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ORIGINAL RESEARCH

Acupoint Catgut Embedding at Stellate Ganglion Combined with Oral Mecobalamin Versus Mecobalamin Monotherapy in Managing Taxane-Induced Peripheral Neurotoxicity: A Clinical Observational Study

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Purpose: Taxane-induced peripheral neurotoxicity (TIPN) severely impacts the quality of life of patients and worsens over time with cumulative drug exposure. This study aims to evaluate the efficacy and safety of Stellate Ganglion Catgut Embedding (SGCE) therapy in treating TIPN patients, exploring a novel approach to managing TIPN.

Patients and Methods: The study was conducted from June 2023 to June 2024 at the Second Affiliated Hospital of Harbin Medical University. Patients (at least two cycles of taxane treatment, including albumin-bound paclitaxel, paclitaxel, docetaxel, etc) were divided into methylcobalamin (MeCbl, n=25) and SGCE (n=21) groups. The former received oral methylcobalamin therapy, while the SGCE group underwent Stellate Ganglion Blockade with Catgut Implantation combined with oral methylcobalamin therapy. Neurotoxicity was assessed using the EORTC QLQ-CIPN15 and FACT/GOG-Ntx scales, with patient quality of life evaluated using the FACT-G scale. Comprehensive outcomes would be assessed on the day of treatment (SGCE or MeCbl treatment) and at the 1st and 3rd weeks post-treatment for all participants. Adverse events were assessed using the CTCAE scales.

Results: The principal findings revealed that according to the EORTC QLQ-CIPN15 sensory, motor, overall scores and FACT/GOG-Ntx scale scores, there were significant decreases in the SGCE group compared to the MeCbl group after 3 weeks of treatment ($P<0.05$). The secondary outcomes showed that the FACT-G scores in the SGCE group significantly increased from baseline ($\boldsymbol{P}=0.011$). Throughout the assessment period before and after treatment, no significant adverse reactions were observed in the patients.

Conclusion: SGCE group produced a more pronounced improvement in symptoms among TIPN patients compared to MeCbl group, enhanced the quality of life of the patients compared with the pre-treatment period, this improvement could be linked to SGCE. Moreover, the patients did not show significant adverse effects.

Keywords: taxane, peripheral neurotoxicity, stellate ganglion, Catgut embedding

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) profoundly disrupted patients' quality of life.[1] It was estimated that 50–90% of individuals undergoing chemotherapy developed acute manifestations of this condition, while 30–40% continued to endure chronic CIPN.[2] The prevalence of chronic painful CIPN stood at 41.22%. Among those treated with taxane-based agents, the prevalence of chronic pain reached 38.35%, second only to platinum-based therapies at 40.44%.[3] Addressing taxane-induced peripheral neuropathy (TIPN) thus emerged as a clinical imperative. Taxanes, by stabilizing microtubules and preventing their depolymerization, effectively arrested the cell cycle of tumor cells, thereby

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inhibiting tumor growth.[4] However, they also disrupted axonal transport, affecting dorsal root ganglia, mitochondria, peripheral nerves, and even central nervous system cells.[5] Thus, TIPN manifested clinically with symptoms such as pain, numbness, and sensory abnormalities. TIPN significantly impaired patients' quality of life and frequently necessitated dose reduction or early cessation of treatment.[6] As patients' survival periods lengthened, the significance of TIPN continued to grow.

Currently, there was a lack of effective prevention and treatment strategies for TIPN. Although Duloxetine was the only medication recommended by ASCO for its management, in Japan, some patients discontinued its use due to unclear benefits and significant side effects.[7] In recent years, several novel therapeutic approaches had shown promising potential in experimental settings for managing TIPN, including certain targeted therapies as tyrosine kinase inhibitors like nilotinib, phosphodiesterase inhibitors such as cilostazol, and monoclonal antibodies targeting matrix metalloproteinase-9 (MMP-9). Moreover, neuromodulation therapy had emerged as a viable treatment option for numerous cases of refractory chronic pain, including TIPN. Related studies had also found that animal models of TIPN might benefit from neuromodulatory treatments.[2] Additionally, commonly used medications like methylcobalamin, oxycodone, and venlafaxine, along with non-pharmacological treatments such as exercise therapy, surgical glove compression, and cryotherapy, had demonstrated some efficacy. However, their clinical applicability remained limited due to small sample sizes, significant side effects, and inconsistent research conclusions, which detracted from their persuasiveness.[8–10]

Currently, therapeutic approaches targeting pain through neuromodulatory mechanisms had garnered increasing attention, thereby driving innovative research in this field. The stellate ganglion, a sympathetic ganglion, regulated the functional activities of multiple systems and organs.[11] Due to the local inflammation and axonal damage induced by taxanes, which promoted spontaneous neuronal activity (particularly bursting), the activation of surrounding glial cells ensued. This activation led to the release of cytokines such as TNF-α and IL-1β, which served as sprouting factors for primary sensory neurons,[12] and exerted excitatory effects on neighboring neurons, leading to manifestations of pain and sensory abnormalities.[12–14] Current experimental evidence indicated that Stellate Ganglion Block (SGB) could dilate blood vessels, alleviate neural and vascular spasms, and further mitigate neuropathic pain by reducing the release of peripheral inflammatory factors and modulating nociceptors.[15,16] Similarly, stimulating the sympathetic nervous system through SGCE had been shown to alleviate pain symptoms in patients with cervical spondylosis.[11] Moreover, the therapeutic approach demonstrated comparative convenience while circumventing the potential adverse effects of hepatorenal toxicity and neurological impairment commonly associated with pharmacotherapy. However, there had been no reports thus far on its application in the treatment of TIPN. This study marked the first attempt to employ SGCE in the treatment of TIPN, aiming to evaluate its efficacy and safety in this context, thereby offering a novel approach for clinical management of TIPN.

