Retrospective Study

Early Treatment with Temporary Spinal Cord Stimulation Effectively Prevents Development of Postherpetic Neuralgia

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Background: Some 7.7% of the Chinese population suffer from herpes zoster each year, with 29.8% proceeding on to develop postherpetic neuralgia (PHN). This amounts to over 32 million people per year. PHN is preceded by 2 phases of pain: acute herpetic neuralgia (AHN), and subacute herpetic neuralgia (SHN). Considering the large individual and economic burden, preventing the transition of AHN/SHN to PHN is crucial. However, to date this has been difficult.

Objectives: To evaluate the efficacy of temporary spinal cord stimulation (tSCS) treatment and prevention of PHN.

Study Design: A retrospective, observational study.

Setting: Department of Pain Medicine.

Methods: From 2013 to 2017, 99 patients with AHN (n = 42), SHN (n = 34), and PHN (n = 23) underwent tSCS treatment (7-14 days) after failed pharmacologic and interventional therapies. Visual analog scale (VAS), Pittsburgh Sleep Quality Index (PSQI), and analgesic consumption were recorded at baseline, post-tSCS, and 1, 3, 6, and 12 months after tSCS treatment.

Results: Pooled results demonstrated statistically significant decreases in VAS scores and PSQI post-tSCS and at 1, 3, 6, and 12 months follow-up ($P < 0.001$). When compared with the PHN group, both AHN and SHN groups were clinically and statistically improved in VAS scores and PSQI ($P < 0.001$). Analgesic consumption decreased in all 3 groups after tSCS treatment, and downward linear gradient of medication in the AHN group was more significant than that in the SHN and PHN groups. At 12 months follow-up, 2.5% (1/40) patients in the AHN group, 16.0% (4/25) in the SHN group, and 62.5% (10/16) in the PHN group had ongoing pain ≥ 3/10 VAS score requiring analgesia. Expressed differently, at 12 months, 97.5% of the AHN group and 84% of the SHN group had pain of 2/10 VAS score or less versus only 37.5% of the PHN group.

Limitations: This was a single-center, retrospective study, which made it difficult to collect complete data for all variables. The therapeutic effect of tSCS could not be studied independently.

Conclusions: This retrospective analyses of 99 patients treated with tSCS (7-14 days) suggests that tSCS may be effective for treating and preventing PHN. Early treatment within 4 to 8 weeks was more likely to result in pain ≤ 2/10 VAS score, improvement in sleep, and no requirement for analgesia at 12 months. Early tSCS may be a promising prevention strategy against the development of chronic neuropathic pain following herpes zoster infection. Further research is justified.

Key words: Herpes zoster, zoster-related pain, postherpetic neuralgia, temporary spinal cord stimulation

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Neuropathic pain is defined as pain secondary to a lesion of the somatosensory system and is labeled as chronic after 3 months (1) . It is at best difficult to treat. Current options include a multidisciplinary approach, medication trial periods of 4 to 8 weeks depending on the medication, interventions such as epidurals, pulsed radiofrequency, and consideration of neuromodulation if the pain is persistent > 6 months, ≥ 5/10 VAS score, and nonresponsive to conservative therapy (2-5).

Herpes zoster is a standard model of neuropathic pain. The prevalence in China has been estimated to be 7.7%, 29.8% of which develop postherpetic neuralgia (PHN) (6). In some patients the pain persists for several months, years, or even indefinitely after the healing of the shingles lesions (7). Herpes zoster–related pain (ZRP) can be classified as acute herpetic neuralgia (AHN) within 1 month of the onset, subacute herpetic neuralgia (SHN) within 3 months of onset, and PHN after 3 months (8-12). PHN is the most common and intractable complication of herpes zoster (11,13). The risk of developing PHN increases with age. Patients younger than 50 years are at a 2% risk of suffering PHN. This increases to 20% over the age of 50 years. A 10-year increase in age within the 50 to 79 years band is associated with a 70% increased risk of PHN (14-18).

A meta-analysis revealed that involvement of other clinical features of herpes zoster, including prodromal pain, severe rash, acute pain, and ophthalmic involvement, resulted in significant increases in the risk of developing PHN. Additionally, immune deficiency or autoimmune diseases (such as HIV, systemic lupus erythematosus, exposure to high-dose corticosteroids) and diabetes mellitus have been associated with increased risk of PHN (17).

PHN is a disease suffered predominantly by the elderly, with an annual incidence of 35% in those older than 80 years (11-13). The management of elderly patients with herpes ZRP is challenging, as the intractability of pain may also increase with age (10,19). A significant proportion of patients with ZRP fail to achieve effective treatment with medication alone due to poor effectiveness of current pharmacologic options, intolerable side effects, and comorbidities of immunosuppression and diabetes mellitus (11,20-24).

