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Predictive Factors Associated with Pain Relief of Spinal Cord Stimulation for Central Post-stroke Pain

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Abstract

The efficacy and predictive factors associated with successful spinal cord stimulation (SCS) for central post-stroke pain (CPSP) have yet to be definitively established. Thus, this study evaluated the rates of pain relief found after more than 12 months and the predictive factors associated with the success of SCS for CPSP. The degree of pain after SCS in 18 patients with CPSP was assessed using the Visual Analog Scale preoperatively, at 1, 6 and 12 months after surgery, and at the time of the last follow-up. After calculating the percentage of pain relief (PPR), patients were separated into two groups. The first group exhibited continuing PPR ≥30% at more than 12 months (effect group) while the second group exhibited successful/unsuccessful trials followed by decreasing PPR <30% within 12 months (no effect group). Pain relief for more than 12 months was achieved in eight out of 18 (44.4%) patients during the 67.3 ± 35.5 month follow-up period. Statistically significant differences were found for both the age and stroke location during comparisons of the preoperative characteristics between the two groups. There was a significantly younger mean age for the effect versus the no effect group. Patients with stoke in non-thalamus were significantly enriched in effect group compared with those with stoke in thalamus. Multivariable analysis using these two factors found no statistical differences, suggesting that these two factors might possibly exhibit the same behaviors for the SCS effect. These results suggest that SCS may be able to provide pain relief in young, non-thalamus stroke patients with CPSP.

Key words: spinal cord stimulation, central post-stroke pain, predictive factor, neuropathic pain

Introduction

Central post-stroke pain (CPSP) is a chronic central neuropathic pain that occurs following stroke.[1)] The prevalence of CPSP varies from 1 to 14%.[2–4)] Pain is severe, persistent, and spontaneous on the hemiplegic side. The main feature of the spontaneous pain associated with CPSP has been described as a burning or aching that often co-exists with sensory disturbances such as allodynia or hypoesthesia.[1–4)] Although the mechanisms of CPSP are still unclear, spinothalamocortical pathway injury appears to be crucial for the development of CPSP.[3–5)] Pharmacological treatment of CPSP mainly consists of the use of pregabalin, antidepressants, and opioid. However, many patients do not respond to pharmacological treatments, only obtain partial relief, or experience intolerable adverse effects.[3,6)] For this reason, non-pharmacological approaches such as neuromodulation therapies have been developed.[7)]

Until recently, motor cortex stimulation (MCS) was one of the main neuromodulation therapies used for central neuropathic pain. Previous studies have also reported that the long-term success rate of MCS for CPSP was approximately 50%.[8)] The absence of severe motor deficit, which demonstrates the preservation of the corticospinal tract, has been proposed as one of the predictive factors of MCS for CPSP.[9)]

Spinal cord stimulation (SCS) is currently the most widely used neuromodulation therapy for chronic neuropathic pain.[10,11)] The reasons for its use include being less invasive, having a low complication rate, and its effectiveness.[11)] Randomized controlled trials

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have documented that SCS was efficacious for particular types of peripheral neuropathic pain, such as failed back surgery syndrome, complex regional pain syndrome type I, and painful diabetic neuropathy.[12–14] However, SCS has not been previously recommended for the treatment of central neuropathic pain.[15,16] Even so, there have been some reports on the efficacy of SCS for treating CPSP patients.[17,18] The number of studies that have examined the use of SCS for CPSP is small, with the success rates ranging in variability from 7 to 60%.[17–20] Thus, the efficacy and predictive factors for the successful use of SCS for CPSP have yet to be determined. Therefore, the aim of this study was to evaluate the rates of pain relief for greater than 12 months and determine the predictive factors that are associated with CPSP pain relief obtained by SCS treatment.

Materials and Methods

Patients and methods

This study was a retrospective review of 18 consecutive patients who underwent surgical insertion of SCS electrodes for the treatment of CPSP between 2010 and 2017. All patients exhibited a poor response to medications prior to undergoing the surgery, including for the use of pregabalin and antidepressants. SCS was performed in patients who presented with upper or/and lower extremity pain. Patients with severe depression, psychiatric disorders, drug abuse, or who could not sufficiently communicate due to severe neurological deficits were excluded from these therapies. The study protocol was approved by the local ethics committees of Nagoya Central Hospital. All patients were informed about the procedure and provided written informed consent prior to participation in the study.

