Retrospective Study

Efficacy of Short-Term Spinal Cord Stimulation in Acute/Subacute Zoster-Related Pain: A Retrospective Study

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Background: Postherpetic neuralgia (PHN) is a refractory condition that impairs the patient's quality of life (QoL), it develops secondary to herpes zoster infection. Therefore, it's important to prevent the transition of acute/subacute zoster-related pain to PHN. Despite of numerous studies, the optimal intervention that reduces PHN incidence is still unknown.

Objective: We evaluate the efficacy of short-term spinal cord stimulation (stSCS) in patients with refractory acute/subacute zoster-related pain.

Study Design: Retrospective study.

Setting: Tertiary referral center/teaching hospital.

Methods: A total of 46 patients who presented with acute/subacute zoster-related pain, and had previously failed conventional therapies, underwent stSCS treatment. Visual analog scale (VAS), Short Form Health Survey 12 items (SF-12), and analgesic consumptions were recorded before stSCS, post-stSCS, 2 weeks, and 1, 3, 6, 9, and 12 months after stimulation.

Results: The VAS scores at post-stSCS, 2 weeks, and 1, 3, 6, 9, and 12 months after stSCS treatment were significantly decreased compared with the baseline score ($P < 0.001$). Thirty-two patients (69.6%, 32/46) achieved the minimal clinically important difference (MCID), including 18 patients (39.1%, 18/46) who achieved complete pain relief (VAS $\leq$ 2). During the follow-up period, the efficacy of stSCS didn't decrease and VAS scores were declining. Similarly, SF-12 scores and analgesic consumptions improved after stSCS treatment. The efficacy of stSCS did not differ significantly among patients with different durations of acute/subacute zoster-related pain starting from the onset of rash. No serious adverse effects were observed in the entire follow-up period.

Limitations: This study was not a randomized prospective controlled study. We did not compare the outcomes with patients presenting with mild or moderate pain, and did not compare the efficacy of stSCS treatment with conventional therapies.

Conclusion: stSCS is a safe, effective, and less invasive analgesic method for patients with refractory acute/subacute zoster-related pain.

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

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Herpes zoster (HZ, also known as shingles) is caused by the reactivation of varicella zoster virus (VZV) after being latent in the sensory ganglia (1,2). It is characterized by blistering skin eruption and neuropathic pain in the affected dermatome (3). Approximately 30% of the population will develop HZ during their lifetime (4), and the risk of incidence increases with older age (> 50 years old)

and immunosuppression (5,6). Postherpetic neuralgia (PHN) is considered as the most common and severe complication of HZ (7). PHN can be defined as persisting pain that lasts after the rash and blisters have healed (8). However, several studies described a time frame for the pain to be defined as PHN. Edmunds et al (9) defined PHN as pain that persists for 30 days after the healing of the HZ rash, while other studies described PHN as pain that persists beyond 90 days (10,11). On the other hand, Dworkin and Portenoy (12) advocated another classification, in which PHN is defined as the pain that persists more than 3 months after the end of one month-long acute period while subacute herpetic neuralgia (SHN) describes pain that resolves within 3 months after the end of the one month long acute phase of HZ. The incidence of PHN ranges between 8% and 19% according to the variable classifications (7,13), and the pain can last up to 12 months in more than 6% of the patients (14). PHN impacts the patient's quality of life (QoL) (15), it causes psychological distress and sleep disorders (13), and inevitably results in the higher demand for quality health care (16) and/or other social resources (17). In this study, we divided the patients into acute and subacute periods according to Dworkin and Portenoy's standardized classification (12).

There are several risk factors associated with higher risk to develop PHN (18,19), such as older age, severe acute pain, and severe rash. Nevertheless, effective management for PHN remains largely obscure. In fact, PHN does not respond well to the existing treatment modalities (20) or pharmacological agents (e.g., anticonvulsants such as gabapentin, tricyclic antidepressants such as amitryptyline, or opioids such as oxycodone) (21,22). Moreover, interventional procedures like epidural injection and selective nerve root blocking cannot achieve long-lasting pain relief that enables patients to carry normal daily activities (23,24). Therefore, it is better to avoid the transition of acute HZ pain to PHN, and this prevention strategy is in line with the international perception concerning chronic pain management (25).

Zostavax® is a live attenuated VZV vaccine recommended for the elder population to prevent HZ and HZ-associated PHN (26). Nevertheless, due to the reduced vaccination efficiency at older age and the waning immunity after vaccination, the cost-effectiveness of vaccination is questionable (27-29). The early administration (within 72 hours) of antiviral drugs was reported to considerably decrease the severity and duration of the HZ eruptive phase and reduce the incidence of PHN (30,31), even in the immunocompromised human immunodeficiency virus-infected patients (32). However, several studies debated the effectiveness of antivirals in ameliorating the chronic pain associated with HZ (33,34). Furthermore, obtaining a quick antiviral treatment might be difficult for individuals in remote areas and some developing countries. Finally, epidural injection could reduce HZ-associated acute pain but it was not effective for PHN prevention after 6 months (35).