Although early interventional treatment can provide fast and complete pain relief for ZRP and potentially reduce the incidence of PHN, multiple comorbidities suffered by elderly patients increase the risk of complication from intervention. Moreover, these interventions commonly fail to achieve long-term pain relief (25-30). Spinal cord stimulation (SCS) has been successfully used for management of chronic neuropathic pain but is currently recommended for use after 6 months of persistent pain, > 5/10 VAS score, and refractory to other conservative therapies (31-33). In this retrospective study, we investigated the efficacy of temporary spinal cord stimulation (tSCS) in 99 patients with ZRP refractory to conservative therapies in acute, subacute, and postherpetic disease phases to find an alternative therapy to medication, epidurals, pulsed radiofrequency, and sympathetic ganglion blocks.

Methods

General Information

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the ethics committee of our hospital (No. 2016041201). Written informed consent was obtained from all patients. The medical records of patients with ZRP who received tSCS treatment from November 2013 to November 2017 were retrospectively studied. All the patients were intolerant of, or refractory to, all previous conventional treatments for a minimum of 1 to 2 weeks. Conservative measures included nonsteroidal antiinflammatory drugs (NSAIDs) (Difene Temmler Werke GmbH, Marburg, Germany), Celebrex (Pifzer Inc., New York, NY), or etoricoxib (Merck Sharp & Dohme BV, Haarlem, The Netherlands), antidepressants, amitriptyline (Hunan Dongting Pharmaceutical Co., Hunan, China), antiepileptic agents pregabalin (Pfizer Inc, Kent T13 9NJ, UK) or gabapentin (Jiangsu Hengrui Medicine, Jiangsu, China), tramadol (Grunenthal GmbH, Aachen, Germany), and opioids Oxycontin (Napp Pharmaceuticals Company, Cambridge, UK) or morphine (Napp Pharmaceutical Limited, Cambridge, UK), or epidural block and pulsed radiofrequency. The pain impaired the patient's quality of life (QoL), and inpatient treatment was required. All data were documented by case report forms, except for the medical records, and 1, 3, 6, and 12-month follow-up questionnaires were competed by telephone or WeChat (Tencent, Shenzhen, China) methods.

A total of 151 patients with ZRP who underwent tSCS treatment were initially screened, and 99 patients who met the inclusion and exclusion criteria for this study were included (Fig. 1). The inclusion criteria were patients with ZRP with refractory, or intolerant to, conservative therapies with persistent pain Visual Analog Scale (VAS) ≥ 5 scores; patients over age 50 years; and