SCS electrode implantation in patients

There were 18 patients (10 men and 8 women) who underwent insertion of the SCS electrodes. The mean age of the patients was 63.9 ± 8.8 years (range 50–76 years). The preoperative mean duration of pain was 4.5 ± 3.6 years (range 1–14 years). The types of stroke were hemorrhage (n = 15) and infarction (n = 3). Location of the stroke was the thalamus (n = 8) and non-thalamus (n = 10). Laterality of pain was right (n = 5) and left (n = 13). The preoperative mean Visual Analog Scale (VAS) value was 7.9 ± 1.3. The mean postoperative follow-up was 67.3 ± 35.5 months (range 12–100 months) for patients with active SCS. Table 1 summarizes the clinical features of the patients and outcomes of the SCS.

SCS electrode implantation procedures

After placing each patient in a prone position, an 18-gauge Tuohy needle, which was included in the electrode package, was inserted into the midline epidural space while under local anesthesia. Subsequently, 4- or 8-contact cylinder type electrodes (Model 3487, 3777, and 977; Medtronic Inc., MN, USA) were then inserted. For the dual lead SCS, two electrodes were placed in parallel and lateral to the midline ipsilateral to the area experiencing the pain. When the insertion of two electrodes was technically difficult to achieve, only one electrode was inserted (patient no. 8 and 9). The tip of the electrodes was advanced to the required spinal level, C4–C7 for upper extremity pain or Th9–Th12 for lower extremity pain. The electrodes were manipulated using radiographic guidance to ensure that the stimulation-induced paresthesia covered the entire region affected by pain. One case (no. 11) required the use of four 4-contact electrodes. After connecting the distal ends of the electrodes to a percutaneous extension cable via a subcutaneous tunnel, the incision was closed.

Test stimulation and implantation of the implantable pulse generator

A test stimulation (=trial) was performed approximately 7 days after the insertion of the electrodes to assess the efficacy and adverse effects. Initial stimulation parameters were started at frequency 30 Hz and pulse width 240 μs. When the effect was insufficient or inducing unpleasant paresthesia, the parameters were changed. "Trial success" was defined as a reduction of ≥50% in the VAS. When the trial did succeed, the electrode was then connected to an IPG (PrimeAdvanced RestoreSensor SureScan MRI neurostimulator, or Intells; Medtronic Inc) placed under the skin at the lower abdominal region while general anesthesia. If a successful trial was not achieved in the patient, the electrodes and percutaneous extension were removed.

Assessment

The degree of pain was assessed using the VAS, which ranged from 0 (no pain) to 10 (maximal pain). The preoperative VAS score was defined as the baseline value, while postoperative outcomes were assessed at 1, 6 and 12 months and at the time of the last follow-up. Percentages of pain relief (PPR) from the preoperative VAS were evaluated at 1, 6 and 12 months and at the time of the last follow-up [PPR (%) = (preoperative VAS − postoperative VAS)/preoperative VAS × 100]. Patients were separated into two groups according to their outcomes. The "effect group" was defined as patients with a continued PPR ≥30% for more than 12 months,

