3 days, 1 month, and 3 months post-CIPN surgery compared to preoperative scores ($P < 0.05$) (Figure 2 and Table 2). Across the 25 patients, The improvement response rates were 68% at 3 days, 64% at 1 month, and 60% at 3 months post-operation ($P < 0.05$) (Figure 3 and Table 3).

The median NRS pain score was significantly decreased from 5.00 (2.00, 7.00) at baseline to 2.00 (0.75, 4.00) by the third day post-operation ($P < 0.001$). This reduction was maintained at 2.00 (1.00, 3.25) at 1 month ($P = 0.001$) and 2.00 (1.00, 3.00) at 3 months ($P = 0.001$), demonstrating stable and long-term pain control. Among the 18 patients reporting pain symptoms, there were 11 response cases at 3 days, 10 at 1 month, and 10 at 3 months post-operation, with all improvements being statistically significant ($P < 0.05$). The corresponding response rates were 61.1% at 3 days, 55.5% at 1 month, and 55.5% at 3 months (Table 2 and Table 3).

Although the median NRS score for numbness was decreased from 7.00 (5.00, 8.00) at baseline to 5.00 (4.00, 7.00) by the third day post-operation ($P < 0.001$), the magnitude of improvement was modest and did not reach the predefined threshold for clinical significance ($\geq 30\%$ reduction from baseline). At 1 month, the score was slightly increased to 6.00 (4.00, 7.00) ($P = 0.043$), before returning to 5.00 (3.50, 7.00) at 3 months ($P = 0.019$). Among the 25 patients with numbness, there were 6 response cases at 3 days post-operation ($P < 0.05$), but only 4 cases at both 1 month and 3 months, which were not statistically significant ($P > 0.05$). The response rates were 24.0% at 3 days, and 16.0% at both 1 and 3 months (Table 2 and Table 3).

A significant reduction in cold sensation was observed, with the median NRS score dropping from 5.00 (4.50, 8.00) at baseline to 2.00 (2.00, 3.00) on the third day post-operation ($P < 0.001$), followed by 3.00 (2.00, 4.50) at 1 month ($P < 0.001$) and 3.00 (2.00, 5.00) at 3 months ($P = 0.001$). Among the 21 patients with cold sensation, 15 response cases were noted at 3 days, 12 at 1 month, and 11 at 3 months, all of which were statistically significant ($P < 0.05$). Response rates for cold sensation relief were 71.4% at 3 days, 57.1% at 1 month, and 52.4% at 3 months (Table 2 and Table 3).

The median NRS score for dyskinesia showed a notable improvement, decreasing from 5.00 (3.75, 8.00) at baseline to 3.50 (2.00, 8.00) on the third day post-operation ($P = 0.002$). This was followed by stable improvement at 1 month (3.50, $P = 0.012$) and a further reduction to 3.00 (1.75, 8.00) at 3 months ($P = 0.010$). Among the 14 patients experiencing dyskinesia, there were 7 response cases at both 3 days and 1 month, and 8 cases at 3 months, all statistically