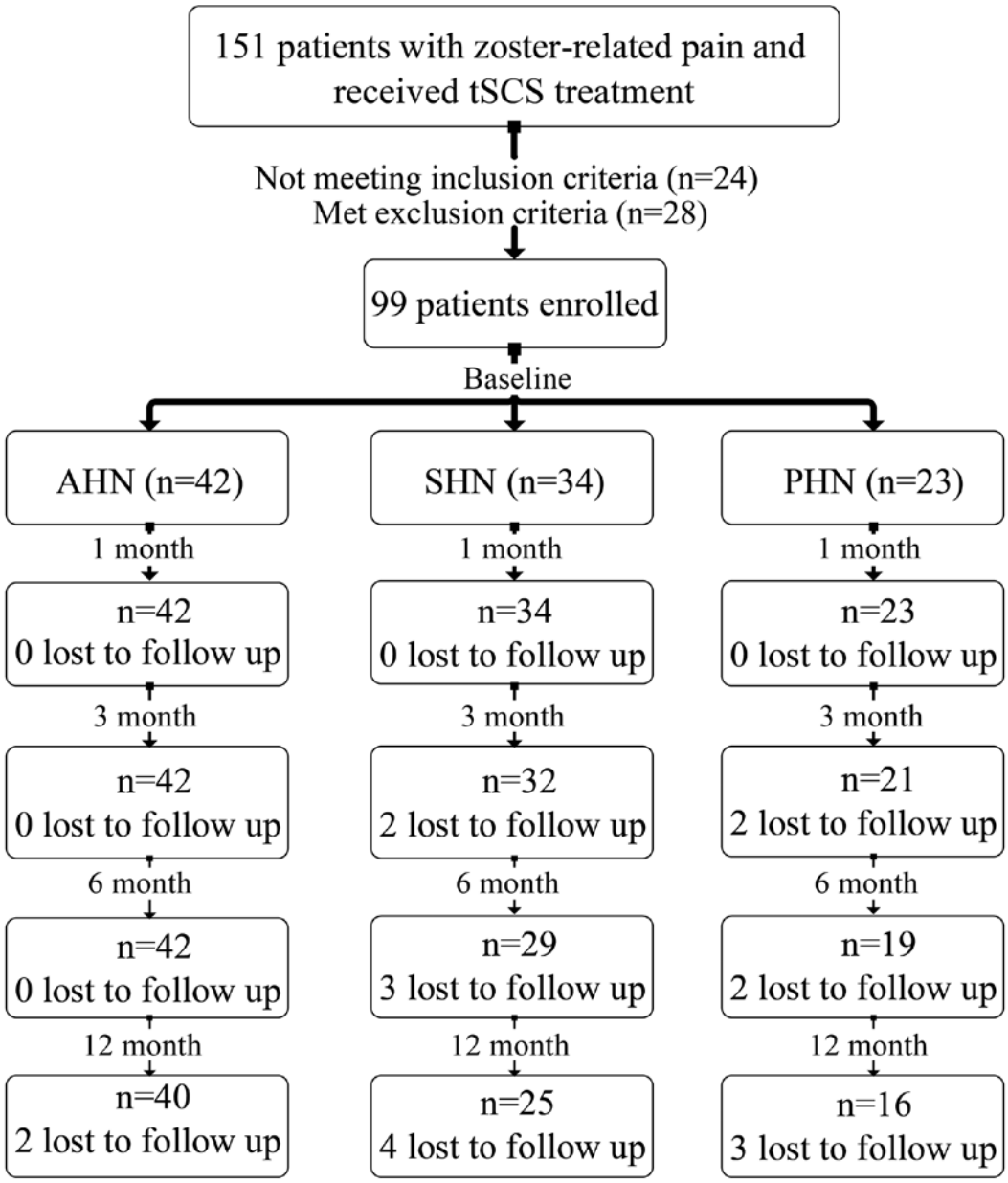

Fig. 1. *Flow diagram presents study design and patient flow at 12 months.*

patients with treatment with tSCS for at least 7 days. Exclusion criteria included patients with malignancy, poorly controlled psychiatric diseases, anticoagulation, trigeminal nerve neuralgia, lead migration or infection resulting in discontinued stimulation, and alternative or additional treatments (permanent implantable pulse generator, or other interventional treatment) during the 1-year follow-up.

The Procedure of tSCS

The target level of the tSCS was based on the herpes zoster–affected dermatome. The procedure of tSCS

was performed in the digital subtraction angiography room, whereby patients were positioned in the prone position and the puncture point was marked under fluoroscopy before the procedure. A 1 x 8 electrodes stimulation lead (Model: 3873, Medtronic Inc., Minneapolis, MN or 3189, Abbott, Plano, TX) was implanted into the epidural space under fluoroscopic guidance with local anesthesia. Initially, the 8-contact lead was implanted at the para midline position in the epidural space to stimulate the spinal dorsal column (Fig. 2A). Adequate paresthesia coverage was defined as coverage of 80% of the pain area. In cases in which the dorsal column stimulation could not obtain adequate paresthesia coverage, a lead was placed laterally in the epidural space (spinal nerve root stimulation) (34-36) (Fig. 2B), or a second lead was placed in the para midline position (Fig. 2C). Successful stimulation was defined as > 50% of the pain area covered by pleasant paresthesia (37).

After the lead implantation, patients received a short-term stimulation ranging from 7 to 14 days (some patients up to 30 days).

Assessment of the Therapeutic Effect

The VAS was used to measure the severity of ZRP (0 = no pain and 10 = intolerable pain). Patients were evaluated at baseline, post-tSCS, and 1, 3, 6, and 12 months after tSCS, respectively. The patients' quality of sleep was assessed by the Pittsburgh Sleep Quality Index (PSQI). The PSQI consists of 19 individual items, creating 7 components that produce one global score. Each item is weighted on a 0 to 3 interval scale. The calculated global PSQI score provided an overall assessment ranging from 0 to 20, whereby lower scores denoted a healthier sleep quality. The items of the PSQI had been summed to create a total score to measure overall sleep quality (38). The VAS, PSQI, and analgesic consumption (including NSAIDs, antiepileptic, antidepressant agents, tramadol, and opioids) were recorded before tSCS, post-tSCS, and 1, 3, 6, and 12 months after tSCS treatment. The total ineffective therapeutic rate was defined as ≥ 3/10 VAS score pain and requiring ongoing analgesia. The rate was evaluated according to the criteria at the time of 3, 6, and 12-month follow-up. Bleeding, infection, lead migration, and so on were recorded during the follow-up.

Statistical Analyses

Data normality were evaluated using the Kolmogorov–Smirnov test and presented as mean ± standard error for continuous variables. The chi-square test or the Fisher exact test was used for categorical variables. The differences between 2 groups were determined using the Student t test or 2-way analysis of variance followed by the Bonferroni post hoc test.

