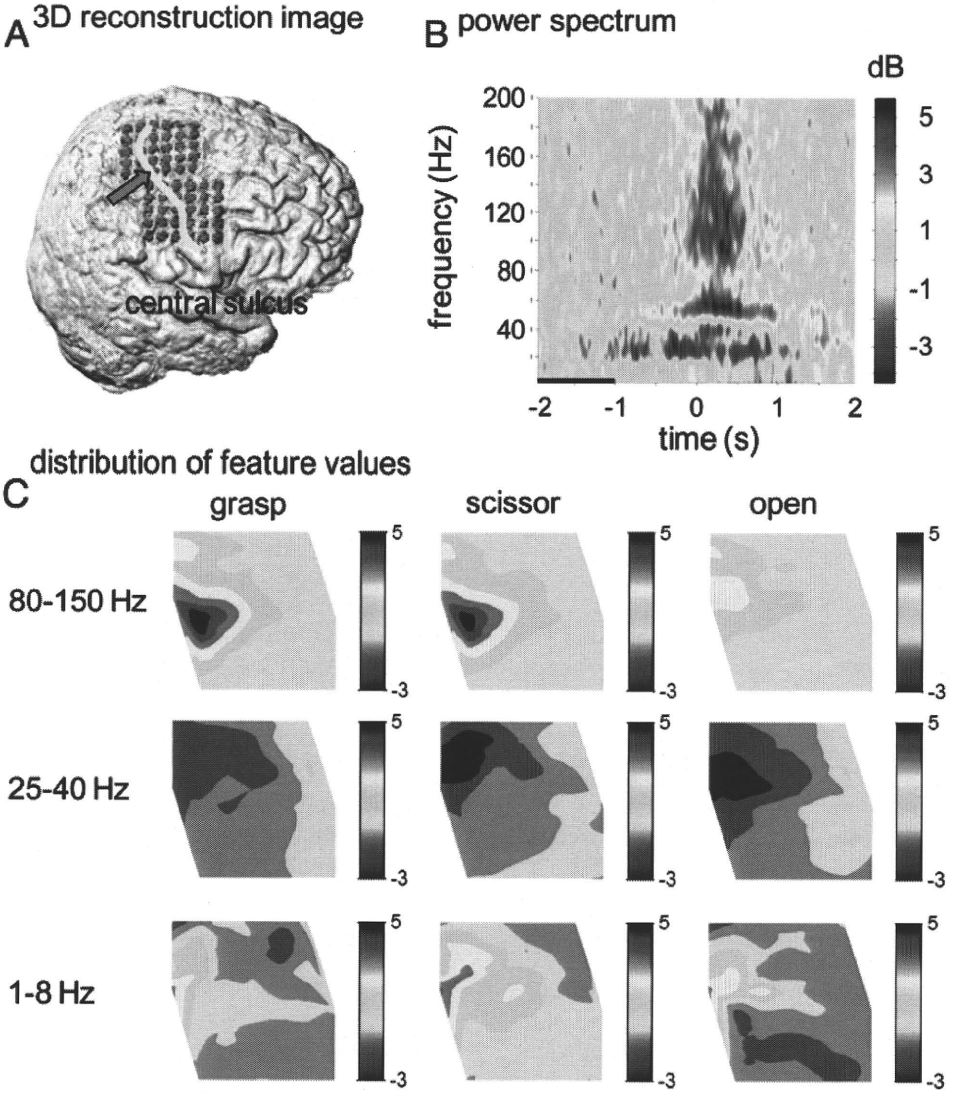

Fig. 2. Power spectrum of the ECoG signals during movement. **A:** Reconstructed MR image of the patient's brain with superimposed *red circles* indicating the position of the 60-channel grid electrodes. The *yellow line* indicates the location of the central sulcus. **B:** A power spectrum time locked to the external cues (Time 0 corresponds to the onset cue). The signals of the primary motor cortex (indicated by the *blue arrow* in **A**) were obtained during the grasping task. The *horizontal black line* shows the normalization period. **C:** Contour map of the mean frequency power bands. For each frequency band and each type of movement, the normalized power at 1 second after the onset of movement was averaged and shown on the location of the electrodes. The alignment of the electrode is the same as in panel **A**.

tween the inferred onset and the actual onset of movement was 0.37 ± 0.29 msec (± SD). The majority of the patient's hand movements were detected before the actual onset of movement (Fig. 5 left). However, the actual onset of movement of the prosthetic hand was delayed from the inferred onset timing due to the processing time (Video 1).

Video 1. A prosthetic hand (with a white glove) mimicking the patient's hand movements. The *markers* on the patient's arm were not used in the present study. Click here to view with Windows Media Player. Click here to view with Quicktime.

At the detected time, the type of movement was correctly decoded with an accuracy of 69.2%. The patient's hand movements inferred by the 2 decoders were performed by a prosthetic hand in real time (Fig. 5 right). Notably, the patient was not trained to control the prosthetic hand. The prosthetic hand was successfully controlled to faithfully mimic the patient's hand movements using only the ECoG signals without any external cues.