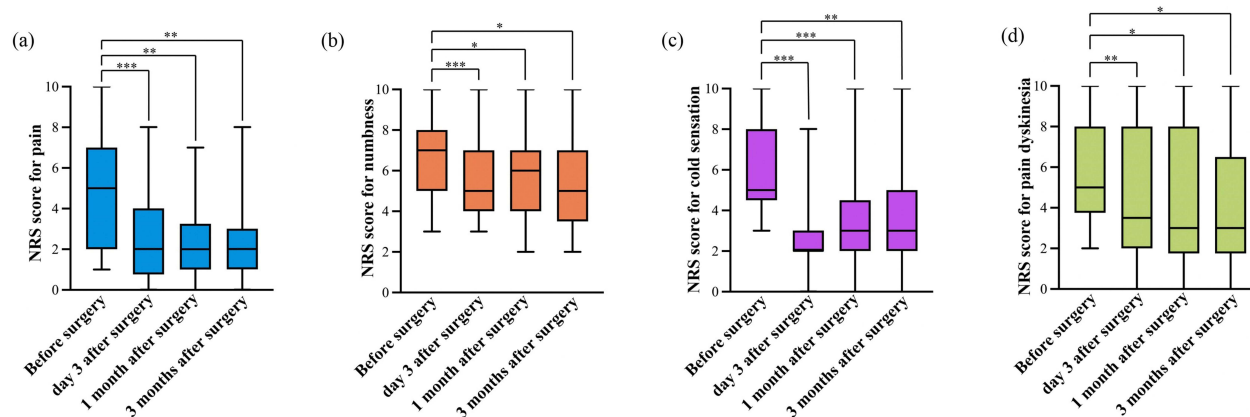


Figure 2 NRS scores at different moments for pain, numbness, cold sensation and dyskinesia analyzed by generalized estimating equation (GEE). (a) NRS scores for pain ($n=18$). (b) NRS scores for numbness ($n=25$). (c) NRS scores for cold sensation ($n=21$). (d) NRS scores for dyskinesia ($n=14$).

Note: * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$.

Abbreviations: T₀, preoperative; T₁, Day 3 after surgery; T₂, 1 month after surgery; T₃, 3 months after surgery.

Table 2 Changes in NRS Scores Over Time Analyzed by Generalized Estimating Equation (GEE)

Parameters	Median (P25, P75)	95%Wald CI	P
Pain (n=18)			
T ₁ vs T ₀	2.00(0.75,4.00) vs 5.00(2.00,7.00)	(-2.78,-0.82)	<0.001
T ₂ vs T ₀	2.00(1.00,3.25) vs 5.00(2.00,7.00)	(-2.89,-0.71)	0.001
T ₃ vs T ₀	2.00(1.00,3.00) vs 5.00(2.00,7.00)	(-3.09,0.83)	0.001
Numbness (n=25)			
T ₁ vs T ₀	5.00(4.00,7.00) vs 7.00(5.00,8.00)	(-1.69,-0.48)	<0.001
T ₂ vs T ₀	6.00(4.00,7.00) vs 7.00(5.00,8.00)	(-1.73,-0.03)	0.043
T ₃ vs T ₀	5.00(3.50,7.00) vs 7.00(5.00,8.00)	(-1.91,-0.17)	0.019
Cold sensation (n=21)			
T ₁ vs T ₀	2.00(2.00,3.00) vs 5.00(4.50,8.00)	(-3.83,-1.69)	<0.001
T ₂ vs T ₀	3.00(2.00,4.50) vs 5.00(4.50,8.00)	(-3.58,-1.06)	<0.001
T ₃ vs T ₀	3.00(2.00,5.00) vs 5.00(4.50,8.00)	(-3.42,-0.90)	0.001
Dyskinesia (n=14)			
T ₁ vs T ₀	3.50(2.00,8.00)vs5.00(3.75,8.00)	(-1.05,-0.23)	0.002
T ₂ vs T ₀	3.50(2.00,8.00)vs5.00(3.75,8.00)	(-1.57,-0.19)	0.012
T ₃ vs T ₀	3.00(1.75,8.00)vs5.00(3.75,8.00)	(-1.62,0.10)	0.010

Abbreviations: T₀, Preoperative; T₁, Day 3 after surgery; T₂, 1 month after surgery; T₃, 3 months after surgery.

significant ($P < 0.05$). The response rates were 50.0% at both 3 days and 1 month, increasing to 57.1% at 3 months (Table 2 and Table 3).

There were three noteworthy cases: one involved a patient with hypertension who discontinued his medication following surgery, and the other two involved a patient with lymphedema who experienced significant reduction in edema of both lower extremities within three months. Additionally, there were two adverse effects, both of them had minor bleeding at the tip of the puncture needle. In each case, the blood loss was less than 5 mL and had no clinical impact. No other adverse effects were noted.

Discussion

In this single-center exploratory study, we found that lumbar sympathiclysis significantly alleviated symptoms associated with bilateral lower limb CIPN, without causing adverse effects such as lumbar plexus nerve injury, male ejaculatory dysfunction, or vascular embolism. Our study suggested that CT-guided lumbar sympathiclysis provided immediate and sustained relief for pain and cold sensation, and gradual improvement in dyskinesia in patients with bilateral lower limb CIPN unresponsive to drug therapy. The sustained response in pain and cold sensation may be due to the anti-inflammatory effects of local sympathectomy, which promotes vasodilation, increased blood flow, and the elimination of toxic chemotherapy byproducts.²⁶ In contrast, the gradual improvement in dyskinesia may be related to the self-repair and regeneration of autonomic nerves and the alleviation of pain, numbness, and cold sensation, indirectly improving motor function.