Spinal cord stimulation (SCS) has been successfully used to manage chronic neuropathic pain of different origins (36) and showed significant effectiveness in specific types of chronic pain (37-39); although, the exact mechanism underlying SCS-induced analgesia for neuropathic pain is not well understood yet (40,41). Therefore, in this study, we investigate the efficacy of short-term spinal cord stimulation (stSCS) in patients with refractory acute/subacute zoster-related pain in order to prevent its development to PHN.

Methods

Retrospective Review

This study was approved by the Human Ethics Committee of The First Affiliated Hospital of China Medical University (NO. 2016-156-2) and was registered with chictr.org.cn, number ChiCTR-ORh-16008764.

After obtaining the approval from the institutional review board, medical records of patients who received stSCS treatment from January 2014 and November 2015 were retrospectively examined.

In the pain center of the First Affiliated Hospital, China Medical University, the medical records for patients with zoster-related pain were documented, and all patients received a follow-up check-up 2 weeks after being discharged from the hospital, and filled a follow-up questionnaire once a month for 12 months.

A total of 62 patients with zoster-related pain who underwent stSCS treatment were initially examined and a total of 46 patients who satisfied the inclusion and exclusion criteria for this study were finally enrolled (Fig. 1). The inclusion criteria for this study were patients presented with HZ within 120 days from the rash onset; patients who received at least one kind of interventional procedure before stSCS, but were still complaining from severe pain [visual analog scale (VAS) $\geq$ 6]. The exclusion criteria were patients with malignant tumor or with a history of malignant tumor (n = 1); patients who were previously diagnosed with psychiatric diseases (n = 1); patients with mild to moderate HZ-associated pain

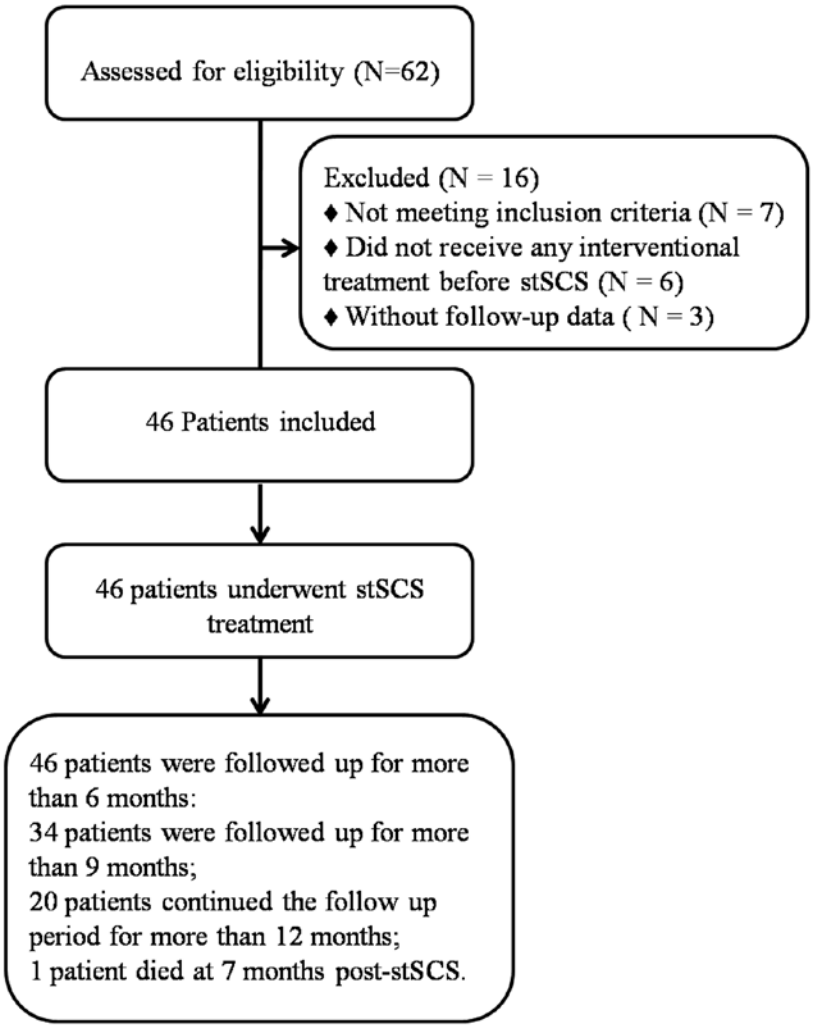

Fig. 1. *Patient flow-diagram illustrating follow-up data, stSCS, short-term spinal cord stimulation.*

(VAS < 6; n = 2); patients presented with HZ beyond 120 days from the rash onset (n = 3); patients who did not receive any interventional treatment before stSCS (n = 6); and patients without available follow-up data after stSCS (n = 3).

Assessment

The severity of HZ-associated pain was measured using the VAS system over a period of 24 hours. The VAS system is a 10 point scoring system, where 0 = no pain and 10 = intolerable pain. Following stSCS treatment, a decrease of at least 3 points was considered as an important improvement in accordance with the guidelines of minimal clinically important difference (MCID) associated with adequate pain management (39).

The patients' QoL, particularly their physical and mental status, preceding stSCS treatment were assessed by the 12-items Short Form Health Survey (SF-12) (42), with a score range from 0 to 100 points and a score < 50 indicates below-average status. SF-12 is an easy to use, one page self-administered questionnaire that is administered by an interviewer (43). Physical Component Summary (PCS) and Mental Component Summary (MCS) were scored using Quality Metric Health Outcomes Scoring Software 2.