Discussion

We have demonstrated that a BMI system using ECoG signals can accurately reproduce a patient's hand movements without training the patient. The system learned the features of the ECoG signals, while the post-stroke patient moved his hand naturally following sound cues. The real-time decoding of ECoG signals was then successfully performed for movements without any external cues. This is the first report describing the control of a prosthetic hand in real-time using a BMI system with ECoG signals. These successful results with a post-

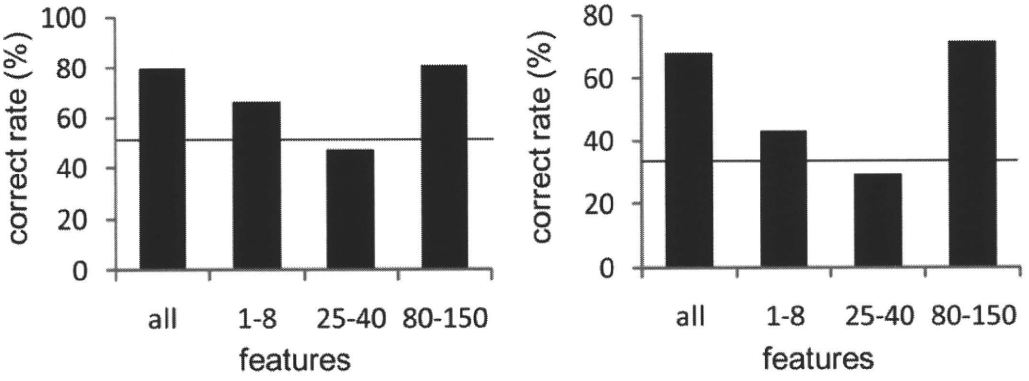

Fig. 3. Classification accuracy of the calibration period. The classification accuracy of the movement state **(left)** and the movement type **(right)** in the calibration period. The accuracy of the 3 frequency bands *(all)* and each single frequency band (1–8, 25–40, and 80–150 Hz) were compared. The *horizontal lines* show the chance level for each classification.

stroke patient indicate the feasibility of the clinical use of ECoG-based BMI.

Control of Prosthetic Hand by Classifying Simple Movements

Although the movement tasks performed in this study were simple compared with those in previous studies,[16,26] the success of our approach suggests a new way to restore the motor function of paralyzed patients. The combination of simple movements generated by the prosthetic hand is useful for activities of daily living.[32] For example, by classifying some simple hand movements with EMG signals, an amputee was able to use a prosthetic hand to improve her quality of life. This method of prosthetic control with simple movements may also be useful for controlling the prosthetic hand with ECoG signals. In addition, it has been shown that most variance in human hand postures can be accounted for by a small number of combined joint movements.[23] This means that, by combining some basic movements, a prosthetic hand could emulate most of the natural postures of a human hand. The control of a prosthetic device, by classifying some simple movements, with ECoG signals will enable a prosthetic hand to be a practical and useful device in a patient's day-to-day life.

Furthermore, ECoG signals have the potential to be decoded to infer more sophisticated movements such as playing the piano. The ECoG signals of epilepsy patients have been used to decode the movements of individual fingers.[16] Our method of controlling the prosthetic hand may be improved by using ECoG signals obtained in patients without motor dysfunction. In addition, the implantation of a high-density electrode array in the central sulcus may increase the information derived from ECoG signals. It is necessary to improve ECoG-based BMIs not only to adjust the control of a prosthetic device for activities of daily living but also to improve the ability to decode human motor representations.

Prosthetic Control by Paralyzed Patients

The clinical candidates for the BMI system are patients without muscle control of their limbs. Therefore, our method should be applicable in patients with complete paralysis. Previously, we showed that ECoG signals could be neurally decoded in patients with monoplegia.[31] Electrocorticography signals from the sensorimotor cortex in patients with brachial plexus avulsion were successfully decoded when the patients only intended or attempted to move their completely paralyzed upper limbs. The intention of movement was inferred accurately by a decoder

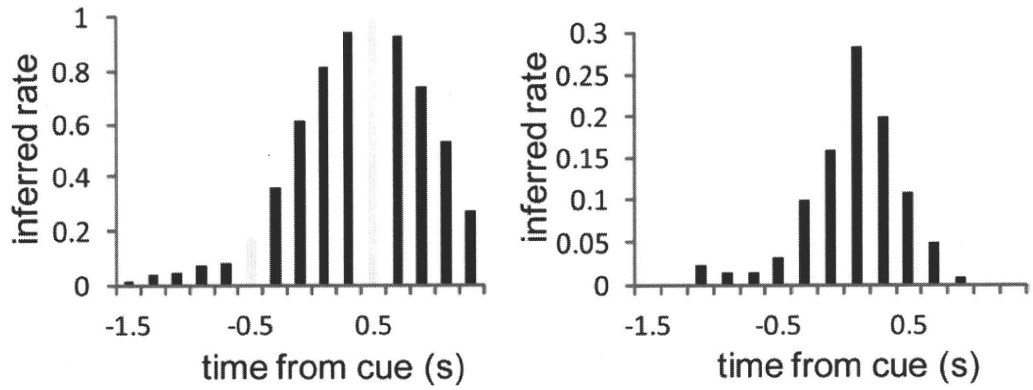

Fig. 4. Left: Onset timing inferred by Decoder 1 for the calibration period. The rate of M inferred by Decoder 1 using the 1-second ECoG signals sliding by 200 msec from –2 to 2 seconds. The horizontal axis shows the middle time of the 1-s ECoG signal (Time 0 corresponds to the onset cue). The *gray bars* correspond to the training data sets of Decoder 1. **Right:** The rate of onset inferred by Decoder 1.

