



Laser speckle contrast imaging to predict the effect of temporary spinal cord stimulation in postherpetic neuralgia patients: A prospective observational study

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Temporary spinal cord stimulation (tSCS) can effectively reduce the pain and severity of postherpetic neuralgia (PHN). However, there are no effective and objective methods for predicting the effects of tSCS on PHN. Laser speckle contrast imaging (LSCI) is frequently used in neurology to evaluate the effectiveness of treatment. To assess the accuracy of LSCI in predicting the impact of tSCS on PHN, 14 adult patients receiving tSCS treatments for spinal nerve-innervated (C6-T2) PHN participated in this observational study. Visual analog scale (VAS) assessments and LSCI blood flow images of the fingers were recorded after the tSCS procedure. The results showed that the VAS scores of all patients decreased significantly. Moreover, the blood flow index (BFI) values were significantly higher than they were before the procedure. Increased blood flow and pain alleviation were positively correlated. The findings indicated that spinal nerve PHN (C6-T2) was significantly reduced by tSCS. Pain alleviation by tSCS was positively correlated with increased blood flow in the hand. The effect of tSCS on PHN may thus be predicted using an independent and consistent indicator such as LSCI.

Keywords: Laser speckle contrast imaging; temporary spinal cord stimulation; postherpetic neuralgia.

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1. Introduction

Following an acute herpes zoster episode, peripheral sensory nerve damage causes chronic pain known as postherpetic neuralgia (PHN) (commonly known as shingles).¹ The pain is characterized by a constant burning or stabbing sensation, with some individuals experiencing allodynia and symptoms that may last for months or even years. As a chronic neuropathic disease, PHN is difficult to treat clinically. Temporary spinal cord stimulation (tSCS) is a technique in which an electrode is implanted in the patient for 7–14 days. It is a simple technique, and tSCS administered within 4–8 weeks may be effective in treating and preventing PHN.² However, the evaluation of the pain associated with PHN is an important part of both diagnosis and treatment. The visual analog scale (VAS) and the simplified McGill Pain Questionnaire are conventional tools for the assessment and quantification of pain. However, these scales rely on the subjective judgment of patients on their pain which vary among individuals, and also cannot quantify the degree of pain. It is also often impossible to obtain an objective and accurate pain assessment in patients with cognitive impairment such as the elderly, infants, and young children. Although the exact processes responsible for the lowering of PHN-associated pain by tSCS are unknown, it has been suggested that tSCS improves the local blood flow around the nerve.³

Laser speckle contrast imaging (LSCI) is an optical imaging technique that enables contact-free dynamic evaluation of blood flow over large areas with great spatiotemporal precision.^{4,5} In rats, LSCI is an effective method for monitoring the microhemodynamics of the pancreas.⁶ The technique is based on speckle contrast analysis that provides an index of blood flow and permits rapid measurements of skin blood flow over extended areas with high resolution. Therefore, it has been proposed as an objective noninvasive imaging technique for the dynamic evaluation of the microvasculature in skin diseases. It is noncontactable and does not involve the use of agents or scanning, and thus has the capability of high spatiotemporal resolution over the extended observation periods. With LSCI, a single image indicating the blood flow index (BFI) over a large skin area can be obtained in real-time, allowing the quantitative objective analysis of the blood flow. Recently, LSCI has been used to evaluate skin blood flow in patients with microvascular diseases,

such as systemic sclerosis.⁷ In migraine associated with the activation of peripheral and/or central trigeminovascular pain pathways, LSCI can detect subtle trigeminovascular variations that are not visible to the naked eye. LSCI was also used to objectively quantify the modulatory effect of the pharmacological intervention for migraine.⁸ However, there is no information of the use of LSCI in the assessment of tSCS. This study investigated the effectiveness of tSCS for PHN using LSCI. The LSCI was anticipated to be an indication of the efficacy of tSCS in individuals with PHN.