The VAS, SF-12, and analgesic consumption (including antiepileptic agents) were recorded before stSCS, post-stSCS, 2 weeks, and 1, 3, 6, 9, and 12 months after treatment.

In addition, after hospitalization (or before stSCS was performed), all patients got a sensory examination (the 10-item Douleur Neuropathique 4 Questionnaire, DN4) in the painful area performed by our pain physicians to identify the HZ-associated pain characteristics. This DN4 questionnaire was completed only once.

Description of stSCS

The therapeutic target area was determined based on the HZ-affected dermatome and it was usually accompanied by hyperalgesia or allodynia (44). The 1 x 8 electrodes test stimulation lead (Model: 3874, Medtronic Inc. Minneaplis, USA) was implanted according to the manufacturer's manual, and implantation was performed under fluoroscopic guidance in the operating room under local anesthesia. Briefly, the patient was positioned in a prone pose and the puncture segment was determined under fluoroscopy. By the means of the paramedial approach, a modified Tuohy needle was inserted into the epidural space above the spinal cord at an appropriate angle. Next, the needle was rotated so that the beveled edge faced the cephalad orientation, the needle stylet was removed, and the needle was pushed to enter the epidural space. Finally, the inserted lead electrode was positioned until the tip was at an appropriate physiological and anatomical level to achieve the best stimulation according to the patient's statement. A successful stimulation was defined as "pleasant paresthesia covering at least 50 percent of the painful area" (45). Every patient received only one lead electrode. The insertion of all lead electrodes were performed successfully;, however, satisfactory paresthesia coverage after leaving the operation room was not achieved by all patients.

After the successful implantation of the leads, the patients would get a short period of stimulation ranging from 7 days to 14 days (the maximum period, according to the manufacturer's protocol in order to avoid infection).

Side Effects

Side effects usually included bleeding at the puncture site, infection, spontaneous lead migration, and increased pain, and they were recorded during the entire follow-up period after the treatment.

Statistical Analysis

Sample size was calculated using SAS version 9.0 (SAS Institute Inc, NC, USA) assuming an 80% power in order to detect a difference of at least 1.5 points in the mean change in VAS before and after stSCS treatment. This calculation was based on a two-tailed t-test with a standard deviation of 3 points, and a significance level of $\alpha = 0.05$. Finally, the simple size was adjusted to 32.

The statistical analysis was performed using Microsoft Excel and SPSS version 18.0 software (SPSS Inc, Chicago, USA). The differences in VAS and SF-12 scores were analyzed by paired t-test. The variations in the consumption of analgesics were assessed using chi-squared test and Fisher's exact test. Differences in stSCS efficacy according to the duration of disease (from the rash onset) were assessed using chi-squared test and Fisher's exact test. A $P < 0.05$ was considered to be statistically significant. Safety analyses were conducted for the incidence of side effects.

Results

Patient General Characteristics

A total for 46 patients (22 men and 24 women) were enrolled in this study after applying the inclusion and exclusion criteria; the patients' general characteristics are summarized in Table 1. The mean age was 69.26 ± 9.26 years old (ranging from 45 to 87 years old), and the mean duration of pain starting from the rash onset was 59.98 ± 28.50 days (ranging from 15 to 120 days). The HZ-associated rash affected the right side in 25 patients (thoracic: 21 patients and lumbar: 4 patients) and the left side in the remaining 21 patients (cervical: one patient; thoracic: 15 patients; and lumbar: 5 patients). All patients underwent at least one interventional procedure before stSCS, with no significant pain relief and the mean duration of stSCS treatment was 9.33 ± 2.77 days (ranging from 3 to 14 days) (Table 1). The DN4 scores collected before stSCS treatment are shown in Table 2, the mean score was 6.48 ± 0.67.

Follow-up Data

Among the 46 patients enrolled in this study, all patients were followed up until 6 months, then 34 patients were followed up for more than 9 months, and finally 20 patients continued the follow-up period for more than 12 months. The mean follow-up period was 11.06 ± 2.97 months. One patient (No. 2) died from natural causes 7 months post-treatment.

Table 1. *General characteristics of the 46 patients presented with acute/subacute zoster-related pain.*