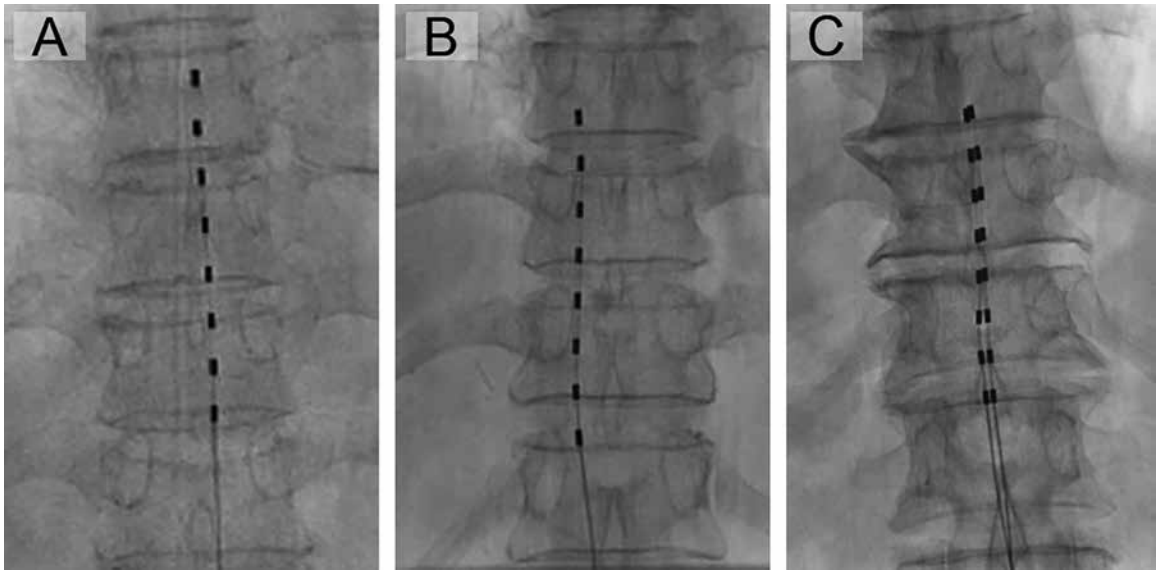

Fig. 2. *Lead placed position of tSCS. (A) One lead for conventional SCS; (B) spinal nerve root stimulation; (C) 2 leads for traditional SCS.*

All statistical analysis was performed using R statistical environment version 3.4.5 (R Foundation for Statistical Computing, Vienna, Austria) and ggplot2 package to produce figures (had.co.nz/ggplot2). A P value < 0.05 was considered statistically significant.

Results

General Characteristics of Patients

Ninety-nine patients (detailed information listed in Appendix Table S1) were included in this retrospective study. All patients were divided into 3 groups (AHN, SHN, and PHN) according to the disease phase. The average age, VAS and PSQI scores, comorbidities, and duration of pain are summarized in Table 1. All patients underwent tSCS successfully and experienced approximately 2 weeks of tSCS treatment (AHN: 12.9 ± 3.1, SHN: 13.9 ± 3.7, PHN: 13.1 ± 4.3). The key difference across the 3 groups is the duration of pain.

VAS Scores

Compared with baseline, the average VAS score for all patients decreased significantly post-tSCS treatment and at 1, 3, 6, and 12 months follow-up (***P < 0.001) (Fig. 3A). Mean VAS scores in the AHN and SHN groups decreased significantly compared with the VAS score of the PHN group at the time of post-tSCS treatment and any follow-up intervals (***P < 0.001). Compared with the VAS scores in the SHN group, the VAS scores in the AHN group declined more at 1, 3, 6, and 12 months follow-up (###P < 0.001) (Fig. 3B). Mean VAS scores rebounded significantly at the time of 1 month after tSCS in the SHN and PHN groups compared with the time of tSCS (Fig. 3B). This was not seen in the AHN group.

PSQI Assessment

The average PSQI scores reduced significantly after tSCS treatment and at all follow-up intervals compared with the PSQI score at the baseline (***P < 0.001) (Fig. 4A). However, the changes in PSQI scores across the 3 groups were different. The PSQI scores in the AHN and SHN groups decreased significantly compared with the PHN group at any time point after tSCS treatment (***P < 0.001) (Fig. 4B). In addition, the PSQI scores reversed significantly 1 month after tSCS in the SHN and PHN groups. Once again this was not seen in the AHN group (Fig. 4B).

Analgesic Consumption

The consumed analgesic agents included were NSAIDs, antiepileptic, antidepressant agents, tramadol, and opioids. Prevalent downward trends for analgesic consumption were observed after tSCS and at 1, 3, 6, and 12 months compared with baseline (Fig. 5A). A linear regression analysis was carried out by calculating the consumption of each medicine in the posttreatment of patients with AHN, SHN, and PHN (Fig. 5B-F). Consumption of antiepileptic agents (Fig. 5B), antidepressant agents (Fig. 5C), tramadol and opioids (Fig. 5D and E), and NSAIDs (Fig. 5F) decreased slower in the PHN

Table 1. *General characteristics of patients.*

Demographic Information	AHN Group	SHN Group	PHN Group	*P* Value
Age, years, mean ± SE	67.450 ± 1.467	72.000 ± 1.351	70.043 ± 1.548	> 0.05
Gender, n, male/female	20/22	22/12	14/9	> 0.05
Pain duration, days, mean ± SE	16.595 ± 1.207	46.441 ± 2.359	640.300 ± 173.695	< 0.001
Left/right, n	20/22	20/14	14/9	> 0.05
Involved dermatome, n				> 0.05
Cervical, n	7	9	1	
Thoracic, n	27	21	20	
Lumbosacral, n	8	4	2	
Comorbidity, n	29	22	14	> 0.05
Duration of tSCS treatment, days	12.952 ± 0.491	13.941 ± 0.643	13.130 ± 0.894	> 0.05
Baseline of PSQI scores, mean ± SE	15.476 ± 0.350	16.522 ± 0.287	16.324 ± 0.311	> 0.05
Baseline of VAS scores, mean ± SE	7.152 ± 0.235	7.162 ± 0.199	6.700 ± 0.227	> 0.05

Abbreviation: SE, standard error.