2. Materials and Methods

2.1. Study participants

The study was registered (No. ChiCTR2100050647) on December 18, 2018 with the China Clinical Trial Registry. Following the exclusion and inclusion criteria, 14 patients with PHN were selected from the Department of Pain Management at the First People's Hospital of Foshan between July 1, 2019 and September 30, 2020. The criteria for eligibility included a diagnosis of classic PHN.⁹ The included patients were aged between 57 and 81 years and had experienced itching, paresthesia, and lancinating or burning pain for more than a month. On a VAS scale of 0 (no pain) to 10 (extreme pain), all patients reported experiencing pain that was at ≥ 7 . The pain was mainly located at the neck, shoulders, and upper limbs innervated by the spinal nerves (C6-T2). All patients agreed to rSCS treatment using LSCI. The patients had not received surgery for cervical or thoracic sympathetic ganglion damage.

The following conditions were excluded: Serious infection, mental illness, coagulation abnormalities, severe liver, kidney, or heart conditions, electrode displacement following SCS surgery, severe adverse drug reaction, surgical failure, infection of the skin or deep tissue at the puncture site, instability, severe cardiovascular or cerebrovascular disease, and failure to comply with professional advice. Informed consent was obtained from patients before the study.

2.2. Study protocol

2.2.1. Medication and procedure

All patients received conventional medication throughout the study.¹⁰ Anticonvulsants such as

pregabalin 75 mg q12 h and neurotrophic drugs such as mecobalamin 0.5 mg q8 h were prescribed.

The tSCS procedure was performed in the Digital Subtraction Angiography (DSA) room. Standard monitors were used to measure electrocardiography, pulse oxygen saturation (SpO_2), noninvasive blood pressure, and heart rate (HR) while the patient was lying on the bed. The target level of the tSCS was based on the dermatome affected by herpes zoster. The puncture point was marked under fluoroscopy. The tunnel needle, followed by an empty glass syringe (about 2 ml air in the empty syringe), was directed into the epidural space. The syringe was then withdrawn and checked for the absence of cerebrospinal fluid or blood. The electrode insertion with eight contacts was implanted under DSA. To stimulate the spinal dorsal column, the electrode position was slightly moved to the paramidline position in the epidural space. The final location of the electrode was positioned, as shown in Fig. 1. The test mode was administrated at a pulse width of $210 \mu\text{s}$, a voltage of 2 V, and a frequency of 40 Hz. Adequate paresthesia coverage was defined as 80% of the pain area. After the procedure, the electrode lead was connected to the receiver and adjusted the voltage, frequency, and pulse width to alleviate the pain. Patients received six days of tSCS treatment.

2.2.2. Laser speckle contrast imaging

The laser speckle contrast imaging (LSCI) was carried out as previously described.¹¹ A Blood Flow Imaging system (SIM BFI WF, Wuhan SIM Opto-Technology Co., Ltd., <http://www.simopto.com>) was used to illuminate the objective with a 785 nm laser, and backscatter of the laser from the surface was collected and imaged, allowing the determination of the blood flow. The pixel values in the

calculated image indicate the blood flow, with larger values indicating faster flow. The working distance between the imaging head and the objective was set at 20–25 cm. The exposure time was set at 20 ms and the blood flow images were saved at 30 fps. The saved images were analyzed with the same software (SIM BFI Software, SIM Opto-Technology Co., Ltd.). The regions of interest (ROI) and the time sections of interest (TOI) were selected using a tool provided by the software, and the mean values of the ROIs and TOIs could thus be calculated and plotted. Furthermore, changes in the blood flow could be determined for different ROIs and TOIs. The application has been validated by Professor Li (Xiaohong Li) and his team for imaging and comparing the blood flow between different fingertips.

2.2.3. Observations

The assigned investigator obtained the VAS scores and blood flow images. All patients used VAS values, ranging from 0 (no pain) to 10 (severe pain), to evaluate their level of pain. The software determined the average BFI values of the ROIs. Baseline VAS scores and blood flow images were obtained before the procedure and at one, three, and six days afterward. The VAS scores were compared between the baseline and the different follow-up time points. The average increase in BFI was estimated as the mean difference between baseline and follow-up for all five fingers. The difference in the VAS score six days after the procedure was calculated as the ratio between the decrease in the score and the baseline value. The interpretation of BFI six days after the process was calculated as the ratio between the mean increase of BFI and the BFI at baseline.