No.	Gender	Age (yr)	Duration of morbidity (Days)	Localization	Interventional procedures pre-stSCS	VAS, pre-stSCS	Did the pain still exist during the stSCS treatment	Duration of stSCS treatment (Days)	VAS, when discharged
01	M	70	55	T10-T11,r	B, C	8	/	4	6
02	M	79	64	T4-T5,r	A	9	N	9	4
03	M	84	38	T6-T8,r	A, B	6	N	7	0
04	M	65	40	T3-T4,l	A	6	/	6	6
05	F	58	34	T2-T3,r	A	7	N	8	1
06	M	65	35	T1-T2,l	A	7	N	10	2
07	F	70	65	T1-T2,l	A, B	8	N	14	3
08	F	80	45	L1-L3,l	A	7	N	12	3
09	F	81	88	T11-T12,l	A, B	7	Y	5	6
10	M	84	75	T5-T6,l	A, B	8	N	9	2
11	M	65	62	T3-T4,r	A	7	N	10	3
12	F	57	76	T5-T6,r	A	8	N	11	4
13	F	63	35	T4-T5,r	A, B	7	N	10	2
14	M	45	40	T1-T2,r	A	7	N	14	3
15	M	78	85	T4-T5,r	A, B	7	N	9	0
16	F	53	65	T8-T9,r	A, B	9	Y	7	8
17	M	81	60	T12-L1,l	A, B	7	N	8	3
18	M	70	26	L1-L2,l	A	7	N	8	3
19	M	85	93	T4-T5,r	A	7	N	9	0
20	F	67	100	T2-T3,r	A	7	/	9	7
21	M	72	19	T3-T4,l	A,B	7	N	13	2
22	F	74	95	T12-L1,l	A	7	N	14	6
23	M	70	58	T8-T9,r	C	8	N	9	1
24	F	69	20	T9-T10,r	A, B	8	N	11	7
25	F	67	21	T12-L1,r	A,B	6	N	8	2
26	M	66	18	T8-T9,r	A, B	6	N	13	0
27	M	77	65	T5-T6,l	A, B	7	N	14	2
28	M	66	70	T1-T2,l	A	6	N	12	6
29	F	76	15	T7-T8,r	A	8	N	12	4
30	F	60	37	T2-T3,l	A	7	N	10	5
31	F	68	50	T7-T8,r	A, B	7	Y	10	6
32	F	80	41	T4-T6,l	A, B	7	N	9	2
33	F	87	45	T5-T7,l	A, B	7	N	9	3
34	F	70	120	L4-L5,r	A	7	N	8	2
35	F	77	70	T6-T7,r	A, B	6	N	7	1
36	M	70	38	T8-T9,r	A,B	8	/	7	8
37	M	72	80	T11-T12,r	A, B	7	N	10	3
38	F	67	76	T10-T11,l	A	8	N	10	3

Table 1 (cont.). *General characteristics of the 46 patients presented with acute/subacute zoster-related pain.*

No.	Gender	Age (yr)	Duration of morbidity (Days)	Localization	Interventional procedures pre-stSCS	VAS, pre-stSCS	Did the pain still exist during the stSCS treatment	Duration of stSCS treatment (Days)	VAS, when discharged
39	F	64	94	T4-T5,l	A	9	N	12	8
40	F	54	100	C8-T1,l	A	6	N	14	2
41	F	69	108	T9-T10,r	A, B	8	Y	3	8
42	F	64	106	L2-L3,l	C	9	N	8	3
43	M	70	42	L1-L2,r	A, B	10	N	9	5
44	M	60	49	T8-T9,l	A	7	N	7	1
45	F	62	29	T10-T11,l	A,B	7	Y	4	7
46	M	55	112	T12-L1,r	A, B	6	N	7	2

F, female; M, male; T, thoracic vertebrae; L, lumbar vertebrae; l, left; r, right; A, selective nerve root block (injection) or epidural block (injection); B, pulsed radiofrequency (bipolar/Bipolar); C, Continuous epidural block; VAS, visual analog scale; stSCS, short-term spinal cord stimulation; /, no paresthesia coverage.

Table 2. *DN4 (Douleur Neuropathique4 Questionnaire) scores collected before the stSCS treatment in 46 patients presented with acute/subacute zoster-related pain, stSCS, short-term spinal cord stimulation.*

10-Item DN4	Number (Percentage)
1-Burning	40 (87.0%)
2-Painful Cold	15 (32.6%)
3-Electric Shocks	34 (73.9%)
4-Tingling	35 (76.1%)
5-Pins and Needles	26 (56.5%)
6-Numbness	22 (47.8%)
7-Itching	31 (67.4%)
8-Hypoesthesia to Touch	32 (69.6%)
9-Hypoesthesia to Prick	27 (58.7%)
10-Brushing	36 (78.3%)

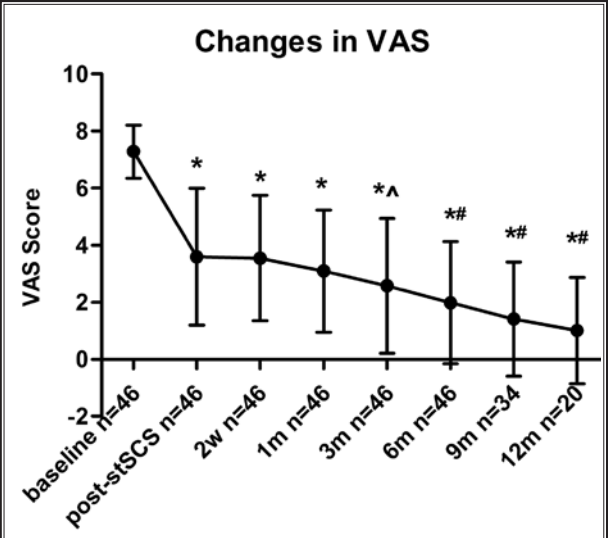

Fig. 2. *Pain level as measured by the visual analog scale (VAS) in patients presented with acute/subacute zoster-related pain. The baseline VAS score, as well as the VAS scores for post-stSCS, obtained before patient discharge, and several follow-up points are presented on the graph (*$P < 0.001$, compared with baseline; ^$P < 0.05$, #$P < 0.001$, compared with when discharged), stSCS, short-term spinal cord stimulation.*

VAS

The mean VAS score before stSCS was 7.28 ± 0.93. Patients obtained a significant pain relief post-stSCS (just before being discharged; 3.59 ± 2.40; $P < 0.001$; Fig. 2), and the effects were maintained during the subsequent follow-up period, $P < 0.001$ compared to the VAS score at the baseline (Fig. 2).