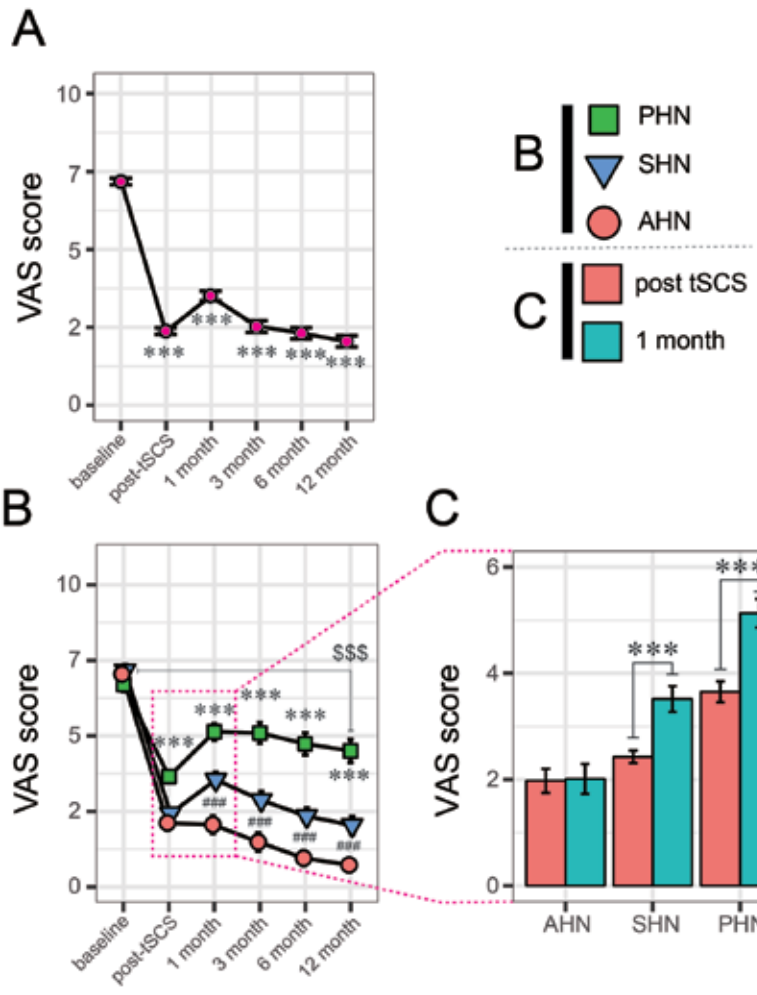

Fig. 3. *Pain level as evaluated by VAS score. (A) The average VAS score for all patients with ZRP decreased significantly after tSCS treatment and at the time of 1, 3, 6, and 12 months follow-up compared with the VAS score at the baseline (***P < 0.001); (B and C) the changes of VAS score across the AHN, SHN, and PHN groups were vastly different at the time of post-tSCS and 1, 3, 6, and 12 months follow-up. First, the average VAS score in the 3 groups reduced significantly compared with the VAS score at the baseline after tSCS treatment and at any follow-up interval ($$$P < 0.001). Second, the mean VAS scores in the AHN and SHN groups dropped significantly compared with the VAS score of the PHN group at the time of post-tSCS treatment and any follow-up intervals (***P < 0.001). Compared with the VAS scores in the SHN group, the VAS scores in the AHN group declined more at the time of 1, 3, 6, and 12 months follow-up (###P < 0.001) (B). Third, the mean VAS scores rebounded significantly at the time of 1 month after tSCS in the SHN and PHN groups compared with the time of tSCS (C). However, the mean VAS scores did not increase in the AHN group.*

group compared with the AHN group. The AHN group had a more rapid decrease in analgesia compared with the PHN group (Fig. 5B-F).

Total Ineffective Therapeutic Rate

The total ineffective therapeutic rate was calculated based on patient pain ≥ 3/10 VAS score and requiring ongoing analgesia. The total ineffective therapeutic rate in the AHN group was 14.28% (6/42), 2.38% (1/42), and 2.5% (1/40) at the time of 3, 6, and 12 months follow-up, respectively. The total ineffective therapeutic rate in the SHN group was 43.75% (14/32), 24.14% (7/29), and 16.00% (4/25) at the same follow-up points, respectively. The total ineffective therapeutic rate in the PHN group was 90.48% (19/21), 68.42% (13/19), and 62.50% (10/16) at the time of 3, 6, and 12 months follow-up, respectively. Expressed differently, at 12 months, 97.5% of the AHN group and 84% of the SHN group had pain of 2/10 VAS score or less versus only 37.5% of the PHN group. The comparative difference can be seen in Table 2.