Materials and Methods

Experimental Design

This study aimed to collect data from cancer patients treated at Harbin Medical University Affiliated Second Hospital between June 2023 and June 2024, who experienced symptoms of TIPN and received treatment with either methylcobalamin alone or a combination of stellate ganglion catgut embedding and methylcobalamin. Patients were divided into the MeCbl group and the SGCE group. Patients in the SGCE group received catgut embedding at the stellate ganglion combined with oral mecobalamin treatment, while those in the MeCbl group received mecobalamin treatment alone. The neurotoxic effects of taxane and the impact on quality of life were assessed on the day of treatment (SGCE or MeCbl treatment) and at the 1st and 3rd weeks post-treatment for all participants. Adverse events and the incidence of related adverse reactions were recorded during the evaluation period.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Histologically confirmed malignant tumors.
2. Age between 18 and 75 years.

3. Good general condition with a Karnofsky Performance Status (KPS) score ≥60.
4. At least two cycles of taxane treatment.
5. Expected survival time > 6 months.
6. Peripheral neuropathy of grade 2 or higher following taxane chemotherapy, as assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Exclusion Criteria

1. Pregnant or lactating women.
2. Patients with severe cardiovascular, cerebrovascular, hepatic, renal, or hematological diseases.
3. Individuals with intellectual disabilities or a history of psychiatric illness who are unable to self-assess.
4. Peripheral neurotoxicity caused by chemotherapy regimens other than taxane.
5. Peripheral neuropathy due to diabetes or preexisting neurological diseases.
6. Peripheral vascular insufficiency.
7. Coagulation disorders.
8. A family history of hereditary neuropathies.

Termination or Exclusion Criteria

1. Patients who fail to complete the study due to various reasons (eg, transfer to another hospital, death).
2. Poor patient compliance, failing to adhere strictly to the clinical protocol design for various reasons.
3. Adverse reactions and complications that preclude continuation of the study.

Groups

MeCbl Group

Patients receiving taxane-based chemotherapy will be administered oral mecobalamin three times daily, each dose 0.5 mg, for a duration of 14 days.

SGCE Group

In addition to the oral mecobalamin regimen (three times daily, each dose 0.5 mg, for 14 days), patients in the SGCE group will undergo SGCE therapy. The procedure will be conducted in accordance with the "the technical operation standards of the embedding acupotomy technique" (Figure 1).

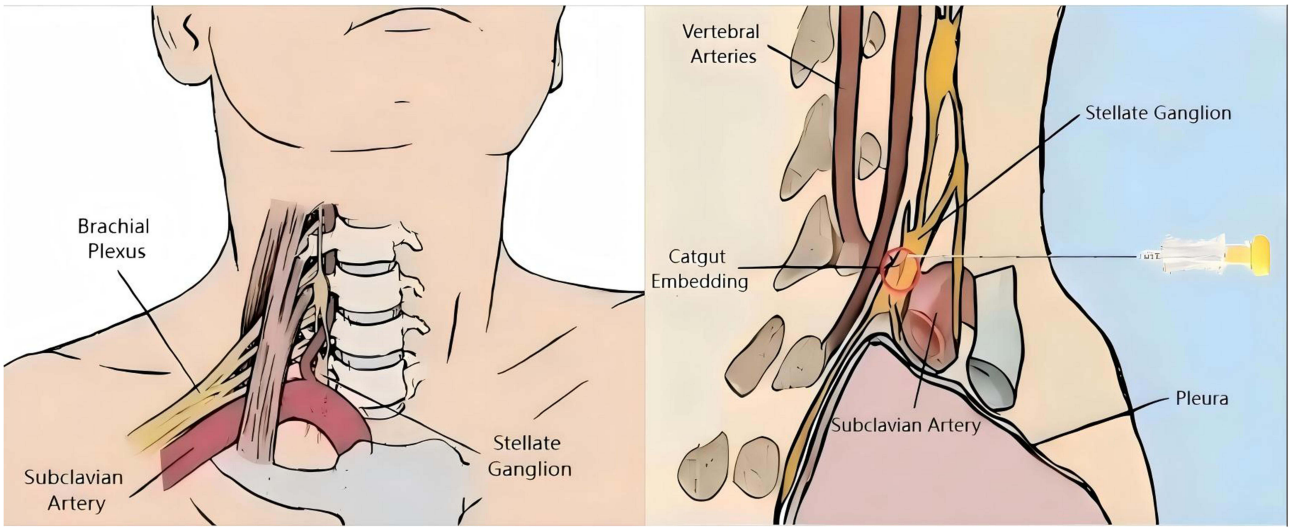

Figure 1 Anatomy of the Stellate Ganglion + Schematic Diagram of Catgut Embedding Procedure.