2.3. Statistics

The primary measurement in the study was the decrease in the post-operative VAS score. The post-operative VAS score was used to estimate the optimal sample size for this investigation. According to preliminary assessments, the average VAS score was 2.0 after the procedure, with a standard deviation (SD) of 1.23. Using $\alpha = 0.05$, $1 - \beta = 0.9$, and $p = 0.8$, a two-tailed analysis by PASS11.0 software (NCSS, USA) indicated a minimum sample size of 12 patients. Fourteen patients were thus enrolled after taking a 20% loss to follow-up into account. SPSS version 23.0 was used to conduct all statistical

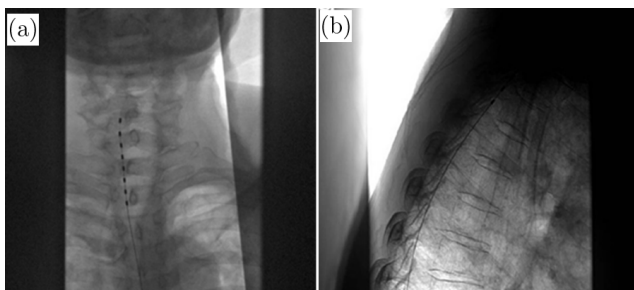


Fig. 1. (a) The electrode lead located at the right side of the cervical spinal dorsal column. (b) The electrode lead located in the epidural space.

analyses. The research data were collected by a designated investigator while another staff member was responsible for data entry and did not participate in the research processes of grouping, follow-up, treatment, registration, and final statistical analysis. The statistical analysis of the data was the responsibility of a professional statistician. Chi-square tests were used to assess differences between continuous variables which were expressed as mean and \pm SD. Categorical variables were presented as frequencies or proportions, and independent-sample *t*-tests or Wilcoxon rank-sum tests were used for analysis. The association between the VAS difference and the mean BFI difference at six days following the surgery was examined using Pearson correlation analysis. *P*-values < 0.05 were considered to be statistically significant.

3. Results

Data from 14 patients with PHN (eight males and six females aged 57–81 years) were analyzed in the study. Detailed information on the patients is shown in Table 1. No significant differences were observed in patient demographics nor PHN severity and duration.

The pain of all patients was found to be effectively alleviated by tSCS, as seen in the follow-up assessments. The VAS scores of the patients were significantly lower ($p < 0.001$) one, three, and six days after surgery compared to those at baseline before the procedure although no marked

Table 1. Basic characteristics of patients with PHN after tSCS treatment.

Parameter	(<i>n</i> = 14)
Age (years, mean \pm SD)	69.64 \pm 11.06
Sex (female/male)	6/8
Duration of symptoms (days, mean \pm SD)	69.86 \pm 53.75

differences in the scores were observed between the one-, three-, and six-day time points. The pain levels of the patients are shown in Table 2.

The BFI values of the five fingers were significantly increased at one, three, and six days after the tSCS ($p < 0.05$) although no significant differences were observed between the one-, three- and six-day time points, as shown in Fig. 2 and Table 3.

Pearson correlation coefficients indicated an association between the BFI values and the VAS scores. There was a positive correlation between the mean variation of BFI and the variation of VAS, with a correlation coefficient of 0.56 ($p < 0.05$). The correlation coefficients are shown in Fig. 3.

4. Discussion

The VAS scores were significantly reduced in all PHN patients after the tSCS treatment. This study showed that spinal nerve-innervated (C6–T2) pain in the neck, shoulder, and upper limbs could be substantially decreased by the use of tSCS. In addition, there was a positive correlation between increased blood flow and pain relief, and we thus suggest that LSCI is effective for evaluating the efficacy of tSCS in patients with PHN.

Pain that lasts for a month or more after the herpes zoster rash healed is known as PHN.¹² It is the most common chronic side effect of herpes zoster and the most typical infection-related neuropathic pain.¹³ The prevalence of PHN rises with age.¹ According to a research, the patient's prodromal pain symptoms, the intensity of the rash, sex, and age are all strongly correlated with morbidity and the severity of PHN.¹⁴ Consistent with the findings of previous studies, as discussed above, the patients with PHN in this study were between 57 and 81 years of age with an average age of 69 years, and had experienced intense persistent pain for at least one month.