Side Effects

No serious adverse events were observed during the procedure and over the entire follow-up period. Serious adverse events were taken to include leakage of cerebrospinal fluid, prolonged bleeding, or epidural hematoma. No patients withdrew from the tSCS treatment because of the side effects. Lead migration (9 cases) and local infection (6 cases) of puncture site were the most common complications during the 12-month follow-up period. Eight patients felt slight discomfort

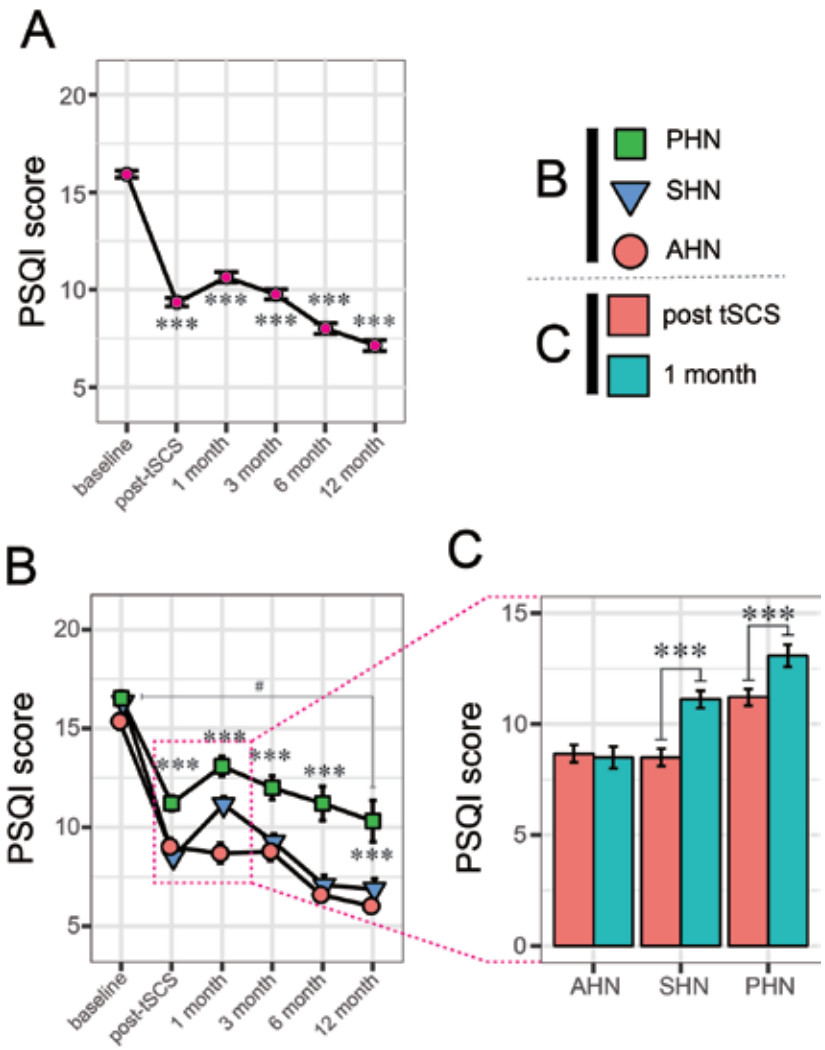

Fig. 4. *Patient's quality of sleep was assessed by the PSQI. (A) The average PSQI scores reduced significantly after tSCS treatment and at all follow-up intervals compared with the PSQI score at the baseline (***P < 0.001); (B) However, the changes in PSQI scores across the 3 groups were different. The PSQI scores in the AHN and SHN groups decreased more significantly compared with the score in the PHN group at any time point after tSCS treatment (***P < 0.001); (C) in addition, the PSQI scores were reversed significantly 1 month after tSCS in the SHN and PHN groups, which occurred in coincidence with the VAS scores.*

because the paresthesia area was larger than the pain area. Treatment with tSCS was not impacted by any complications.

Discussion

The potential impact on patient QoL and the increased demand on the health care system creates an imperative to prevent patients transitioning from AHN or SHN to PHN. Furthermore, management can be difficult as the majority of patients suffering from herpes zoster are elderly and are more likely to experience multiple comorbidities. This makes drug management more challenging, as the risk of drug interactions is high. Epidural nerve block or sympathetic ganglion block can be effective traditional interventional treatments for early-stage ZRP once a medication has proved ineffective (27). However, there are possible complications associated with such procedures, including hypotension, urinary retention, and nausea and vomiting because of the epidural nerve block (39). SCS is an accepted, safe, reversible, and effective technique at relieving pain, improving function, and overall QoL in chronic neuropathic pain. Furthermore, tSCS treatment without an implantable pulse generator is a simple and economical technique for patients. In this study, we investigated the efficacy of tSCS therapy for treating ZRP and preventing the early herpes zoster–associated pain developing to PHN.