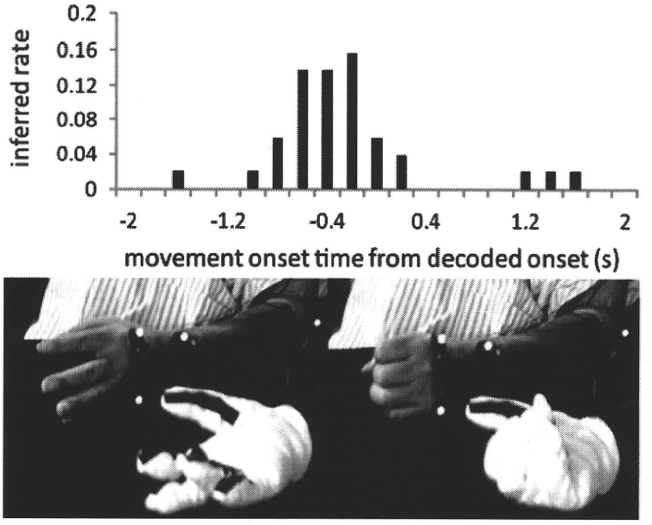

FIG. 5. Real-time decoding and prosthetic hand control with ECoG. **A:** The distribution of the actual movement onset timing from the nearest inferred onset timing by Decoder 1 (free-run period). **B:** Representative photographs of the prosthetic hand (with a white glove) controlled by the poststroke patient's ECoG signals in real time. A prosthetic hand (with a white glove) mimicked the patient's hand movements. The *markers* on the patient's arm were not used in the present study.

trained by the same method used in the present study. By using simple and common movements that can be easily planned by patients, our method may be applicable to a large number of paralyzed patients as a clinically beneficial device to restore their motor functions.

Usefulness of ECoG Signals From the Gamma Band Power

Decoding analysis of the ECoG signals revealed that the gamma band power was the most informative in inferring the state and type of hand movement among the 3 frequency bands. This result was consistent with previous studies in which human movements were inferred using ECoGs.[18,21] Moreover, the power increase of the gamma band correlates with the firing activities of neurons representing neural information.[19,20] Thus, the information contained within the gamma band facilitates the use of ECoG signals in a clinically applicable BMI system.

Among the currently available signal platforms for BMI, intracortical recordings have been shown to provide the largest amount of information to decode movements by using the firing activities of neurons.[24,26] However, this method is associated with difficulties in maintaining stable long-term signals and substantial technical difficulties in recording the signals. Therefore, clinical application of these signals is impeded.[13] Electrocorticography signals are superior to intracortical signals with respect to stability and durability, as demonstrated in monkeys over a 1-year period.[4] On the other hand, with noninvasive signal platforms, such as EEG and MEG, it is difficult to record the gamma band power on a trial-by-trial basis.[27] With ECoG, the gamma band power is consistently available to infer movements on a trial-by-trial basis and may be recorded for a much longer time than intracortical recordings. Therefore, although ECoG is an invasive recording technique, it provides a promising signal that could be used for a BMI in the clinical setting.

Conclusions

The real-time decoding of the ECoG signal using the gamma band power was applied successfully to allow a paralyzed patient to control a prosthetic hand. This success may lead to the development of a clinically feasible BMI system that uses the safe and stable ECoG signals. Our method of using the combination of simple movements paves the way for the restoration of motor function in paralyzed patients using a prosthetic arm controlled by a BMI through ECoG signals.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Hirata, Yanagisawa, Kamitani. Acquisition of data: Hirata, Yanagisawa, Goto, Fukuma. Analysis and interpretation of data: Hirata, Yanagisawa, Kamitani. Drafting the article: Yanagisawa. Critically revising the article: Hirata. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Yanagisawa. Administrative/technical/material support: Hirata, Saitoh, Goto, Kishima, Fukuma, Yokoi, Kamitani, Yoshimine. Study supervision: Hirata, Kamitani, Yoshimine.

Appendix

Construction of the Decoders

The decoder is a mathematical algorithm used to calculate a linearly weighted sum of the features $x = (x_1, x_2, \cdots, x_N)$ plus a bias for each class of movement ("linear detector function," $g_{class}(x)$). In the equation, x_i corresponds to the i-th feature of N features, $w_{i,class}$ is the weight of the i-th feature, and $w_{0,class}$ is the bias. Here, each feature corresponds to a certain frequency band power for each electrode. That is, 3 (frequency bands) × 60 (electrodes) = 180 features that were used for this calculation. The weights $w_{0,class}$ and $w_{i,class}$ were determined for each class of movement such as grasping, opening, and scissor-shape hands.

$$g_{class}(x) = w_{0,class} + \sum_{j=1}^{N} w_{i,class} \times x_i$$

The class with the maximum value of $g_{class}(x)$ was chosen as the predicted movement class.[11,31] In the case of Decoder 1, the class corresponds to 1 of 2 states: R or M. For Decoder 2, the class corresponds to 1 of 3 types of movement: grasping, opening, and scissor-shape hand movements. The selected class indicated the predicted movement state or movement type.