A total of 32 patients (69.6%, 32/46) obtained a favorable MCID and among them a total of 18 patients (39.1%, 18/46) were extremely satisfied with a complete pain relief (VAS ≤ 2) upon discharge from the hospital.

At the 6 month follow-up point, a total of 27 patients (58.7%, 27/46,) still suffered from zoster-related pain, including 3 patients (3/46, 6.5%) presenting with

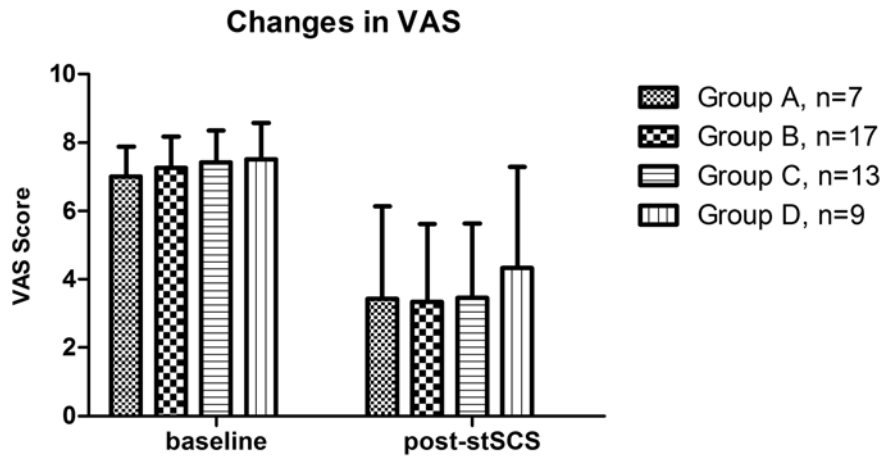

Fig. 3. *The VAS changes in 4 groups of acute/subacute zoster-related pain patients subdivided based on the duration of disease (starting from the rash onset) upon discharge. Group A (15 to 30 days, n = 7); Group B (31 to 60 days, n = 17); Group C (61 to 90 days, n = 13); Group D (91 to 120 days, n = 9). Data are presented as bar charts indicate no significant differences in stSCS effects among the 4 groups (all P > 0.05; A vs B, P = 0.47; A vs C, P = 0.48; A vs D, P = 0.27; B vs C, P = 0.45; B vs D, P = 0.18; C vs D, P = 0.22), stSCS, short-term spinal cord stimulation.*

severe pain (VAS ≥ 6). On the other hand, a total of 31 patients achieved excellent pain relief (VAS ≤ 2; 67.4%, 31/46, $P < 0.01$, compared with post-stSCS). At 12 months post-stSCS treatment, we did not observe severe pain in any of the followed up patients (20 patients), although 5 patients (25.0%, 5/20) presented with mild to moderate pain. Moreover, at the end of the follow-up period (12 months) we observed that the efficacy of stSCS did not decrease since a total of 16 patients achieved a complete pain relief (VAS ≤ 2; 80.0%, 16/20) and the VAS score declined (Fig. 2).

Additionally, we subdivided the patients into 4 groups according to the duration of disease (starting from the rash onset): Group A (15 to 30 days, n = 7); Group B (31 to 60 days, n = 17); Group C (61 to 90 days, n = 13); and Group D (91 to 120 days, n = 9). There were no significant differences in stSCS effects (VAS scores upon discharge) among these 4 groups ($P > 0.05$, Fig. 3).

SF-12

Given the pain burden associated with HZ, the mean PCS score (34.0 ± 4.83) of the SF-12 was lower than the mean MCS score (42.1 ± 4.13) at the baseline ($P < 0.01$), and similarly the 2 mean scores were both below average status at the baseline (Fig. 4), However, after stSCS treatment, the physical and mental component scores increased significantly compared to baseline thus indicating the improvement of patients' QoL. These effects were maintained during the entire follow-up period (Fig. 4).

Consumption of Analgesic (Including Antiepileptic Agents)

The consumed amounts of pre-existing analgesic agents, including strong opioids, tramadol, gabapentin, and pregabalin, were either abolished or significantly reduced indicating the adequate pain management of post-stSCS treatment (Fig. 5). Upon discharge, a total of 11 patients (11/46, 23.9%) were either free from the usage of pharmaceutical agents, or needed a small dose of gabapendin (< 900 mg/day without additional analgesics).

Side Effects

There were no cases of prolonged bleeding at the puncture site, epidural hematoma, infection, increased pain, or other serious side effects post-stSCS treatment and during the entire follow-up period. Further, no patients withdrew from the treatment due to adverse reactions. Lead migration was the only complication observed in 7 cases (7/46, 15.2%) which eventually caused the loss of pain relief in 4 cases.