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Efficacy Evaluation

The quality of life of both groups was assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) scale. Neurotoxicity outcomes were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-item scale (EORTC QLQ-CIPN20) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) subscale.[17]

The FACT-G is a 27-item questionnaire designed to measure the four domains of health-related quality of life (HRQOL) in cancer patients: physical, social, emotional, and functional well-being. As one of the commonly used quality of life assessment tools, FACT-G had been content-validated among mixed cancer diagnoses in the United States and partially validated in Chinese patients (unspecified cancer types).[18]

The EORTC QLQ-CIPN20 included 20 items, grading the functional impact of sensory (9 items), motor (8 items), and autonomic TIPN symptoms (3 items).[19] However, subsequent research found that a streamlined 15-item version, excluding questions with low total correlation (involving hearing loss, orthostatic hypotension, blurred vision, erectile dysfunction, and driving difficulties), was equally reliable and reduced the number of items for patient response.[20,21] Therefore, this study used the 15-item version (QLQ-CIPN15), further subdivided into sensory and motor symptom rating modules to detail changes in the patient's condition.

The FACT/GOG-Ntx subscale is an 11-item neurotoxicity module added to the FACT-G core quality of life measurements.[20] It had satisfactory reliability, validity, sensitivity to change, and responsiveness in assessing TIPN in cancer patients.[17,22] This study used the FACT/GOG-Ntx subscale in conjunction with the EORTC QLQ-CIPN15 score to enhance the accuracy of the assessment.

Adverse events were evaluated and graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis

Statistical analysis encompassed all patients in both the SGCE and MeCbl groups. The Shapiro–Wilk test was employed to assess the normality of basic patient characteristics, all patient scores, and treatment-related adverse events (TRAEs). If basic patient characteristics, intergroup patient scores, and TRAEs conformed to a normal distribution, an independent samples *t*-test was used to compare baseline characteristics and various scores between the SGCE and MeCbl groups. Otherwise, the Mann–Whitney *U*-test was applied, with the Hodges–Lehmann method calculating the confidence intervals (95% CI) for the differences between the two groups. For intragroup patient scores, if they conformed to a normal distribution, a paired samples *t*-test was used to evaluate the various scores in the SGCE and MeCbl groups. Otherwise, the Wilcoxon signed-rank test was employed, with the Hodges-Lehmann method calculating the 95% CI for the differences between the two groups. Additionally, the Wilcoxon signed-rank test was used to assess the treatment efficacy within groups. A p-value <0.05 was considered statistically significant. Statistical data processing was conducted using SPSS 27.0 for Windows software (IBM Corp., Armonk, NY, USA).

Results

Patient Baseline Characteristics

This study included 53 patients who developed TIPN after undergoing taxane therapy at the Second Affiliated Hospital of Harbin Medical University between June 2023 and June 2024 and met the inclusion criteria. The patients were divided into an SGCE group (SGCE + mecobalamin treatment) with 25 patients and a MeCbl group (oral mecobalamin alone) with 28 patients. Four patients in the SGCE group and three in the MeCbl group were lost to follow-up. A total of 46 patients were ultimately available for efficacy evaluation, with 21 in the SGCE group and 25 in the MeCbl group (Figure 2). The baseline characteristics of the two groups were balanced, with no statistically significant differences in age, gender, type of cancer, stage, surgical history, radiotherapy history, and diabetes status. A higher proportion of female patients was observed in both groups, with 80.95% (N=17) in the SGCE group and 76.00% (N=19) in the MeCbl group. The most common type of cancer was breast cancer, accounting for 43.48% (N=20), while the least common was esophageal cancer, with only 2.17% (N=1). The majority of patients were in stages III–IV, with 80.95% (N=17) in the

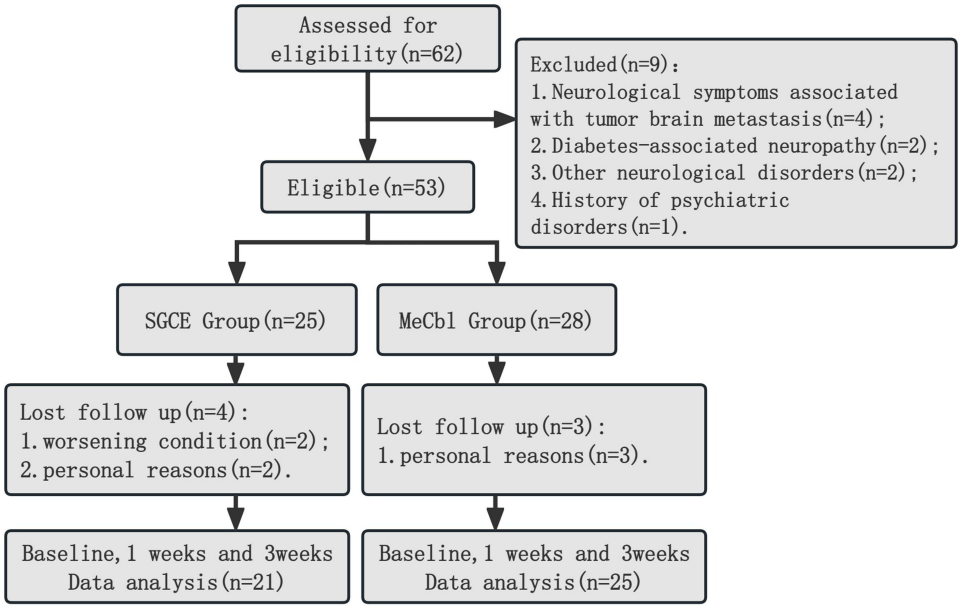

Figure 2 Study Design and Grouping.