Individual weights and biases for each class were determined using the linear SVM applied to a training data set.[25] First, the SVM algorithm was applied to each pair of class. The discriminant function, $g_{i,j}(x)$ for the discrimination of Class i and j, is expressed by a weighted sum of the features plus the bias. Using a training data set, a linear SVM finds the optimal weight and bias for the discriminant function. The pairwise discriminant functions comparing Class i and the other classes were simply added to yield the linear detector function:

$$g_i(x) = \sum_{m \neq i} g_{i,m}(x)$$

The SVM algorithm was implemented using Matlab 2007b.

Fivefold Cross-Validation

To test the generalization of the decoders, we used 5-fold

cross-validation as a performance measure.[2,3] We randomly divided the trials into 5 blocks, using 4 for training and 1 for testing. We then used all of the training data to train the classifier and evaluated its performance on the test data. This routine was repeated 5 times, and the averaged correct percentage over all runs is presented as a measure of decoder performance.

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Supplemental online information:

Video: http://mfile.akamai.com/21490/wmv/digitalwbc.download.akamai.com/21492/wm.digitalsource-na-regional/jns10-1421.asx (Media Player)

http://mfile.akamai.com/21488/mov/digitalwbc.download.akamai.com/21492/qt.digitalsource-global/jns10-1421.mov (Quicktime)

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LETTER TO THE EDITOR

Importance of distinction between paroxysmal and continuous patterns of pain during evaluation of pain after brachial plexus injury

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We read with great interest the manuscript of Bonilla et al. entitled "Pain and brachial plexus lesions: evaluation of initial outcomes after reconstructive microsurgery and validation of a new pain severity scale" [3]. The authors described a new pain scoring scale to quantify pain after brachial plexus injuries and used it to assess patients' pain before and after reconstructive surgery. Within this scale, [3] the authors integrated pain intensity scale (measured on a scale ranging from 0 to 10), with other parameters like the disability in daily activities and sleep, pain frequency, use of pain medication, and the number of zones affected by pain.

We agree with the authors that the use of such a multi-dimensional pain scale would be useful as a standard outcome measure across studies for BPA pain that would greatly enhance the comparability, validity, and clinical applicability of these studies. Whereas most of the available reports used pain intensity scales, such as the visual analogue scale as the sole outcome measure, the new pain scale integrated factors beyond changes in pain intensity which may be more objective and of more relevance to the patient outcome.

One limitation of the above-mentioned pain scale is that it did not distinguish between the different patterns of BPA pain. It is well known that BPA pain has two patterns which are quite distinct from each other in terms of frequency and pain quality [5, 6]. Continuous background pain is usually described as burning, throbbing, and/or aching sensations and continues for a long duration, whereas paroxysmal pain is usually described as "electrical shock" or "shooting" paroxysms and usually lasts only for a few seconds [5, 6]. Although the authors included pain frequency [3], described as no pain to continuous pain, in their pain scale, this may not be sufficient to allow distinction between the two types of pain. Instead, we suggest that pain character (burning vs shooting) be also included during evaluation [1, 4]. Each type of pain should be quantified separately using visual analogue scale [1, 4]. Separate rating for the two patterns of pain will be particularly useful in evaluating the outcome of neurosurgical procedures for BPA pain [1, 6], thereby allowing clinicians to study the differential effects of the procedures on pain. Sindou et al. reported that DREZotomy was more effective for paroxysmal than continuous pain [6]. They explained the differential effects of DREZotomy based on the distinct pain origin for each type of pain [6]. Paroxysmal pain is said to originate from hyperactive neurons in the dorsal horn, whereas continuous pain extend beyond the dorsal horn up to the thalamus [6]. Also recently, our group reported that electrical motor cortex stimulation was more effective for continuous than paroxysmal pain [1]. Therefore, it can be said that pain classification is important to appropriately select patients

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for treatment and to better understand the underlying mechanisms of pain as well [1, 4]. Finally, such distinction goes in line with several previous reports which have emphathized that classifying neuropathic pain, according to their different components, will help to develop a mechanism-based treatment [2].

Conflicts of interest None.

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Differential Efficacy of Electric Motor Cortex Stimulation and Lesioning of the Dorsal Root Entry Zone for Continuous vs Paroxysmal Pain After Brachial Plexus Avulsion

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BACKGROUND: Pain after traumatic brachial plexus avulsion (BPA) has 2 distinct patterns: continuous burning pain and paroxysmal shooting pain. Lesioning of the dorsal root entry zone (DREZotomy) is more effective for paroxysmal than continuous pain. It is unknown, however, whether electric motor cortex stimulation (EMCS) has a differential effect on continuous vs paroxysmal BPA pain.

OBJECTIVE: To analyze the differential effect of EMCS and DREZotomy on continuous vs paroxysmal BPA pain in a series of 15 patients.

METHODS: Fifteen patients with intractable BPA pain underwent DREZotomy alone (n = 7), EMCS alone (n = 4), or both procedures (n = 4). Pain intensity was evaluated with the Visual Analog Scale, and separate ratings were recorded for paroxysmal and continuous pain. Pain relief was categorized as excellent (> 75% pain relief), good (50%-75%), or poor (< 50%). Favorable outcome was defined as good or better pain relief.

RESULTS: Eight patients had EMCS; 7 were followed up for an average of 47 months. Of those 7 patients, 3 (42%) with continuous pain had favorable outcomes compared with no patients with paroxysmal pain. Eleven patients had DREZotomy; 10 were followed up for an average of 31 months. Of those 10 patients, 7 (70%) with paroxysmal pain had favorable outcomes compared with 2 (20%) with continuous pain.