Discussion

PHN is a debilitating chronic neuropathic pain that can develop following an acute HZ infection. It affects

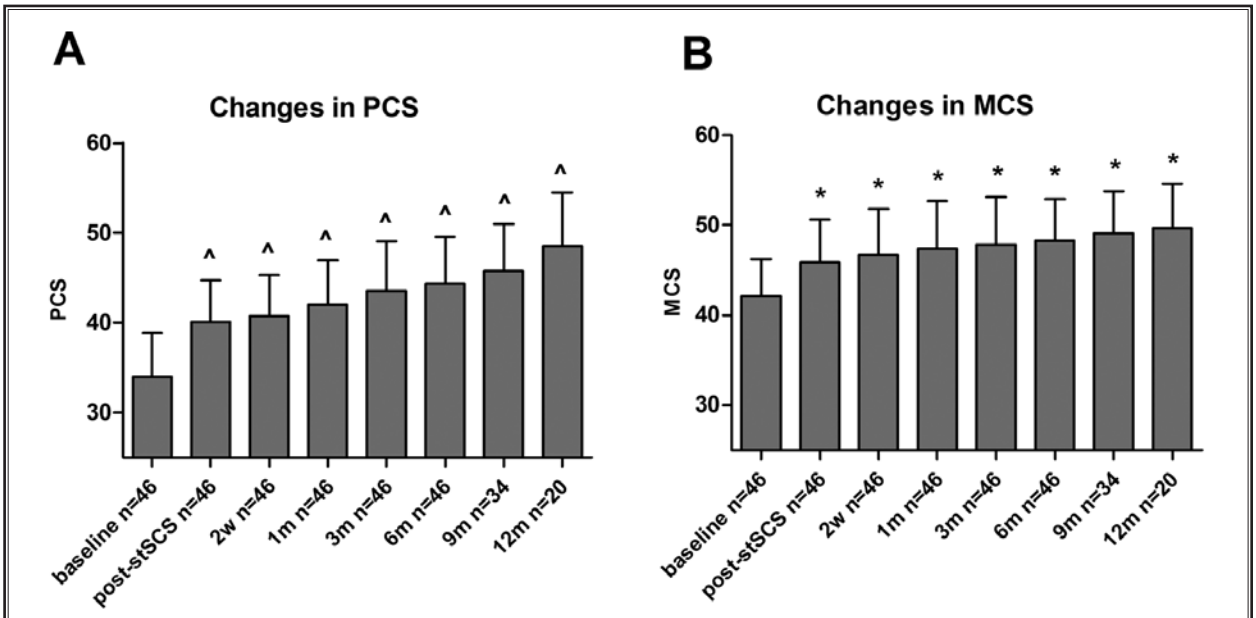

Fig. 4. *PCS and MCS of SF-12 scores for patients presented with acute/subacute zoster-related pain. The baseline, post-stSCS (obtained before patient discharge), 2 week scores as well as the follow-up scores obtained at 1, 3, 6 ,9, and 12 months are presented on the graph (*P < 0.05, ^P < 0.001, compared with baseline), stSCS, short-term spinal cord stimulation.*

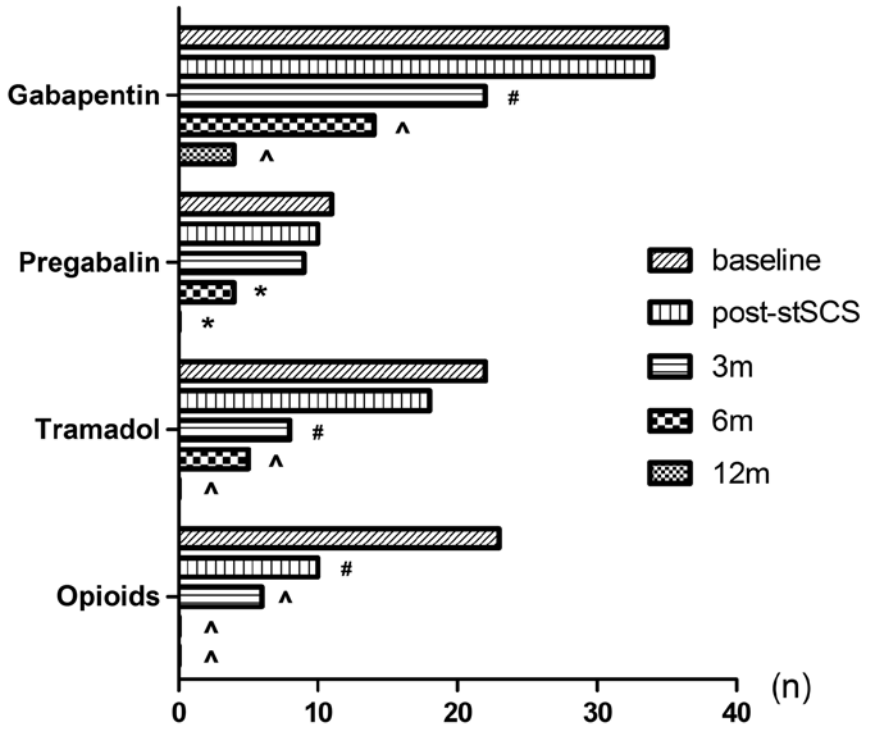

Fig. 5. *Alteration in the consumption of gabapentin, pregabalin, tramadol, and strong opioids in patients presented with acute/subacute zoster-related pain at the baseline, post-stSCS treatment as well as the follow-up period at 3, 6m and 12 months post-stSCS treatment. (*P < 0.05, #P < 0.01, ^P < 0.001, compared with baseline), stSCS, short-term spinal cord stimulation; n, number of patients.*