SGCE group and 84.00% (N=21) in the MeCbl group. Fewer patients were in stages I–II, with four in each group, accounting for 19.05% and 16.00%, respectively. Most patients had undergone surgery, with 76.00% (N=19) in the MeCbl group and 61.90% (N=13) in the SGCE group. However, the proportion of patients who had received radiotherapy was low (three in the SGCE group and eight in the MeCbl group). Only one patient in the MeCbl group had diabetes, but they had no symptoms of diabetic peripheral neuropathy prior to the study (Table 1). All patients had received taxane therapy (including albumin-bound paclitaxel, paclitaxel, docetaxel, etc).

Table 1 Essential Attributes Of The Eligible Patients

Characteristic	Totality	SGCE Group	MeCbl Group	*P value*
Age (year, Mean±SD)	55.72±9.099	54.43±9.097	56.80±9.142	0.385
Sex (n,%)				0.688
Male	10(21.74)	4(19.05)	6(24.00)	
Female	36(78.26)	17(80.95)	19(76.00)	
Tumor type (n,%)				
Breast cancer	20(43.48)	8(38.10)	12(48.00)	0.753
Lung cancer	8(17.39)	5(23.81)	3(12.00)	
Oophoroma	11(23.91)	5(23.81)	6(24.00)	
Head and neck tumors	4(8.70)	1(4.76)	3(12.00)	
Cervical carcinoma	2(4.35)	2(9.52)	0(0.00)	
Esophageal cancer	1(2.17)	0(0.00)	1(4.00)	
Tumor stage (n,%)				
I–II	8(17.39)	4(19.05)	4(16.00)	0.788
III–IV	38(82.61)	17(80.95)	21(84.00)	
Surgery				
Yes	32(69.57)	13(61.90)	19(76.00)	
No	14(30.43)	8(38.10)	6(24.00)	0.306

(*Continued*)

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Table 1 (Continued).

Characteristic	Totality	SGCE Group	MeCbl Group	*P value*
Radiotherapy				
Yes	11(23.91)	3(14.29)	8(32.00)	
No	35(76.09)	18(85.71)	17(68.00)	0.165
Diabetes				
Yes	1(2.17)	0(0.00)	1(4.00)	0.359
No	45(97.83)	0(0.00)	24(96.00)	

Score Results

The neurotoxicity and quality of life scores during treatment for both groups were as follows (Figure 3, Mean±SD): The SGCE group showed a general downward trend in QLQ-CIPN15 sensory scores, motor scores, total scores, and FACT/GOG-Ntx scores, while the MeCbl group remained stable or even showed an upward trend in some cases. Both the SGCE and MeCbl groups exhibited an upward trend in FACT-G scores post-treatment, but the SGCE group's increase was more pronounced, and the MeCbl group's early changes were less noticeable.