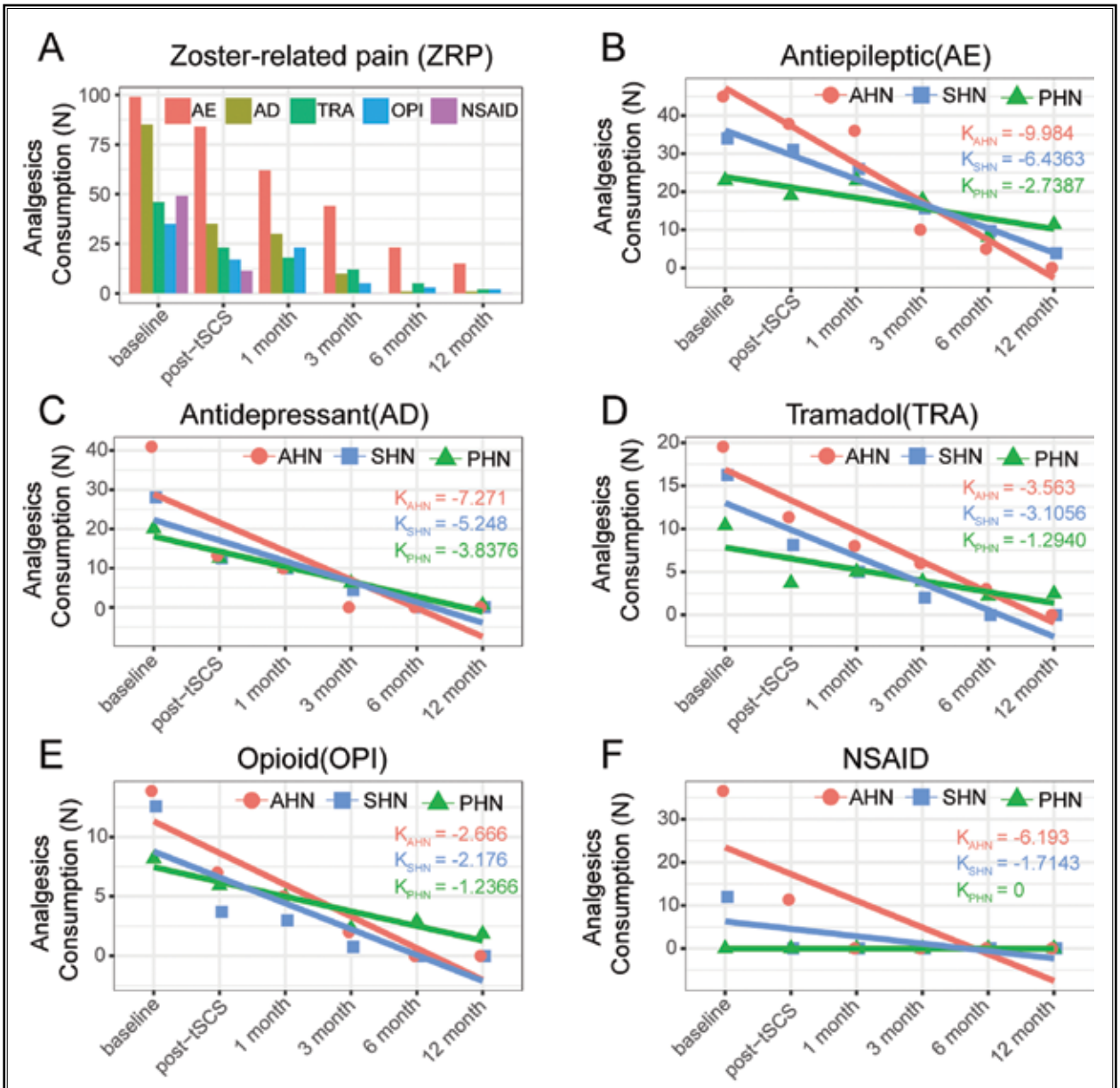

Fig. 5. *The consumed analgesic agents included were NSAIDs (AHN or SHN), antiepileptic, antidepressant agents, tramadol, and opioids. (A) Prevalent downward trends for analgesic consumption were observed after tSCS and at the 1, 3, 6, and 12 months follow-up intervals compared with the amounts at the baseline; (B-F) a linear regression analysis was carried out by calculating the consumption of each medicine in the posttreatment of AHN, SHN, and PHN patients. (B) Consumption of antiepileptic agents; (C) antidepressant agents; (D, E, and F) tramadol, opioids, and NSAIDs decreased slower in the groups of SHN and PHN compared with the AHN group. The linear gradient slope of the AHN group was largest, whereas the slope of PHN was smallest.*

Table 2. *The incidence of PHN at 3, 6, and 12 months for AHN, SHN, and PHN.*

Group	Incidence of PHN (no. of PHN/no. of patients, % of PHN)		
	3 month	6 month	12 month
AHN group	6/42, 14.29%	1/42, 2.38%	1/40, 2.50%
SHN group	14/32, 43.75%	7/29, 24.14%	4/25, 16.00%
PHN group	19/21, 90.48%	13/19, 68.42%	10/16, 62.50%
Total	39/95, 41.05%	21/90, 23.33%	15/81, 18.51%

Previous Studies

Several trials have been performed exploring the analgesic effects of tSCS for SHN or PHN (30,36,40-42). Harke et al (40) first observed successful analgesia against AHN with tSCS in 4 patients. A recent review showed that 77.8% of patients treated with tSCS achieved 57% pain relief for 3.2 months (43). However, previous studies are sparse and lack long-term follow-up.