the patients' QoL at the physical and psychological aspects and creates a constant higher demand on the health care system (46). None of the different treatment modalities for coping with the chronic PHN pain was proven to have curative value in all cases (20-24). Therefore, in this study we investigated the efficacy of stSCS in treating acute/subacute episodes of HZ-associated pain and preventing their further development to PHN. The exact mechanisms underlying SCS-induced analgesia for neuropathic pain remain unclear (40,41). Animal models of neuropathic pain have shown that the SCS-induced analgesia involves the release of acetylcholine in the dorsal horn of the spinal cord (47). In addition, the descending antinociceptive system via the serotonergic pathway plays an important role in the antinociceptive effect of SCS (48,49), as well as in the mechanism of neuropathic pain development (50).

Previous studies investigated the analgesic effects of SCS in patients with zoster related pain, and their clinical results were consistent with the results observed in this study (51-53). However, due to the small number of cases investigated and the lack of a follow-up period, the clinical value of SCS was underestimated, especially in the acute/subacute period. In a previous study investigating the efficacy of SCS in PHN using permanent implantable pulse generator (IPG) implants, Harke et al (51) observed successful analgesia against acute pain in 4 patients. On the other hand, Spiegelmann and Friedman (54) suggested that SCS had a relatively weak efficacy for PHN. Additionally, the use of permanent implants (i.e., IPG) will create a heavy financial burden on both the medical insurance and individuals (16). Yanamoto et al (52) reported that 63.6% of the patients (21/33) achieved an excellent pain relief and reported that temporary SCS was an effective analgesic method for early PHN within one to 6 months of its onset. Moreover, Moriyama (53) proved that temporary SCS treatment can successfully produce pain relief in patients who previously failed continuous epidural blocks therapy. He observed that out of 14 patients presented with acute/subacute zoster-related pain, 12 patients achieved excellent pain relief upon the SCS introduction (VAS $\leq$ 2).

Finally, Kumar et al (55) reported a favorable outcome for SCS treatment versus conventional therapies in treatment of the neuropathic pain of failed back surgery syndrome; however, they observed a direct correlation between the early intervention via SCS and the patient's chance to achieve complete pain relief. In this study, we divided the patients into 4 groups according to the duration of the acute/subacute zoster-related pain and calculated the changes in the VAS scores, but we did not obtain significant differences in the efficacy of stSCS among the 4 groups. This indicates that the long-term pain alleviation and patient satisfaction were not associated with the early intervention with stSCS in the case of acute/subacute zoster-related pain. However, there might be significant differences between acute/subacute zoster-related pain and PHN, but this speculation has to be confirmed using a larger sample size.

Patients enrolled in this study presented with severe pain in the acute/subacute period that was refractory to conventional therapies and the possibilities of spontaneous pain relief in such patients are usually low (18,19). In this study, we demonstrated a plausible long-term benefit of stSCS treatment in HZ-associated pain. By the end of stSCS treatment (patients discharge from the hospital), 39.1% of the patients (18/46) achieved excellent pain relief (VAS $\leq$ 2), and this number increased to 67.4% (31/46), 73.5% (25/34), and 80.0% (16/20) at 6, 9, and 12 months post-stSCS treatment, respectively.

In this study, a total of 14 patients showed poor improvement towards stSCS treatment (14/46, 30.4%, Fig. 6). Spontaneous lead migration was observed in 4 cases (No. 1, 4, 20, 36; 4/46, 8.7%) and those patients could not achieve the paresthesia coverage in the painful area. This displacement can be attributed to the surgeon's inexperience with the stSCS procedure (n = 2, No. 1, 4) or to the wider and thicker cervical spine cord (n = 2, No. 20, 36) which can cause direct reduction in pain relief. The increase in cervical spine mobility is a risk factor for cervical lead migrations (56). In case No. 4, the surgeon encountered difficulties in positioning the lead in the desired cervical levels (C7) due to the wider distance from the lumbar vertebrae 2-3. Eventually, the surgeon was able to position the lead at the desired level but it was not in an appropriate position of the epidural space which generated poor paresthesia coverage during the treatment. Therefore, in the remaining patients we found that introducing the percutaneous lead through the modified Tuohy needle at upper thoracic spine levels instead of at the upper lumbar spine levels was a better alternative, in order to adjust the position of the lead easily and avoid the cumulative drag and resistance to insertion (56).