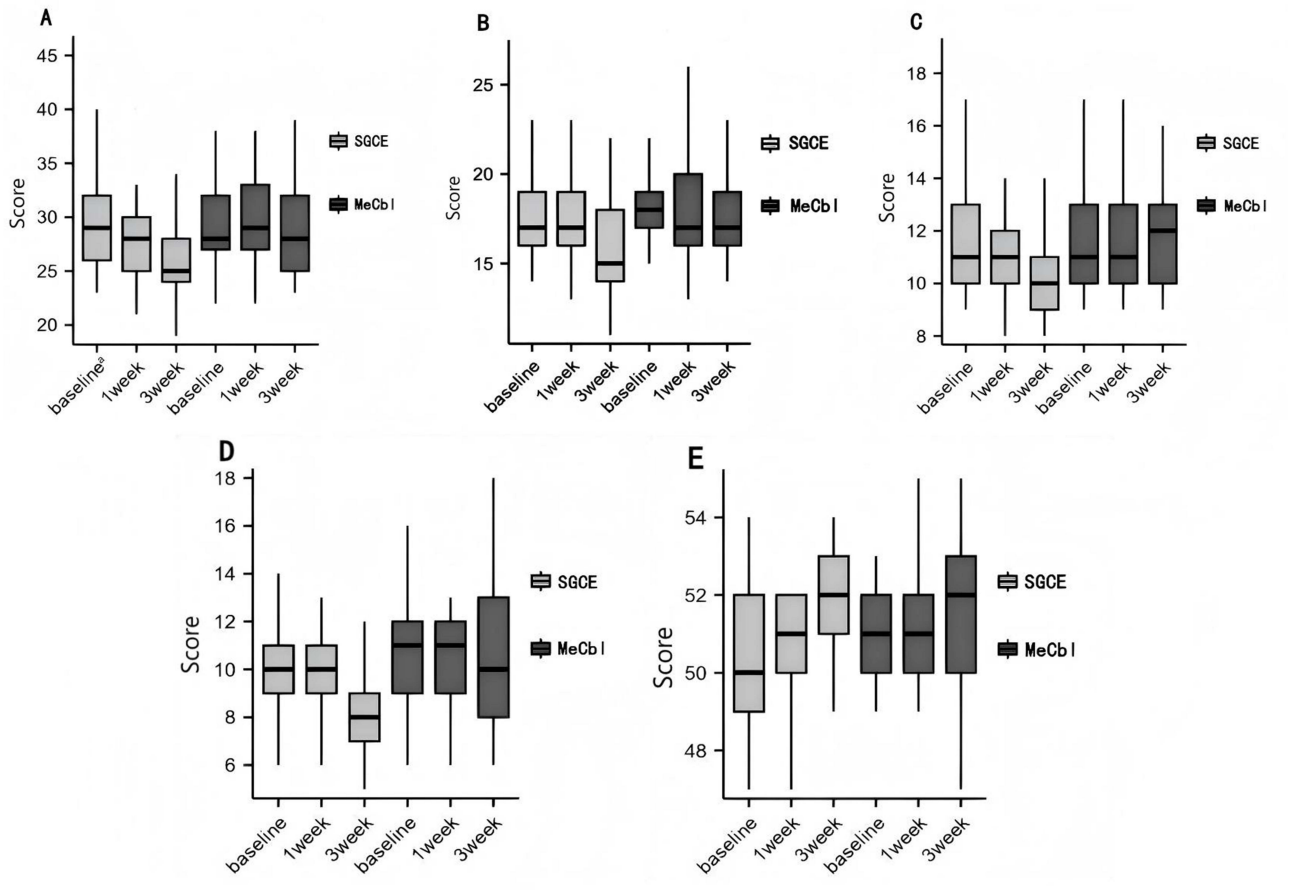

Figure 3 Changes in Neurotoxicity and Quality of Life Scores During Treatment (Mean±SD).
Notes: (**A**) QLQ-CIPN15 Total, a streamlined 15-item version of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20-Item Scale. (**B**) QLQ-CIPN15 Sensory. (**C**) QLQ-CIPN15 Motor. (**D**) FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity Subscale. (**E**) FACT-G, Functional Assessment of Cancer Therapy-General Scale. [a]Score taken immediately before the treatment on the day of assessment. Lower QLQ-CIPN15 and FACT/GOG-Ntx scores indicate lower neurotoxicity, while higher FACT-G scores indicate better quality of life.

After testing with the Shapiro–Wilk method, most group scores did not conform to a normal distribution. Therefore, the Mann–Whitney *U*-test was used to evaluate intergroup patient scores and treatment-related adverse reactions, while the Wilcoxon signed-rank test was employed for intragroup patient scores.

The EORTC QLQ-CIPN15 scores showed that the SGCE group's sensory scores differed significantly from baseline after one week (***P***<0.001), with a median difference of −0.500 (95% CI: −1.000 to −0.500). The difference continued to increase after three weeks (***P***=0.001), with a median difference of −2.500 (95% CI: −3.500 to −1.000). The MeCbl group only showed slight reductions in scores after one and three weeks, which were not statistically significant (***P***>0.05), but the difference between the two groups was significant after three weeks (***P***=0.032). In the motor scores, the SGCE group showed a statistically significant difference from baseline after one week (***P***=0.003) and an even more pronounced difference after three weeks (***P***<0.001). The MeCbl group did not show a significant difference from baseline after three weeks, but there was a statistically significant difference between the two groups after three weeks (***P***=0.041). The total scores of the SGCE group changed significantly from baseline after one and three weeks (***P***<0.001), while the MeCbl group showed no significant changes. The difference between the two groups was statistically significant after three weeks (***P***=0.030).

The FACT/GOG-Ntx scores of the SGCE group did not differ significantly from baseline after one week (***P***=0.228), but the difference increased rapidly after three weeks (***P***<0.001). The MeCbl group showed a trend of increasing differences from baseline during treatment, but no significant difference was observed after three weeks (***P***=0.199), and there was a statistically significant difference between the two groups after three weeks (***P***=0.032).

In the FACT-G scores assessing quality of life, the SGCE group showed a significant improvement in quality of life after three weeks (***P***=0.011). Although there was an overall improvement trend, no statistically significant differences were observed when comparing the scores after one week to baseline or when comparing the scores continuously with the MeCbl group (***P***>0.05) (Tables 2 and 3).

Table 2 Comparison of Neurotoxicity and Quality of Life Changes Within Groups and Relative to Baseline

Results	Median Differences Within Groups and Relative to Baseline[a] (95% CI)		Comparison of Changes Within Groups and Relative to Baseline[b]			
	SGCE Group	MeCbl Group	Z value		P value	
			SGCE Group	MeCbl Group	SGCE Group	MeCbl Group
QLQ-CIPN15 sensory scores						
Baseline	–	–	–	–	–	–
1week	−0.500(−1.000-(−0.500))	0.000(−0.500–0.000)	−3.500	−0.728	<0.001	0.467
3 week	−2.500(−3.500-(−1.000))	−0.500(−1.000–0.000)	−3.259	−1.622	0.001	0.105
Motor scores						
Baseline	–	–	–	–	–	–
1 week	−0.500(−1.000-(−0.500))	−0.500(−0.500–0.000)	−2.950	−1.604	0.003	0.109
3 week	−2.000(−2.500-(−1.000))	−0.500(−1.000–0.500)	−3.502	−1.023	<0.001	0.306
Total scores						
Baseline	–	–	–	–	–	–
1 week	−1.500(−2.000-(−1.000))	−0.500(−1.000–0.000)	−3.573	−1.384	<0.001	0.166
3 week	−4.500(−6.000-(−2.000))	−1.000(−2.000–0.500)	−3.450	−1.381	<0.001	0.167
FACT/GOG-Ntx						
Baseline	–	–	–	–	–	–
1 week	0.000(−0.500–0.000)	0.000(−0.500–0.000)	−1.069	−1.000	0.285	0.317
3 week	−1.500(−2.500-(−1.000))	−0.500(−1.000–0.500)	−3.375	−1.284	<0.001	0.199
FACT- G						
Baseline	–	–	–	–	–	–
1 week	0.500(−0.500–1.000)	0.500(0.000–0.500)	1.205	1.435	0.228	0.151
3 week	1.500(0.500–2.500)	0.500(−0.500–1.000)	2.556	1.043	0.011	0.297