Table 1 Clinical features of the patients and outcomes of the SCS

No.	Age	Sex	Stroke		Pain			Sensory disturbance		SCS				Result		Initial parameters		Last parameters	
			Type	Location	Duration (year)	Laterality	Site	Hypo	Allo	Motor weakness	Pre-VAS	Location	Electrode	Trial success	Effect >12 m	Fr (Hz)	PW (μs)	Fr (Hz)	PW (μs)
1	67	M	Hemo	Thal	14	R	UE, LE	+	+	ms	8	C	8c × 2	×	NA	40–60	240	–	–
2	69	M	Hemo	Non-thal	9	R	UE, LE	+	+	–	8	Th	8c × 2	○	×	30	450	30	450
3	50	M	Hemo	Non-thal	5	L	LE	+	+	mi	8	L	8c × 2	○	○	30	450	30	450
4	64	M	Hemo	Thal	1	L	LE	+	–	mi	7	Th	8c × 2	○	×	30	450	10	450
5	63	F	Inf	Non-thal	7	L	LE	+	+	ms	6	Th	8c × 2	○	○	30	450	30	450
6	59	F	Hemo	Non-thal	1	L	UE, LE	–	–	mi	7	Th	8c × 2	○	○	30	450	30	450
7	70	F	Hemo	Non-thal	5	L	UE, LE	–	–	–	9	Th	8c × 2	○	○	30	450	30	450
8	68	M	Hemo	Thal	6	L	UE, LE	+	+	mi	7	Th	8c × 1	×	NA	30	120	–	–
9	75	F	Hemo	Non-thal	1	R	LE	–	+	mi	8	Th	8c × 1	×	NA	20–60	450	–	–
10	75	M	Hemo	Non-thal	3	L	UE, LE	+	+	mi	6	Th	8c × 2	×	NA	20–60	450	–	–
11	56	M	Hemo	Thal	2	R	UE, LE	+	+	–	6	C, Th	4c × 4	○	○	30	240	30	240
12	47	F	Inf	Non-thal	2	L	LE	+	+	–	8	Th	8c × 2	○	○	100	240	20	240
13	62	M	Inf	Non-thal	1	L	UE, LE	–	+	ms	10	Th	8c × 2	○	○	20	240	20	240
14	57	M	Hemo	Thal	2	L	UE, LE	+	+	–	10	C, Th	8c × 2	×	NA	10–260	240	–	–
15	76	F	Hemo	Thal	4	L	UE, LE	+	+	–	9	C, Th	8c × 2	×	NA	10–40	60–240	–	–
16	73	F	Hemo	Thal	6	L	UE, LE	+	+	ms	9	Th	8c × 2	○	×	60	200	50	200
17	66	M	Hemo	Thal	9	L	UE	+	+	mi	9	C	8c × 2	○	×	10	240	200	300
18	53	F	Hemo	Non-thal	3	R	UE, LE	–	+	ms	8	C, Th	8c × 2	○	○	20	300	25	200

Allo: allodynia, C: cervical, F: female, Fr: frequency, Hemo: hemorrhage, Hypo: hypoesthesia, Inf: infarction, L: left, LE: lower extremity, M: male, m: month, ms: moderate/severe, mi: minimal, NA: not applicable, PW: pulse width, R: right, SCS: spinal cord stimulation, thal: thalamus, Th: thoracic, UE: upper extremity, VAS: Visual Analog Scale, 4c: four-contact electrode, 8c: eight-contact electrode.

while the "no effect group" was defined as patients with trials that were either successful or unsuccessful who then exhibited a decreasing PPR <30% within 12 months.

Statistics

All values are expressed as the mean ± SD. Wilcoxon rank sum test was performed to investigate differences of age, duration of pain, and preoperative VAS scores. Fisher's exact test was performed to investigate differences of sex, location of stroke, type of stroke, sensory disturbance, motor weakness, and site of pain. Logistic regression analysis was performed using candidate independent variables, which had a P <0.05 for the univariate analysis. We used "exactRankTests" and "coin" packages for the Wilcoxon rank sum test, which are included in the statistical software R version 3.4.1 (URL: https://www.r-project.org/). P-values of <0.05 were considered to be significant.

Results

After trial success was achieved in 12 out of 18 (66.7%) patients implanted with the SCS electrodes, these 12 patients were then implanted with an IPG system. However, four of these patients exhibited a diminished effect of the SCS within 12 months. Therefore, eight out of 18 (44.4%) patients were able to achieve more than 12 months pain relief during the 67.3 ± 35.5 month follow-up period (range 12–100 months). Table 2 presents the characteristics and VAS changes for the effect group patients. The mean VAS for the effect group patients improved from 7.8 to 3.5. None of the patients required removal of the system due to infection.

Table 3 shows the comparisons of the preoperative characteristics between the effect and no effect groups.