In the other 10 patients presented with poor pain relief (No. 9, 16, 31, 41, 45; 22, 24, 28, 30, 39; 10/46, 21.7%), we observed that those patients initially achieved complete and satisfactory paresthesia

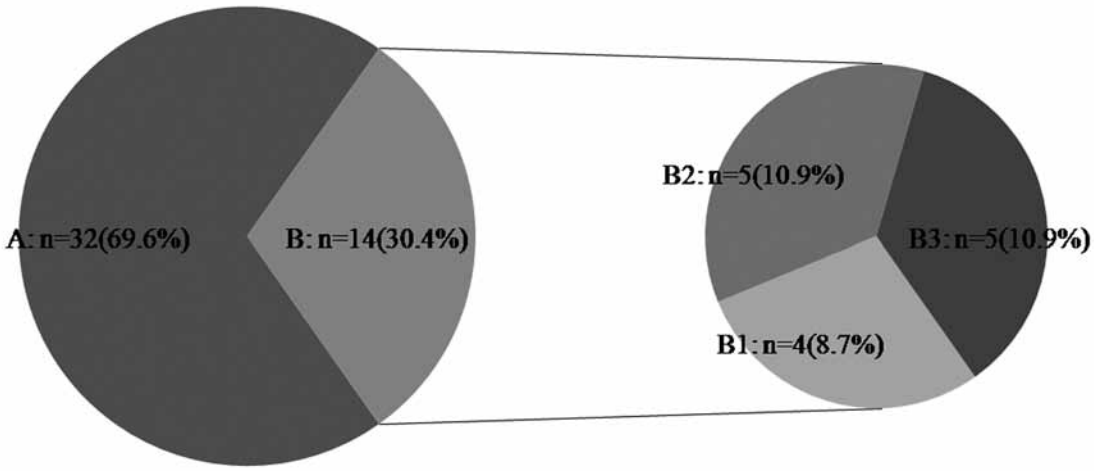

Fig. 6. *Pie charts depicting the response of acute/subacute zoster-related pain patient's to stSCS treatment upon discharge. A: 32 patients (69.6%, 32/46) obtained minimal clinically important difference, including 18 patients (39.1%, 18/46) who were extremely satisfied with an excellent pain relief (VAS ≤ 2). B: 14 patients (30.4%, 14/46) showed poor improvement in pain relief. B1: Among these 14 patients, spontaneous lead migration was observed in 4 cases (8.7%, 4/46); B2: 5 (10.9%, 5/46) patients got satisfactory coverage during the stSCS treatment, but still achieved poor pain relief; B3: 5 patients (10.9%,5/46) who achieved satisfactory coverage and excellent pain relief during the stSCS treatment, but after the stSCS was removed, the pain returned to its pre-treatment level.*

coverage. However, during the stSCS treatment, 5 patients complained of a persistent chronic pain (No. 9, 16, 31, 41, 45, 5/46, 10.9%). In those patients, stSCS treatment was not successful despite our attempts to elevate the stimulation level to a higher voltage to suppress the pain but they still complained of the usual chronic pain and additionally they experienced unbearable discomfort in unrelated areas. The DN4 scores in those 5 patients were 5, 4, 5, 6, 5, respectively. It has been reported that SCS did not provide analgesia for all types of pain and SCS was usually effective for neuropathic or sympathetically mediated pain states (36). In the other 5 poor-responder cases, permanent implantation of IPG was recommended to those patients (No. 22, 24, 28, 30, 39, 5/46, 10.9%) in order to obtain longer stimulation. However, none of them accepted the IPG insertion due to the financial burden (IPG costs $25,000 USD in China). Therefore, in those patients, the pain reemerged within several hours after the stimulation was stopped. Their therapy was terminated after reaching the maximum treatment period (14 days), and their chronic pain regained its initial intensity. We speculate that in those patients, the peripheral and central sensitization were irreversible with stSCS treatment (57).

In this study, we observed that none of the treated patients withdrew from the treatment due to adverse reactions, which indicated that stSCS is a safe procedure with minor complications.

Further, in this study, we observed that in the cases who achieved a satisfactory paresthesia coverage in the painful area, those patients had a greater chance to attain MCID or even a complete pain relief (69.6 %, 32/46 patients) and the dosage of pharmaceutical agents significantly dropped, or no drug therapies were required. Similarly, patients who attained excellent pain relief displayed improved PCS and MCS scores.

The persistent existence of long-term pain relief, reduction of analgesics consumption, and improvement in QoL indicate the curative effect of SCS. This curative effect can't be simply explained by the classical gate control theory or the release of acetylcholine that was reported to induce the immediate and short-term action of SCS (41). Instead, the extended pain relief caused by SCS can be attributed to the reversal of central sensitization (spinal neuronal plasticity) (58). Researchers observed that the stimulation of the dorsal column did not only attenuate the dorsal horn neuronal excitability in nerve-injured rats (59), but it also normalized the long-term potentiation of spinal wide

dynamic range neurons (60). This mechanism of central sensitization may be involved in the explanation of hyperalgesia (61). If SCS can reverse the development of central sensitization, performing SCS at the early stage of neuropathic pain may help prevent the development of pain hypersensitivity or at least limit its severity and duration. Therefore, in clinical practice, we recommend that stSCS should be the first line of treatment, especially in patients with refractory and severe acute/subacute zoster-related pain.

Conclusion

In conclusion, stSCS can provide persistent long-term pain relief and improvement in the QoL in patients with refractory and severe acute/subacute zoster-related pain. Results obtained from this study prove stSCS is a safe, effective, and less invasive analgesic method for patients. Furthermore, stSCS may have a curative effect at early stages of neuropathic pain.

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