Table 2. Follow-up period and VAS scores (*n* = 14).

	Follow-up period			
	Pre-surgery	1 day	3 day	6 day
VAS scores	8.07 \pm 0.73	2.79 \pm 0.58*	2.79 \pm 0.58*	2.36 \pm 0.63*

Notes: * $p < 0.001$, pre-tSCS treatment compared with the follow-up time points of one day, three days, and six days.

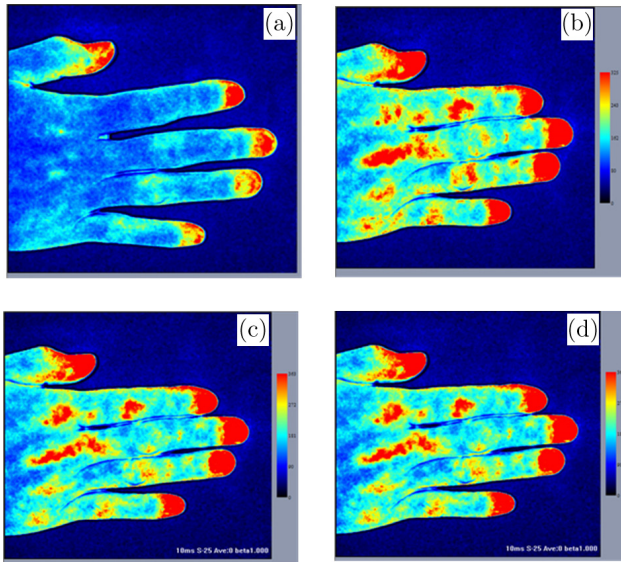


Fig. 2. Images of the LSCI-irradiated hands of the patients. (a) Before the procedure. (b)–(d) One, three, and six days after the procedure.

Over 50% of PHN patients have involvement of the cervical and thoracic dermatomes.¹⁵ Intercostal arteries from the posterior aorta in the thoracic area give rise to radicular arteries, which make up the main blood supply to the spinal column. A single radiculomedullary artery may supply the upper thoracic cord, making this area particularly vulnerable to ischemic injury. Cervical and thoracic transforaminal epidural steroid injections have been reported, and spinal cord infarcts can lead to paraplegia and even death. Thus, catastrophic events can occur from vascular injury resulting from needle placement. To protect the fragile blood supply to the cervical and thoracic spinal cord, extra precautions must be maintained.¹⁶ In this study, the thoracic spinal cord was punctured from the lumbar spine to protect the blood supply of the

cervical and thoracic spinal cord. This procedure is safer for patients than cervical or thoracic transforaminal epidural steroid injections.

SCS is a recognized, secure, reversible, and successful method for treating chronic neuropathic pain¹⁷ but its exact mechanism of action is still up for debate. Grade B suggestions for treating PHN include spinal cord stimulation.¹⁸ SCS has been shown to be successful in the treatment of herpes zoster-related discomfort that has lasted past the acute stage in elderly patients.¹⁹ Early tSCS may thus be a promising prevention strategy against chronic neuropathic pain following herpes zoster infection.² Our study showed that, with an average of 69 days, the pain intensities of the patients were significantly reduced by the tSCS treatment. The intensity of the pain was evaluated by VAS scores which are a subjective assessment by patients of their pain. The VAS score cannot accurately assess pain intensity due to its subjectivity and differences between individuals and is also difficult to use in certain cases, such as elderly patients with cognitive impairment or communication difficulties. Clinicians tend to forego certain modalities of treatment that can be challenging.²⁰ Therefore, a more objective and accurate means of pain assessment is needed.