Table 3 Comparisons of the preoperative characteristics between the effect and no effect groups

	Effect	No effect	P-value
n	8	10	
Age	57.5 ± 7.5	69.0 ± 6.6	0.0043[a]
Sex			0.3416
Male	3	7	
Female	5	3	
Duration of pain (years)	3.3 ± 2.2	5.5 ± 4.2	0.2812
Stroke location			0.0248[a]
Thalamus	1	7	
Non-thalamus	7	3	
Stroke type			0.0686
Hemorrhage	5	10	
Infarction	3	0	
Sensory disturbance			
Hypoesthesia	3	7	0.1176
Allodynia	4	7	0.5588
Motor weakness			0.6001
Minimal	2	5	
Moderate + severe	3	2	
Site of pain			0.7888
UE	0	2	
LE	6	6	
UE + LE	2	2	
VAS (preope)	7.8 ± 1.4	8.1 ± 1.2	0.5769

[a]Statistically significant. LE: lower extremity, UE: upper extremity, VAS: Visual Analog Scale.

Table 2 Characteristics and VAS changes of patients achieving more than 12 months pain relief

No.	Age	Sex	Stroke location	Follow-up (m)	VAS					PPR (%)			
					Preope	1 m	6 m	12 m	Last	1 m	6 m	12 m	Last
3	50	M	Non-thal	100	8	1	1	1	1	87.5	87.5	87.5	87.5
5	63	F	Non-thal	98	6	1	2	2	2	83.3	66.7	66.7	66.7
6	59	F	Non-thal	98	7	1	1	1	1	85.7	85.7	85.7	85.7
7	70	F	Non-thal	98	9	1	2	6	6	88.9	77.8	33.3	33.3
11	56	M	Thal	57	6	1	1	1	1	83.3	83.3	83.3	83.3
12	47	F	Non-thal	38	8	4	5	5	5	50	37.5	37.5	37.5
13	62	M	Non-thal	37	10	4	7	7	7	60	30	30	30
18	53	F	non-thal	12	8	5	5	5	5	37.5	37.5	37.5	37.5

F: female, M: male, m: month PPR: percentage of pain relief, thal: thalmus, VAS: Visual Analog Scale.

There were statistically significant differences found for both the age and stroke location (P <0.05). The mean age for the effect group (57.5 ± 7.5 years) was significantly younger than that for the no effect group (69.0 ± 6.6 years). Patients with non-thalamus stroke were significantly enriched in effect group compared with those with stroke in thalamus. There were no statistically significant differences noted for the other preoperative characteristics such as sex, duration of pain, stroke type, sensory disturbance, motor weakness, site of pain, and preoperative VAS scores. There were also no statistically significant differences observed for the logistic regression analysis when examining age and stroke location between the effect and no effect groups.

The success rate of the trial in patients with thalamus stroke was 50% (4/8), which was low compared with that observed for the non-thalamus stroke 80% (8/10). Furthermore, three out of four thalamus stroke patients with a successful trial exhibited a diminished effect for the SCS within 3 months after IPG implantation. In contrast, only one out of eight non-thalamus stroke patients exhibited a diminished effect for the SCS. Magnetic resonance images showed similar findings for the eight thalamic stroke patients, such as having a small and posterior location for the stroke. In addition, no apparent differences were noted between the patients who achieved pain relief and those who exhibited no effect (Fig. 1).

Discussion

Effects of SCS for CPSP are controversial. Table 4 lists some of the results and details that have been reported when using SCS for CPSP. Furthermore, the guidelines and recommendations published by the European Federation of Neurological Societies (EFNS) and the Neuropathic Pain Special Interest Group (NeuPSIG) do not recommend the use of SCS for the treatment of CPSP.[15,16] These decisions were based on two previous reports. In the first report, SCS procedures were performed in 60 patients with intractable pain including 10 patients with CPSP. This study used various types of electrodes such as the 1- or 2-contact cylinder type electrodes, and