Notes: Lower QLQ-CIPN15 and FACT/GOG-Ntx scores indicate lower neurotoxicity, while higher FACT-G scores indicate better quality of life. [a]The Hodges–Lehmann method was used to assess the median difference within groups from baseline. [b]The Wilcoxon signed-rank test was used to evaluate changes within groups from baseline.

Table 3 Comparison of Neurotoxicity and Quality of Life Changes Between Groups

Results	M[a](P_{25}, P_{75})		Median Differences Between Groups[b] (95% CI)	Comparison of Changes Between Groups[c]	
	SGCE Group	MeCbl Group		Z value	P value
QLQ-CIPN15 sensory scores					
Baseline	17.00(15.50,19.50)	18.00(16.50,19.50)	−1.000(−2.000–1.000)	−0.712	0.476
1 week	17.00(15.50,19.00)	17.00(16.00,20.00)	−1.000(−2.000–1.000)	−1.171	0.242
3 week	15.00(14.00,18.00)	17.00(15.50,19.50)	−2.000(−3.000–0.000)	−2.144	0.032
Motor scores					
Baseline	11.00(10.00,13.00)	11.00(10.00,13.50)	0.000(−1.000–1.000)	−0.145	0.884
1 week	11.00(9.50,12.00)	11.00(10.00,13.00)	0.000(−1.000–1.000)	−0.808	0.419
3 week	10.00(9.00,11.50)	12.00(9.50,13.00)	−1.000(−2.000–0.000)	−2.039	0.041
Total scores					
Baseline	29.00(26.00,32.50)	28.00(27.00,32.50)	−1.000(−3.000–2.000)	−0.454	0.650
1 week	28.00(25.00,30.50)	29.00(26.50,33.00)	−1.000(−4.000–1.000)	−0.955	0.339
3 week	25.00(23.50,28.50)	28.00(25.00,33.00)	−3.000(−6.000–0.000)	−2.169	0.030
FACT/GOG-Ntx					
Baseline	10.00(8.50,11.00)	11.00(9.00,12.00)	−1.000(−2.000–1.000)	−1.181	0.238
1 week	10.00(8.50,11.00)	11.00(9.00,12.00)	−1.000(−2.000–1.000)	−0.985	0.325
3 week	8.00(7.00,9.50)	10.00(8.00,13.00)	−2.000(−3.000–0.000)	−2.149	0.032
FACT- G					
Baseline	50.00(49.00,52.5)	51.00(50.00,52.00)	−1.000(−2.000–1.000)	−0.990	0.322
1 week	51.00(50.00,52.00)	51.00(50.00,52.00)	0.000(−1.000–1.000)	−0.414	0.679
3 week	52.00(51.00,53.00)	52.00(50.00,53.00)	1.000(0.000–2.000)	−1.093	0.275

Notes: Lower QLQ-CIPN15 and FACT/GOG-Ntx scores indicate lower neurotoxicity, while higher FACT-G scores indicate better quality of life. [a]Median scores and interquartile ranges for each group. [b]The Hodges–Lehmann method was used to assess the median difference within groups from baseline. [c]The Mann–Whitney *U*-test was used to evaluate changes between groups.

Adverse Reactions

The SGCE group's procedure was performed under ultrasound guidance after local anesthesia, administered by experienced physicians following standard protocols. The patients' wounds were minimal, and no significant treatment-related adverse events were reported during follow-up. No adverse reactions related to methylcobalamin administration were reported by either group of patients.

Discussion

In this study, SGCE demonstrated a more pronounced reduction in TIPN severity compared to MeCbl after 3 weeks of treatment, with patient-reported symptoms such as numbness and tingling exhibiting considerable improvement. Notably, SGCE achieved statistically significant differentiation from baseline in CIPN15 scores as early as week 1 of intervention, a contrast to the nonsignificant trajectory observed in the MeCbl group. But no substantial deterioration of TIPN manifestations occurred in MeCbl-treated patients during observation, only marginal progression was noted in CIPN15 motor subscale scores, lacking statistical significance. Clinically meaningful enhancements in quality of life were evident in the SGCE cohort through favorable patient feedback post-treatment. Furthermore, MeCbl recipients also displayed modest upward trends in quality-of-life metrics (Figure 3), maintaining relative stability throughout the trial without notable symptom exacerbation. We postulated a potential therapeutic role of mecobalamin in TIPN management. But current conclusions remain constrained by methodological limitations including small sample size, non-blinded allocation, and participant attrition biases.