The tSCS can stimulate the peripheral nerve through electrical stimulation. To enhance local blood flow surrounding the nerve and facilitate nerve healing, the electric field electrolyzes micro-tissue proteins, releases vasoactive chemicals, triggers axonal and segmental reflexes, and promotes vasodilation.³ SCS reduces pain by increasing blood flow to the upper extremities at slightly lower cervical levels (C3–C6), which are associated with reduced sympathetic activity, increased vasomotor center activity, and the release of neurohumoral

Table 3. A comparison of the BFI of fingers at different follow-up time points ($n = 14$).

Fingers	Presurgery	Follow-up period		
		1 day	3 day	6 day
The thumb	539.70 ± 150.08	715.65 ± 180.4*	675.62 ± 202.66*	738.08 ± 156.70*
The index	522.95 ± 152.01	700.15 ± 181.61*	669.10 ± 192.17*	709.59 ± 153.48*
The middle	545.99 ± 185.41	720.20 ± 170.10*	708.76 ± 203.17*	756.63 ± 163.48*
The ring	523.84 ± 180.52	702.64 ± 172.91*	691.15 ± 209.0*	714.95 ± 169.24*
The little	507.49 ± 193.00	719.55 ± 164.88*	686.70 ± 180.72*	698.68 ± 176.61*

Notes: Pre-tSCS treatment compared with the follow-up time points of one day, three days, and six days. * $p < 0.001$.

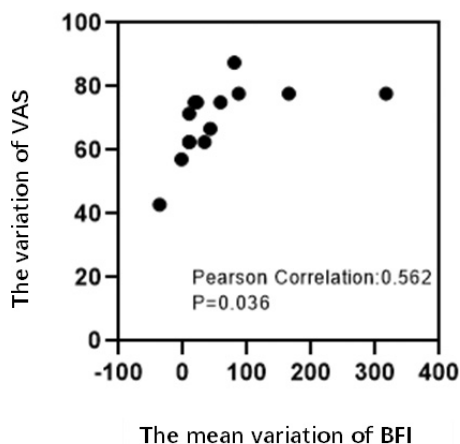


Fig. 3. Association between increased blood flow and pain relief (correlation coefficient of 0.56).

substances.²¹ As shown by the studies described above, it is hypothesized that the reduction in pain is associated with increases in the local blood flow. High time- and space-resolution LSCI has been used in various fields in the life sciences, providing a real-time and contactless assessment of blood flow over large areas.^{22,23} According to several investigations, the LSCI approach can forecast the clinical outcomes of a sciatic nerve block.¹¹

Moreover, as the composition and distribution of vascular nerves differ between the upper and lower limbs, the use of this approach in the upper limbs requires investigation.²⁴ A case report showed that LSCI might be an alternative to measure selective cervical nerve root block (C6,7).²⁵ Compared with temperature-based measurements such as infrared thermography, the novel LSCI technique was also found to be effective for the evaluation of stellate ganglion block.²⁶ Thus, on the basis of the results of previous studies and the findings of the current research, it is suggested that the LSCI technique can predict the effect of tSCS treatment, and the increase of blood flow and pain relief are correlated.

The study has several limitations. First, the sample size was small. SCS is an expensive technology with stringent requirements. The number of cases covered in this study was constrained by the fact that few hospitals in China can use this technology. Therefore, to assess the applicability and reliability of the LSCI, larger sample sizes are required. Second, there may be changes in the blood flow in deep tissue and the increased blood flow on the skin surfaces of the upper limbs caused by tSCS may also affect the deep blood flow. Deep blood flow

was not evaluated in this study. Third, the period of observation was only six days. The degree of discomfort or blood flow could not be gauged after the removal of the electrode lead. Finally, in addition to the SCS treatment, there are many other interventional therapies for PHN, including paravertebral block, stellate ganglion block, and pulsed radio-frequency therapy.¹⁸ Future studies should explore the use of the LSCI technique for predicting the impact of interventional treatment.

5. Conclusion

In conclusion, the study showed that spinal nerve-innervated PHN can be significantly relieved by tSCS (C6-T2). The pain alleviation resulting from tSCS was positively correlated with increased blood flow in the hand. LSCI may thus be a valid and trustworthy method for assessing the impact of tSCS on PHN.

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Conflicts of Interest

The authors declare that there are no conflicts of interest relevant to this paper.

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