CONCLUSION: EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain. It may be prudent to use EMCS for residual continuous pain after DREZotomy.

KEY WORDS: Brachial plexus avulsion pain, Continuous pain, Differential efficacy, DREZotomy, Motor cortex stimulation, Paroxysmal pain

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Deafferentation pain is a major disabling symptom after traumatic brachial plexus avulsion (BPA).[1] Of patients with BPA, as many as 90% complain of significant early pain, but only 25% continue to experience severe pain 4 years after injury.[1] Post-BPA pain is known to be almost constantly unbearable and resistant to all classes of analgesic drugs.[2]

ABBREVIATIONS: BPA, brachial plexus avulsion; **CS,** central sulcus; **DREZotomy,** lesioning of the dorsal root entry zone; **EMCS,** electric motor cortex stimulation; **VAS,** Visual Analog Scale

Typically, post-BPA pain has 2 distinct types: continuous background pain described as burning, throbbing, and/or aching sensations and electric shooting paroxysms lasting a few seconds to minutes.[1,2] These 2 distinct types of pain appear to be the clinical expression of 2 different pain generators. Paroxysmal pain is thought to originate from hyperactive neurons in the dorsal horn, whereas continuous pain is thought to originate from supraspinal structures, particularly the thalamus.[2-4]

Since the early work of Sindou et al[5] and Nashold et al[6] in the 1970s, lesioning of the dorsal root entry zone (DREZotomy) has been

the preferred procedure for treatment of intractable BPA pain. DREZotomy is designed to destroy hyperactive neurons in the substantia gelatinosa either by microsurgical incision and bipolar coagulation[5] or by thermocoagulation.[6] The reported pain relief rate immediately after DREZotomy is 75% to 98%, but sustained benefit is observed in only two-thirds of patients after 2 years.[2,7] The major complications of the DREZotomy are weakness in the ipsilateral leg and sensory disturbances, which are seen in 5% to 10% of patients.[7,8]

During the past 2 decades, electric motor cortex stimulation (EMCS) has been used to treat deafferentation pain, particularly central post-stroke pain and trigeminal neuropathic pain.[9-11] Recently, several groups, including ours, used EMCS as a "last resort" treatment for patients with BPA pain who failed or refused DREZotomy.[12-16] In these small studies, EMCS yielded a moderate success rate of 40% to 50%.[12-16] A major limitation for the use of EMCS for BPA pain remains the lack of reliable predictive factors for success, which is particularly important considering the modest success rate of EMCS for BPA and the high cost of treatment.[9-11]

Sindou et al[2] first reported that DREZotomy has a differential effect on the 2 patterns of BPA pain by showing that DREZotomy was more effective for paroxysmal than continuous pain. Conversely, none of the previous EMCS studies analyzed the differential effect of EMCS on continuous vs paroxysmal BPA pain.[12-16] Such a differential effect may be important with regard to selection of treatment for patients. We report our observations in 15 patients with BPA pain who underwent EMCS or DREZotomy and our analysis of the differential effect of EMCS and DREZotomy on continuous vs paroxysmal BPA pain.

PATIENTS AND METHODS

Patient Population

Between January 1997 and January 2010, 15 consecutive patients with intractable pain after BPA were referred to our institute and underwent a total of 19 procedures: DREZotomy alone (n = 7), EMCS alone (n = 4), or both procedures (n = 4). Two patients had EMCS after failed DREZotomy, whereas 2 patients had DREZotomy after failed EMCS. All patients were men. The mean age was 47 years (range, 31-72 years) for DREZotomy patients and 51 years (range, 30-67 years) for EMCS patients. The mean duration of pain was 12.8 years (range, 2-35 years) before DREZotomy and 10 years (range, 0.8-28 years) before EMCS. Injuries were sustained in motorcycle accident (n =13), after a fall from a height (n =1), and by a falling tree (n =1). In the majority of patients (n = 9), pain appeared within 1 month of injury; the longest interval between injury and onset of pain was 2 years. All patients had sensory and motor deficits of varying degrees (Table 1).

Patient Selection

Most patients showed pseudomeningocele on CT myelography. In all patients, pain was severe enough to interfere with normal daily activities. Pain was unresponsive to a wide variety of medications, including tricyclic antidepressants, anticonvulsants, and narcotic analgesics, for at least 12 months.

TABLE 1. Patient Clinical Characteristics[a]