Taxane is now available in various forms including paclitaxel, albumin-bound paclitaxel, and liposomal paclitaxel. Notably, albumin-bound paclitaxel demonstrated heightened propensity for inducing TIPN. However, due to reasons such

as the current exploratory phase of this study and the small sample size, the various types of doses of paclitaxel, etc., were not analyzed. Current treatments for TIPN primarily focus on the use of antiepileptic drugs, antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioids.[23] Pharmacotherapeutic agents in this class exhibit high-prevalence adverse effect profiles including dizziness, fatigue, nausea, impaired concentration, hepatic/renal impairment, and agent-specific toxicities. Non-pharmacological interventions span kinesiotherapy, cryotherapy, compressive glove therapy, and traditional Chinese medicine (TCM) modalities encompassing herbal decoctions and acupuncture. While demonstrating modest efficacy in limited cohorts,[8–10] implementation challenges arise from suboptimal patient compliance attributable to therapeutic complexity. In recent years, neuromodulation has emerged as a viable therapeutic option for refractory chronic pain conditions including TIPN, encompassing modalities such as dorsal column spinal cord stimulation (SCS), dorsal root ganglion stimulation (DRG-S), and peripheral nerve field stimulation (PNFS).[2] While pain specialists may recommend neurostimulation interventions following conventional treatment failure, the evidence base remains limited in certainty due to the absence of prospective comparative outcome studies. Moreover, in American guidelines, sympathetic blocks, including Stellate Ganglion Block (SGB), are listed as a first-line treatment for complex regional pain syndrome.[24] Additionally, there are numerous reports on the use of SGB to treat TIPN patients.[25] However, SGB carries risks such as drug toxicity, spinal or vertebral artery puncture injuries, arrhythmias, and even death,[26–28] therapeutic protocols demonstrate procedural complexity, frequently resulting in suboptimal treatment adherence. Therapeutic modalities involving neural modulation (SCS/SGB) demonstrate the feasibility of alleviating peripheral neuropathic symptoms through neural functional regulation. SGCE, operating within this paradigm, exhibits dual advantages: maintaining therapeutic efficacy while implementing a triweekly treatment protocol. This approach obviates anesthetic nerve block requirements, circumvents drug-related toxicity, and potentially enhances treatment compliance through reduced procedural frequency.

Taxane stabilizes microtubule structures, inhibits the formation of the mitotic spindle, and thereby arrests cell growth, inducing apoptosis in tumor cells. However, this also affects the stability of microtubules, including those in neuronal axons, leading to distal sensory neuron axonal degeneration (also known as Wallerian degeneration or programmed axonal degeneration), which is considered a crucial step in the development of TIPN.[29] Targeting the essential driver of axonal degeneration, SARM1, has been recognized as a promising approach to prevent TIPN.[30] Additionally, taxane can induce mitochondrial swelling, vacuolation, structural loss, and the release of pro-inflammatory factors, resulting in neuronal mitochondrial damage and impairing neuronal function.[8,31]

While explicit mechanistic studies on SGCE remain absent, some evidence implicated dorsal root ganglion-derived inflammatory cytokines as pivotal contributors to TIPN pathogenesis.[5,32] A study had found SGCE may attenuate pro-inflammatory cytokine secretion.[33] Thus, we made a bold speculation about the mechanism of SGCE: Dorsal root ganglia (DRG), composed primarily of sensory neurons, are thought to primarily transmit noxious stimuli.[34] Due to a more permeable blood-nerve barrier, DRGs accumulate high levels of taxane, leading to corresponding pain and numbness in the extremities. Following peripheral nerve injury, endogenously released ATP binds to sensory nerve terminals, activating afferent neurons that signal sympathetic neurons in the stellate ganglion. Subsequently, sympathetic nerve fibers release ATP and norepinephrine, among other neurotransmitters,[14] which activate satellite glial cells (SGCs) and further release ATP.[35] Injured DRGs also express several ATP autoreceptors on sympathetic nerve fibers[13] and sensory neurons, further enhancing neurotransmitter release.[36,37] This positive feedback loop, exacerbated by high ATP concentrations, facilitates the formation of large pores, mediating the release of cytokines like TNF-α and IL-1β. These cytokines act as sprouting factors for primary sensory neurons,[12] increasing nearby neuronal excitability and causing abnormal sensory neuron activity, leading to pain[6] (Figure 4).

The positive feedback and mixed stimulation of neurotransmitters induced by ATP binding to autoreceptors on sympathetic nerve fibers[38] may help explain why influencing the stellate ganglion can alleviate pain symptoms. SGCE therapy may interfere with sympathetic nerve function through foreign body stimulation or inflammatory factors affecting the stellate ganglion and alleviating symptoms such as TIPN pain. TIPN patients often exhibit increased expression of IL-1β, IL-6, and TNF-α,[5,32] with IL-6 correlating with the severity of neuropathy. Wang M and others[33] found that following SGCE therapy, levels of TNF-α, IL-6, and IL-1β significantly decreased in patients, reaffirming the potential of SGCE therapy to regulate inflammatory factor expression through its impact on SGCs. Additionally, some researchers