Clinical Use of this Study

In this study, we screened 151 patients with ZRP who underwent tSCS treatment. Of the 99 patients who met inclusion and exclusion criteria, 42 had AHN (< 30 days), 34 had SHN (< 90 days and ≥ 30 days), and 23 had PHN (≥ 90 days). We found that pain intensity decreased and the patients' sleep improved significantly after tSCS treatment compared with the baseline for all the patients. Furthermore, when compared with PHN the group, AHN and SHN groups demonstrated significant reduction in average VAS and PSQI scores at all follow-up intervals ($P < 0.001$) (Figs. 3 and 4). In addition, the VAS score in the AHN group decreased more compared with the SHN group ($P < 0.001$) (Fig. 3). At 12 months follow-up, 2.5% (1/40) patients in the AHN group, 16.0% (4/25) in the SHN group, and 62.5% (10/16) in the PHN group had ongoing pain ≥ 3/10 VAS score requiring analgesia. This indicates that earlier tSCS treatment may be more beneficial for patients with ZRP. These results were consistent with the results observed by the previous studies (30,40-42), demonstrating that patients who were within 3 months from the onset of herpes zoster achieved excellent pain relief after tSCS treatment. Recently, Dong et al (42) demonstrated a plausible long-term benefit of tSCS treatment in 46 cases of ZRP, with 80% of patients achieving pain relief (VAS ≤ 2) after 12 months follow-up. However, the study showed that the efficacy of tSCS did not differ significantly among patients with different durations of acute/subacute ZRP starting from the onset of rash, which is not consistent with our study. The Dong et al (42) study did not observe the long-term effect of tSCS in AHN and SHN, although the sample size was small, possibly preventing this finding.

Interestingly, we found that the VAS and PSQI scores in the SHN and PHN group rebounded at 1-month follow-up after tSCS therapy, and then went down continuously at 3, 6, and 12 months. Alternatively, the VAS and PSQI scores in the AHN group reduced consistently after tSCS treatment. This indicates a possible correlation between the early intervention with tSCS and the decreased progression to PHN. In the clinic, we have observed that several patients with PHN with 1 year or less duration of pain who had progressed to permanent SCS implant achieved a complete pain relief and subsequently had the system removed. This is in line with the previous study by Kumar et al (44,45), which found that early intervention with SCS provided better pain relief and longer periods of effective control. Furthermore, the earlier the application of SCS therapy, the more superior was the long-term pain relief and patient satisfaction (45).

For better pain relief by conventional SCS, the stimulation paresthesia should be stronger than the pain stimulus, otherwise it is difficult to achieve excellent pain relief (46,47). As such, an ideal distribution of paresthesia coverage is the key point for achieving a good tSCS effect. The tSCS procedures of 99 patients were done successfully with at least 80% or more of the painful area covered by stimulation paresthesia. One more lead would be considered in cases of failure to acquire stable stimulation paresthesia by dorsal column stimulation. In our experience, if the herpes zoster distribution localizes at the cervical, thoracic, and high lumbar segment (such as L1, 2, and 3), the spinal nerve root stimulation method would be used with priority because of its capability of providing more stimulation paresthesia (36,48). Otherwise conventional SCS will be used.

In this study, we did not observe any serious complications, such as epidural hematoma, spinal cord injury, or nerve damage, except 9.09% (9/99) lead migration and 6.06% (6/99) local infection.

Limitations

There are some limitations in our study. First, the retrospective nature of the study and low follow-up of some patients made it difficult to collect complete data for all variables. Second, the therapeutic effect of tSCS could not be studied separately, furthermore, the procedures of tSCS were done by different physicians. Finally, a single-center, retrospective study can cause some bias. Future multicenter studies could be improved by prospectively evaluating a larger number of patients, which could lower the bias.

Conclusions

This retrospective analysis of 99 patients treated with tSCS (7-14 days) suggests that tSCS may be an effective treatment for neuropathic pain secondary to herpes zoster infection. Early treatment within 4 to 8 weeks was more likely to result in pain ≤ 2/10 VAS score, improvement in sleep, and no requirement for analgesia at 12 months. Early tSCS may be a promising prevention strategy against the development of PHN. Further research is justified.

Acknowledgments

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Appendix *Table S1. General characteristics of the 99 patients who presented with ZRP.*

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