Patient	Procedure	Age y, Sex	Level of Injury	Cause of Injury	Side	Pain Duration, y	Pain Onset	Pain Pattern	Pain Quality	Global VAS	Previous Treatments
1	DREZ	40/M	C6-C8	Motorcycle	R	18	Immediate[b]	Con + Paroxy	B + Elec	8	Medicine
2	DREZ	72/M	C5-C8	Motorcycle	L	12	Immediate	Con + Paroxy	B + Elec	8	Medicine
3	DREZ	35/M	C6-T1	Motorcycle	L	7	3 mo	Con + Paroxy	B + Elec	9	SCS
4	DREZ	43/M	C8-T1	Motorcycle	R	23	Immediate	Con + Paroxy	Squeezing + Elec	8	Medicine
5	DREZ	52/M	C6-T1	Motorcycle	R	35	Immediate	Con + Paroxy	B+ Elec	7	Medicine
6	DREZ	47/M	C5-T1	Motorcycle	L	2	Immediate	Con + Paroxy	B+ Elec	9	Medicine
7	DREZ	35/M	C5-C8	Motorcycle	R	18	1 y	Con + Paroxy	B + Elec	10	Medicine
8	EMCS	64/M	C7-T1	Motorcycle	L	28	NA	Con	Cramping	8	Medicine, SCS
9	EMCS	67/M	C5-T1	Falling tree	R	0.8	Immediate	Con + Paroxy	Cramping + Elec	8	Medicine
10	EMCS	55/M	C5-C7	Motorcycle	L	2.5	Immediate	Con	Paresthesia	8	Medicine, SCS
11	EMCS	30/M	C6-T1	Motorcycle	L	23	1.5 y	Con + Paroxy	B + Elec	7	Medicine
12	DREZ + EMCS	56/M	C5-T1	Fall from a height	L	4.3	Immediate	Con + Paroxy	Throb + Elec	9	Medicine, SCS, DBS
13	EMCS + DREZ	59/M	C6-T1	Motorcycle	L	10.2	2 y	Con + Paroxy	B + Elec	9	Medicine, DBS
14	DREZ + EMCS	31/M	C7-T1	Motorcycle	L	5.9	NA	Con + Paroxy	B + Elec	7	Medicine, rTMS, SCS
15	EMCS + DREZ	49/M	C7-T1	Motorcycle	L	6	Immediate	Con + Paroxy	B + stabbing	3	Medicine, rTMS

[a]B, burning; Con, continuous; DBS, deep brain stimulation; DREZ, dorsal root entry zone lesioning; Elec, electric shooting-like; EMCS, electric motor cortex stimulation; Paroxy, paroxysmal; rTMS, repetitive transcranial magnetic stimulation; SCS, spinal cord stimulation; VAS, Visual Analog Scale.
[b]Within 1 month of injury; throb, throbbing.

We typically recommend DREZotomy as a primary option for intractable BPA and reserve EMCS for intractable residual pain after DREZotomy. However, in the present study, some patients declined DREZotomy and preferred EMCS as a first choice for fear of DREZotomy-related complications such as leg weakness.

Previous Treatment Trials

Six patients (40%) had previous surgical procedures for pain treatment without adequate relief. Four patients had undergone spinal cord stimulation, 1 had deep brain stimulation, and 1 had both procedures. Two patients had undergone repetitive transcranial magnetic stimulation preoperatively to predict the efficacy of permanent EMCS.[14]

Pain Characteristics

Thirteen patients (86%) suffered from both continuous and paroxysmal pain, whereas 2 patients (14%) had isolated continuous pain. Ten patients described the quality of continuous pain as burning, 2 as cramping, 1 as throbbing, 1 as squeezing, and 1 as paresthesia. Twelve patients described the quality of paroxysmal pain as electric, whereas 1 patient described it as stabbing. The frequency of paroxysmal pain was available in 10 patients. Three patients had paroxysms at a rate of 10 to 12 per day, 1 at 2 to 3 per day, 4 at 3 to 5 per hour, 1 at 1 per hour, and 1 at 3 per minute. In most patients, pain predominated in the distal portion of the upper limb, particularly the hand. Median Visual Analog Scale (VAS) for pain was 8 of 10 (range, 3-10; Table 1).

Evaluation of Pain Relief

We distinguished between continuous and paroxysmal pain by their distinct quality and duration (please see above). Using VAS, we recorded separate ratings of pain intensity for each type of pain ranging from 0 (no pain) to 10 (worst possible pain).[17] VAS was evaluated before surgery, immediately after surgery, and at follow-up visits every 6 months.[14] The degree of pain relief was categorized as excellent for VAS reduction $> 75\%$, good for VAS reduction of 50% to 75%, and poor for VAS reduction $< 50\%$. A favorable outcome was defined as good or better pain relief.[2]

Surgical Procedure

EMCS

Eight patients were treated with EMCS alone or in combination with DREZotomy (Table 1). Trial electrodes were implanted in the subdural space over the precentral gyrus in all patients and additionally within central sulcus (CS) in 4 patients. We restricted implantation within CS to patients with severe persistent motor weaknesses, who therefore had low potential for further deterioration.

The location of the CS was identified by its characteristic omega shape on magnetic resonance surface images. Under general anesthesia, a craniotomy of a 5- to 6-cm area was performed over the sensorimotor cortex corresponding to the upper extremity. A 20-grid electrode (4-5 array, 0.3-cm electrode diameter, 0.7-cm separation; Unique Medical Co, Tokyo, Japan) was placed subdurally. The location of the CS was then confirmed by phase reversal of somatosensory evoked potentials. Occasionally, somatosensory evoked potentials could not be obtained because of complete deafferentation. In that case, we relied solely on CS anatomic localization by magnetic resonance imaging.

In case of CS implantation, the arachnoid membrane of the CS was microsurgically dissected, and the vessels within that sulcus were freed to expose the hidden lateral walls of precentral and postcentral gyri. One or two 4-plate electrodes were then additionally implanted within the CS[14] (0.3-cm electrode diameter, 0.7-cm separation; Unique Medical Co, or Resume; Medtronic, Inc, Minneapolis, Minnesota).

After implantation of test electrodes, electrical stimuli were delivered to various parts of the grid electrode and the 4-plate electrode aiming to identify the best location for pain relief. One or 2 weeks later, a second surgery was performed under general anesthesia. The test electrodes were replaced by a Resume electrode, and an implantable pulse generator (ITREL III; Medtronic, Inc.) was then placed subcutaneously in the chest or abdomen.