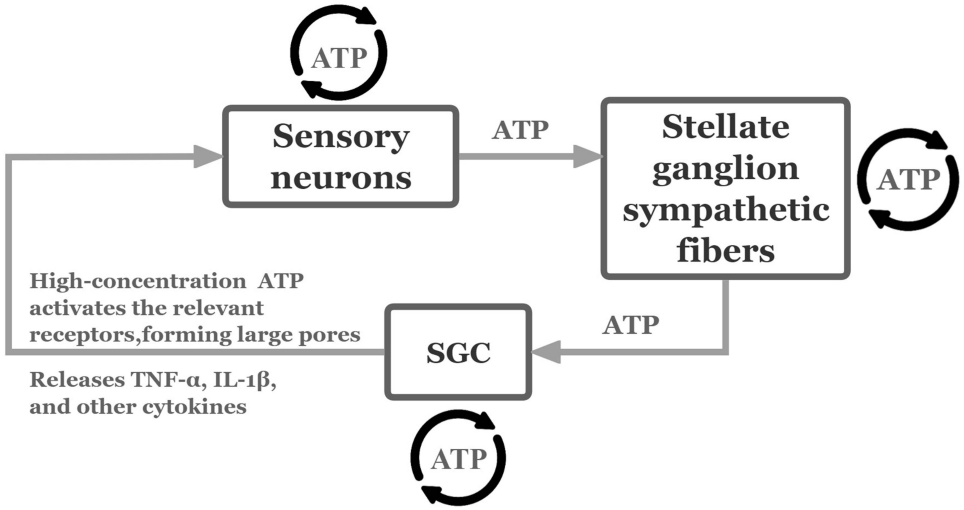

Figure 4 Pathogenic Mechanisms Associated with Dorsal Root Ganglion in TIPN Patients Suffering from Pain.

believe that signals from acupuncture or implantation stimulation conflict with pain signals in TIPN, reducing pain perception and reflex sensitivity, while central nervous system pain transmission mechanisms are inhibited.[39] Furthermore, some scholars suggest that SGCE therapy can stimulate the central nervous system to release neurotransmitters such as serotonin, acetylcholine, and endogenous opioid-like substances, enhancing pain tolerance and reducing patient symptoms.[40] While there have been no reports of SGCE therapy for TIPN treatment, numerous cases exist for treating conditions like facial neuralgia and herpes zoster,[41–43] with related studies on cervical spondylosis treatment in China.[10,44] These studies directly or indirectly affirm the efficacy of SGCE therapy in treating neuropathies and suggest the feasibility of applying this therapy to TIPN treatment in our study.

The SGCE group underwent SGCE therapy under local anesthesia guided by ultrasound, performed by experienced physicians with standardized procedures, significantly reducing the likelihood of adverse events and affirming the safety of this treatment approach. However, the limited sample size may bias the occurrence rate of adverse events. Similar procedures such as SGB are more common and have a larger patient base, where complications such as bleeding and infection may occur post-treatment. Severe adverse events like subarachnoid or vertebral artery puncture, Horner's syndrome, hoarseness, arrhythmias, and even fatalities have been reported.[26–28]Similar vigilance is necessary during SGCE to mitigate such treatment-related complications. With ultrasound providing visualization, it assists in avoiding vascular penetration and other critical structures, enhancing the safety and efficiency of the embedding technique. This further reduces the incidence of adverse reactions associated with embedding therapy, ultimately improving patients' quality of life. While low in incidence, SGCE intervention may entail non-negligible iatrogenic sequelae. Though patients may present self-initiated requests for TIPN prophylaxis post-taxane therapy, prudent clinical practice dictates that such neuro-modulatory approaches should be considered adjunctive rather than primary prevention. Implementation should only proceed after comprehensive risk-benefit disclosure and documented informed consent attesting to patient understanding of potential complications.

This study still has some shortcomings. Assessment of TIPN in patients relied solely on scales, which are subject to significant patient subjectivity. Future evaluations will incorporate objective indicators such as electromyography. Variations in the selection of implantation sites by different physicians may slightly affect treatment efficacy and pain exacerbation. Additionally, the short evaluation period and lack of follow-up limit the data quality for assessing prolonged TIPN symptoms. The study also did not report on the long-term monitoring of patient characteristics. Furthermore, the unblinded nature of the treatment modalities might introduce the potential bias. Lastly, due to the small sample size, the statistical power of the study is limited, potentially increasing the risk of Type II errors. The loss to follow-up of 7 patients further reduces the sample size. Therefore, necessitating larger-scale studies to confirm the experimental results.

Conclusion

This study demonstrated that for the majority of patients, Acupoint Catgut Embedding at Stellate Ganglion combined with Oral Mecobalamin therapy might alleviate symptoms of TIPN and improve patients' quality of life compared to before treatment, with no significant adverse reactions observed during therapy, affirming its safety. Compared to other traditional and Western medical treatments, SGCE with Oral Mecobalamin therapy might be faster, more convenient, and associated with fewer adverse effects, making it potentially more suitable for TIPN patients. But the certainty of evidence is limited due to a lack of prospective comparative studies, clinical and methodological heterogeneity, and low sample size. Future research should primarily focus on establishing large-scale randomized controlled clinical trials to validate the efficacy of this therapeutic approach. Concurrently, it is imperative to integrate objective biomarkers such as electromyography (EMG) and conduct comprehensive subgroup analyses addressing critical variables including taxane types, dosages, and treatment durations. Furthermore, implementing this intervention during the initial phase of taxane-based chemotherapy regimens would also be crucial for determining its prophylactic potential against TIPN.

Ethics Approval

This study has been approved by the Medical Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Ethics Review Approval No.: YJSKY2023-203). Written informed consent will be obtained from all participants prior to treatment. The study was performed in accordance with the 1964 Declaration of Helsinki and later amendments.

Disclosure

The authors report no conflicts of interest in this work.

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