While postoperative numbness were significantly improved immediately after treatment but long term effect was limited. This may be due to the non-regenerative nature of neurons and the inherent challenges in nerve repair per se.²⁷ Despite this limitation, the procedure provided some benefit to patients with refractory CIPN, maintaining a consistent, albeit modest symptom relief.

Current approaches to CIPN management—including neuromodulation techniques such as transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation, acupuncture, and physical therapy—have demonstrated variable and often modest efficacy.^{15,28–30} For instance, a recent multicenter, placebo-controlled RCT of a wireless TENS device for chronic CIPN demonstrated preliminary efficacy primarily for painful symptoms (eg, burning/sharp pain and cramping), with between-group differences ranging from 1.21 to 1.37 points on a 0–10 NRS in predefined symptomatic

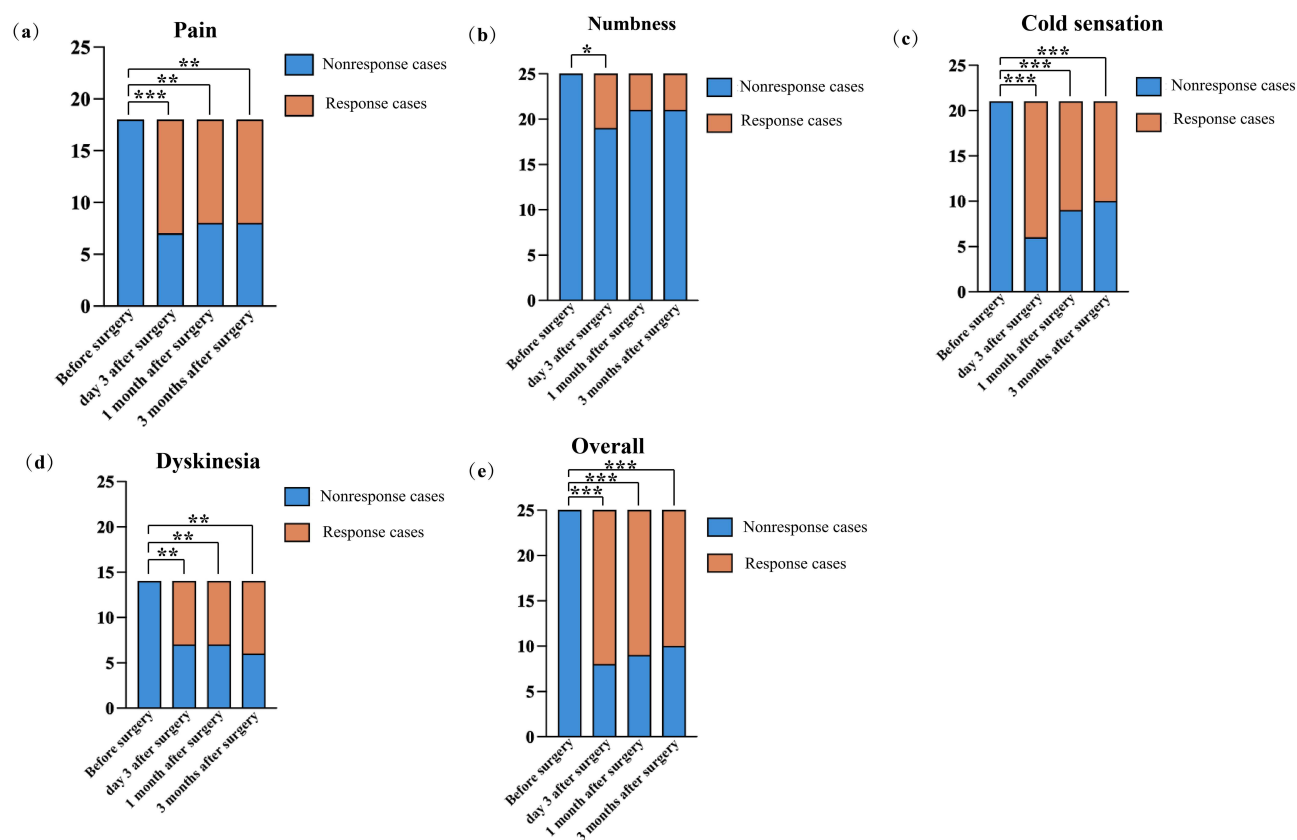


Figure 3 Distribution of response rates for pain, numbness, cold sensation, dyskinesia, and overall effectiveness analyzed by Fisher's exact test. (a) Number of response cases for pain (n=18). (b) Number of response cases for numbness (n=25). (c) Number of response cases for cold sensation (n=21). (d) Number of response cases for dyskinesia (n=14). (e) Number of response cases for overall (the number of cases with at least one of the four response cases of pain, numbness, cold sensation and dyskinesia)(n=25).

Note: *P < 0.05, **P < 0.01, and ***P < 0.001.

Abbreviations: T₀, Preoperative; T₁, Day 3 after surgery; T₂, 1 month after surgery; T₃, 3 months after surgery.

subgroups. However, no significant effects were observed for numbness or tingling.²⁸ In contrast, our exploratory study on CT-guided lumbar sympathectomy demonstrated significant and sustained improvement not only in pain and cold sensation but also, to a degree, in dyskinetic symptoms. Notably, the intervention provided rapid and substantial symptom relief, with 60% of patients achieving a clinically meaningful response ($\geq 30\%$ NRS reduction) in at least one core symptom at three months. While direct efficacy comparisons cannot be drawn from different study designs, the magnitude, rapidity, and breadth of symptom relief observed with lumbar sympathectomy—particularly targeting refractory, multimodal symptoms—suggest it may represent a more invasive yet potentially more targeted and effective interventional option for a specific subset of patients with severe, pharmacotherapy-resistant, lower-limb CIPN.