The stimulation parameters used were an amplitude of 0.9 to 5 V, frequency of 25 to 50 Hz, and pulse width of 210-350 microseconds with bipolar configuration. Chronic stimulation was applied continuously for 15 to 30 minutes on each occasion 3 to 6 times a day.[14]

DREZotomy

DREZotomy was performed in 11 patients (Table 1) according to the Nahold et al[6] radiofrequency thermocoagulation technique. The lesioning electrode was introduced into the intermediolateral sulcus at the site of rootlet avulsion for a depth of 2 mm and angled 25° to 30° in the sagittal plane. A series of radiofrequency coagulation lesions were made along the longitudinal extent of the intermediolateral sulcus, including 1 level above and 1 level below the injured segments. The lesions are made at intervals of 1 mm at 70°C for 30 seconds (Model RFG-3C Graphics RF Lesion Generator, Radionics, Burlington, Massachusetts). Thermocoagulation was performed under monitoring of somatosensory evoked potentials and motor evoked potentials.

Statistical Analysis

We compared the percent VAS reduction of continuous and paroxysmal pain for EMCS using the 2-sample t test and for DREZotomy using the paired t test. A value of $P < .05$ was considered statistically significant.

Ethical Considerations

Written informed consent was given by each patient before the procedure. Approval was obtained from the local Ethics Review Board of Osaka University Hospital for data analysis.

RESULTS

EMCS

Eight patients had trial EMCS: 6 had both paroxysmal and continuous pain, and 2 had isolated continuous pain. Of those 8 patients, 1 patient who had both types of pain declined permanent electrode implantation. The remaining 7 patients underwent permanent EMCS and were followed up long term for an average of 47 months (range, 12-112 months).

The percentage of patients with favorable outcomes ($> 50\%$ VAS reduction) was higher for continuous than paroxysmal pain, both during the trial and with long-term stimulation (Figure 1; Table 2). During the trial, 4 of 8 patients (50%) with continuous pain had favorable outcomes compared with 2 of 6 patients (33%) with paroxysmal pain (Table 2). At the latest follow-up visit, 3 of 7 patients (42%) with continuous pain had favorable outcomes compared with 0 of the 5 patients (0%) with paroxysmal pain

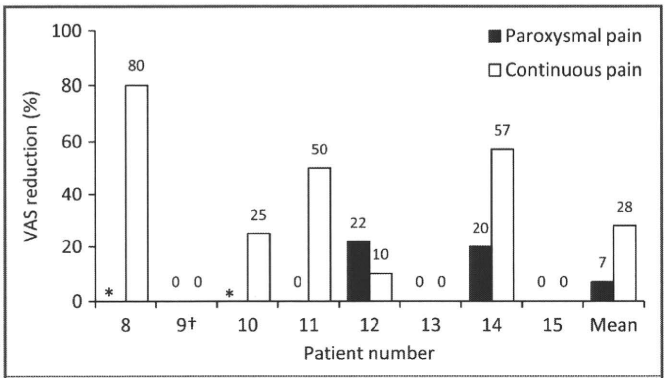

FIGURE 1. *Visual Analog Scale (VAS) reduction percent for paroxysmal and continuous pain in 8 patients who underwent electric motor cortex stimulation (EMCS) and had long-term follow-up. The mean VAS reduction percent tended to be greater for continuous pain than for paroxysmal pain (28% vs 7%;* P = *.11, 2-sample t test). EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. *These 2 patients had isolated continuous pain. †Patient 9 failed trial stimulation and had no permanent implantation.*

(Figure 1), and the mean percent VAS reduction was greater for continuous pain than for paroxysmal pain (28% vs 7%; $P = .11$, 2-sample t test). Of the 2 patients who underwent EMCS after DREZotomy, 1 patient had good pain relief for continuous pain, whereas the other had poor pain relief for both types of pain.

DREZotomy

All 11 patients who underwent DREZotomy suffered from both paroxysmal and continuous pain. One patient had < 6 months of follow-up and therefore was excluded from analysis of long-term results. The remaining 10 patients were followed up long-term for an average of 31 months (range, 12-61 months).

The percentage of patients with favorable outcomes was higher for those with paroxysmal than for those with continuous pain in both initial and long-term results (Figure 2 and Table 2). Immediately after surgery, 10 of 11 patients (91%) with paroxysmal pain had favorable outcomes compared with 8 of 11 patients (72%) with continuous pain (Table 2). At the latest follow-up, 7 of 10 patients (70%) with paroxysmal pain had favorable outcomes compared with 2 of 10 patients (20%) with continuous pain (Figure 2), and the mean percent VAS reduction was greater for paroxysmal pain than continuous pain (63% vs 26%; $P = .01$, paired t test).

Complications

There was no perioperative mortality for either procedure.