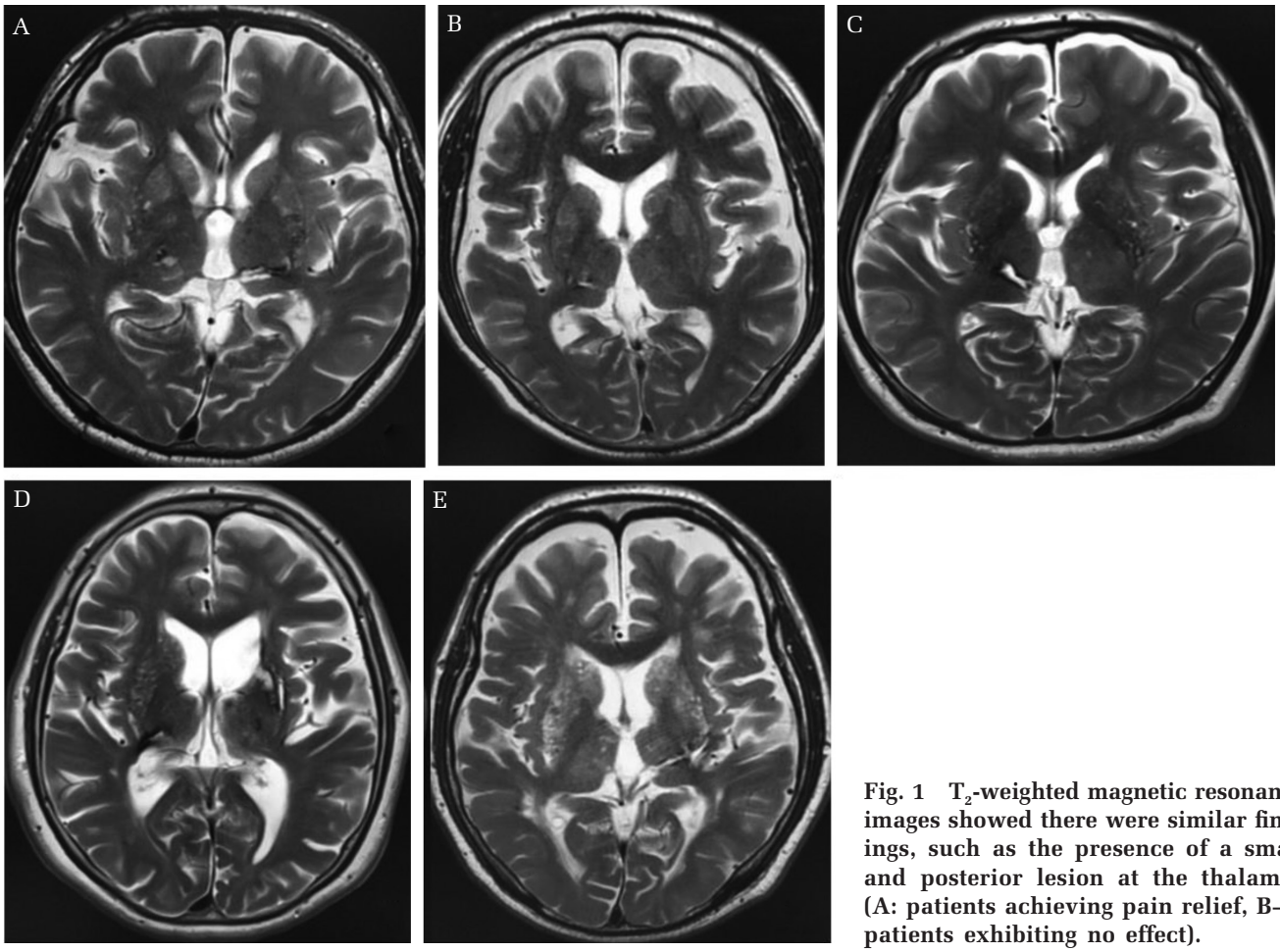

Fig. 1 T_2-weighted magnetic resonance images showed there were similar findings, such as the presence of a small and posterior lesion at the thalamus (A: patients achieving pain relief, B–E: patients exhibiting no effect).