Table 3 Response Rates of Improvement in Pain, Numbness, Cold Sensation, Dyskinesia, and Overall (%)

Categories	Day 3 After Surgery	1 Month After Surgery	3 Months After Surgery
Pain (n=18)	61.1% (11/18)	55.5% (10/18)	55.5% (10/18)
Numbness (n=25)	24.0% (6/25)	16.0% (4/25)	16.0% (4/25)
Cold sensation (n=21)	71.4% (15/21)	57.1% (12/21)	52.4% (11/21)
Dyskinesia (n=14)	50.0% (7/14)	50.0% (7/14)	50.0% (7/14)
Overall (n=25)	68% (17/25)	64% (16/25)	60% (15/25)

Note: The overall response rate was the proportion of the total number of patients with one or more response cases of pain, numbness, cold sensation, and dyskinesia.

This study has limitations. First, the single-arm design without a control group limits causal inference. Second, no formal sample size calculation or power analysis was performed due to the exploratory nature of this first-in-kind study. Third, while a $\geq 30\%$ NRS reduction defined treatment response, validated minimally important difference thresholds for numbness, cold sensation, and dyskinesia are lacking. Fourth, the small sample size and short-term follow-up warrant verification in larger, longer studies. Additionally, the reliance solely on subjective patient-reported outcomes (NRS scores) without complementary objective measures (eg, nerve conduction studies, quantitative sensory testing) limits the mechanistic insight and scientific robustness of our findings.

Conclusions

Preliminary findings suggest, CT-guided lumbar sympathectomy may be a potentially effective and safe minimally invasive intervention for refractory lower extremity CIPN, providing significant and rapid relief for pain and cold sensation, along with gradual improvement in dyskinetic symptoms. Further clinical applications will require larger-scale and controlled trials for verification to confirm its long-term efficacy and safety.

Data Sharing Statement

The data used and analyzed during the current study are available from the corresponding author, Guanglun Xie, upon reasonable request.

Ethical Statement

The study was reviewed and approved by the Biomedical Ethics Committee of Henan Cancer Hospital (No. 2022-KY-0077-002). Written consent was obtained before participation.

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Disclosure

Jiaojiao Suo and Fang Zhang are co-first authors for this study. The authors declare that they have no conflicts of interest for this work.

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