Table 4 Results and details that have been reported when using SCS for CPSP

Author	Simpson et al.[19]	Katayama et al.[20]	Aly et al.[17]	Yamamoto et al.[18]	Tanei et al.
Year	1991	2001	2010	2016	This
Number of CPSP	10	45	30	22	18
Achieving pain relief	6	3	7	12	8
Success rates (%)	60.0	6.7	23.3	54.5	44.4
Criteria of pain relief	Divided into four category	PPR ≥60%	PPR ≥30%	PPR ≥30%	PPR ≥30%
Follow-up period (range)	No detail	No detail	28 months (6–62)	24 months	67 months (12–100)
Type of electrode	1c or 2c, 2 or 4-pole plate	4-pole plate	4c	4c or 8c	4c or 8c
Procedure	Laminectomy	Small laminectomy	Puncture	Puncture	Puncture
Dual SCS	No	No	Yes	Yes	Yes
Rate of dual SCS	–	–	No detail	100%	90%

the 2- or 4-pole plates.[19] Study results showed that it was not possible to definitively prove that SCS could successfully treat CPSP, even though six out of the 10 patients were able to achieve some pain relief. In the second study, SCS was performed in 45 patients with CSPS using the 4-pole plate electrodes, with a positive SCS effect defined as providing more than 60% pain relief. However, the results of the study found that only 7% of the patients (3/45) were able to obtain satisfactory pain relief.[20] It is likely that one of the reasons for the extremely low success rate in this study was due to the fact that the criterion was more severe than that used in other recent studies.[17,18] Furthermore, these studies used old cylinders type electrodes with a low number of contact, or plate types which was necessary to perform laminectomy to insert the devices.

Starting in the 2000's, there has been an improvement in the SCS devices that are being used, with percutaneous insertion of cylinder type electrodes becoming one of the main procedures. By inserting two cylinder type electrodes, this makes it possible to perform dual-lead SCS, which can be easily used to induce paresthesia over the entire painful area.[21] This procedure makes it possible to properly stimulate the dorsal horn without spreading the stimulus to other areas, and elevate the stimulation voltage without inducing an unpleasant paresthesia. All of these behaviors were able to enhance the analgesic effect of SCS.[21] In addition, newer devices such as multiprogrammable, position-adaptive stimulation, magnetic resonance imaging compatibility devices, and a rechargeable SCS system have been recently created and released for general implementation.[10] It has been reported that when using these new devices, it has been possible to successfully treat some of the CPSP patients by SCS.[17,18] Aly et al.[17] were the first to report the potential pain relief by SCS in CPSP patients when using either single- or dual-lead SCS. While they did not describe the exact details on the ratio of single- or dual-lead SCS, they did report that the trial showed there was over a 30% pain reduction in 15 out of 30 CPSP patients, with 10 patients subsequently undergoing IPG implantation. In addition, there were seven (23.3%) out of the 30 patients who did achieve long-term pain relief. Yamamoto et al.[18] examined the efficacy of dual-lead SCS for CPSP when using 4- or 8-contact electrodes. The SCS trial found there was over a 30% pain reduction in 68.1% (15/22) of the patients, with 54.5% (12/22) exhibiting long-term pain reductions. Our current study, which also used dual-lead SCS and used the same criterion over a 30% pain reduction, found the trial success rate was 66.7% (10/18) with 44.4% (8/18) achieving more than 12 months of pain relief. The criterion of test stimulation was used over a 50% pain reduction because of removing placebo effects. These results demonstrate that the use of these new SCS devices can reduce the pain in some CPSP patients.

Predictive factors associated with SCS pain relief for CPSP remain unclear. The univariable analysis in our current study showed that both age and localization of the stroke lesion were associated with pain relief of more than 12 months. However, multivariable analysis using these two factors found no statistical differences, thereby suggesting these two factors might exhibit the same behaviors for the SCS effect. In other words, the effect group was associated with younger ages and non-thalamus stroke,

while the no effect group was associated with older ages and thalamus stroke. Previous reports have also examined the association of age and the effect of SCS.[19] In one study, outcome success rates were compared and even though they were 45.5% for thalamus lesions versus 63.6% for non-thalamus lesions, these differences were not statistically significant.[18] Thus, the low success rate of the trials for the thalamus stroke patients suggests that SCS may not provide pain relief for CPSP after a thalamus stroke. Mean age of four cases of the diminishing SCS effect was 68.0, and three out of four were thalamus stroke patients. Moreover, the diminishing SCS effect that was seen within 3 months in patients with thalamus stroke indicated that the observed effects were probably placebo. Magnetic resonance image results also did not show any apparent differences between the group that achieved pain relief and the no effect patients. However, of interest is that the stroke locations were similar and mainly located within the ventroposterolateral (VPL) of the thalamus. The VPL of the thalamus is a synaptic area of the spinothalamocortical pathway and medial lemniscus thalamocortical pathway.

Thalamic pain syndrome, which was first reported in 1906,[22] occurs after stroke of the VPL of the thalamus.[23,24] It was subsequently determined that the stroke lesion was not only in the thalamus but also involved other sensory pathways that can induce CPSP.[25,26] These sensory pathways consist of the dorsal column, medial lemniscus, thalamus, and the brain cortex. Thalamic pain syndrome is now considered to be a part of the CPSP category. There are several etiologic theories that have been proposed for CPSP such as central imbalance, central disinhibition, and central sensitization.[3,7,25,26] When there is abnormal integration between the normal dorsal-lemniscus pathway and the damaged spinothalamic tract, this could potentially induce abnormal nociception and thermal sensation (central imbalance). The VPL of the thalamus also involves networks of GABAergic neurons. Therefore, strokes occurring in the thalamus can cause central disinhibition, and induce activation of cortical areas that result in pain (central disinhibition). It been reported that a spontaneous bursting pattern of multifocal asynchronous electrical activity has been observed in deafferented thalamic neurons, with the increased synaptic activity leading to spontaneous pain (central sensitization).[27] Furthermore, it has also been shown that neurochemical and excitotoxic inflammatory changes after stroke can influence the neuronal plasticity and excitability.[28]

One of the proposed mechanisms of pain relief by SCS is based on the gate control theory.[29] This theory hypothesizes that there is a pain inhibitory system that functions above the level of the lesion, with electrical stimulation above the lesion driving the inhibitory mechanism. However, the mechanisms of pain relief by SCS for CPSP cannot be explained by the gate control theory, since the electrode stimulation occurs below the level of the stroke lesion. As a result, it is currently believed that SCS induces both inhibition at the spinal segmental level and activation of the supraspinal regions. Previous studies have demonstrated that SCS can induce the release of gamma-aminobutyric acid and acetylcholine, thereby suppressing glutamate release in the dorsal horn, which plays an important role in the reduction of pain.[30–33] Previous studies have used neuroimaging technology to examine the effects of SCS on the supraspinal process.[34–36] Results of these studies demonstrated that SCS induced modulations in the somatosensory and emotional areas of brain, which is referred to as the pain matrix.[37] This pain matrix is comprised of a network of brain structures, which includes the thalamus, anterior cingulate cortex, somatosensory cortices, and other regions.[38] The thalamus is a relay and the center of these pain matrix regions. Therefore, when damage to the VPL of the thalamus occurs, SCS may not be able to induce enough neuromodulation within the brain matrix. Thus, this may be one of the reasons for the low SCS success rates in patients with CPSP due to thalamus versus non-thalamus lesions.

Conclusion

Spinal cord stimulation was performed in 18 patients with CPSP, with 44.4% of the patients exhibiting pain relief of more than 12 months during a 5.5-year follow-up period. Predictive factors for more than 12 months of pain relief included both age and the location of the stroke. Multivariable analysis using these two factors found no statistical differences, thereby possibly indicating that these two factors exhibit the same behaviors for the SCS effect. Overall, our results indicate that SCS may provide pain relief in young and non-thalamus stroke patients with CPSP. Moreover, the thalamus is the relay and center of these pain matrix regions, and which can be induced by SCS caused neuromodulation. In addition, SCS may not be able to induce a large enough effect in patients with CPSP caused by thalamus versus non-thalamus lesions. The limitations of this current study include the retrospective design and the small sample size. Prospective controlled studies with larger sample sizes will need to be undertaken to definitively prove the current findings.

Conflicts of Interest Disclosure

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (e.g. honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (e.g. personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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