EMCS

One patient (Patient 13; 12%) had local infection 9 months after implantation. This diabetic patient presented with a deep wound infection and dehiscence but no †meningeal irritation

TABLE 2. Results of 15 Patients With Electrical Motor Cortex Stimulation or Dorsal Root Entry Zone Lesioning for Brachial Plexus Avulsion Pain[a]

Patient	Age, y/Sex	Pain Pattern	Procedure	VAS Reduction, %				Follow-up, mo	Complications or Comments
				Paroxysmal Pain		Continuous Pain			
	Initial			Long-term	Initial	Long-term			
1	40/M	Con + Paroxy	DREZ	100	100	0	33	61	No
2	72/M	Con + Paroxy	DREZ	88	57	66	0	28	No
3	35/M	Con + Paroxy	DREZ	100	66	80	0	15	No
4	43/M	Con + Paroxy	DREZ	100	0	0	0	24	No
5	52/M	Con + Paroxy	DREZ	100	100	100	100	17	No
6	47/M	Con + Paroxy	DREZ	88	100	86	14	12	Sensory disturbances and transient leg weakness
7	35/M	Con + Paroxy	DREZ	100	100	100	100	9	Sensory disturbances
8	64/M	Con	EMCS	NA	NA	90	80	36	Death after 36 mo (ICH)
9	67/M	Con + Paroxy	EMCS	0	0	25	0	0	No permanent implantation
10	55/M	Con	EMCS	NA	NA	25	25	76	Removal after 76 mo
11	30/M	Con +Paroxy	EMCS	88	0	84	50	50	No
12	56/M	Con + Paroxy	DREZ	0	0	0	0	24	No
			EMCS	56	22	76	10	112	No
13	59/M	Con + Paroxy	EMCS	0	0	30	0	9	Removed after 9 mo owing to infection
			DREZ	100	100	75	14	53	No
14	31/M	Con + Paroxy	DREZ	100	11	57	0	60	No
			EMCS	33	20	71	57	19	No
15	49/M	Con + Paroxy	EMCS	0	0	33	0	24	No
			DREZ	100	NA	100	NA	6	Follow-up < 6 mo

[a]Con, continuous; DREZ, dorsal root entry zone lesioning; ICH, intracerebral hematoma; EMCS, electrical motor cortex stimulation; Paroxy, paroxysmal; VAS, Visual Analog Scale.

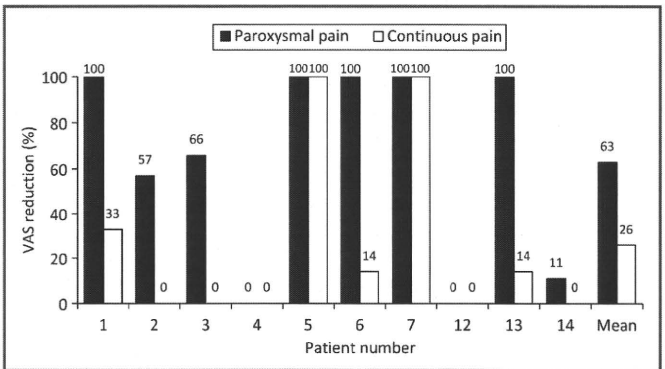

FIGURE 2. *Visual Analog Scale (VAS) reduction percent for paroxysmal and continuous pain in 10 patients who underwent lesioning of the dorsal root entry zone (DREZotomy) and had long-term follow-up. The mean percent VAS reduction was greater for paroxysmal pain than continuous pain (63% vs 26%; P = .01; paired t test). DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain.*

signs. The infection was cured after removal of the EMCS device and bone flap and antibiotic therapy. At operation, the infection was limited to the subgaleal space and did not extend to epidural or subdural space. No electrode dislocation, cerebrospinal fluid leak, new neurological deficit, or any other complications were recorded in our patients. One patient died 3 years after implantation of a cause unrelated to the surgical procedure (intracerebral hemorrhage).

DREZotomy

Two patients had postoperative neurological complications (18%). Patient 6 had paresthesia and mild weakness of the ipsilateral leg along with diminished pain sensation in the left hemibody. Both sensory disturbances and weakness improved on further follow-up. Patient 7 showed postoperative diminished sensations in the right hemibody, which improved on later follow-up.

DISCUSSION

DREZotomy has been reported to be more effective for paroxysmal than continuous BPA pain.[2] Conversely, there is no report describing a differential effect of EMCS on these 2 types of BPA pain.[12-16] The main finding of this study is that EMCS also had a differential effect. We found that EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. We also found that DREZotomy was effective for both types of pain but was more effective for paroxysmal pain. With EMCS, 3 of 7 patients with continuous pain (42%) had a long-term favorable outcome, whereas no patients reported improvement of paroxysmal pain. With DREZotomy, 7 of 10 patients with paroxysmal pain (70%) had a long-term favorable outcome compared with 2 of 10 patients (20%) with continuous pain.

Our finding that DREZotomy was more effective for paroxysmal pain than continuous pain is consistent with a previous report.[2] To the best of our knowledge, this is the first study to show that EMCS is effective only for continuous BPA pain.[12-16] Before our investigation, only 10 patients have been reported in the literature to receive EMCS for BPA pain. The overall success rate of EMCS for BPA pain in our study was 42% (3 of 7 patients), which is comparable to the 50% (5 of 10 patients) reported in these previous studies.[12,13,15,16] However, each of these studies evaluated only a single global rating for BPA pain and did not distinguish between continuous and paroxysmal pain.[12-16] Increasingly, the distinction between different patterns of neuropathic pain is thought to be important to better understand the underlying mechanisms for each pattern of pain and to study the differential effects of treatment.[17]

From a practical point of view, the differential effect of DREZotomy and EMCS on the 2 types of BPA pain may be helpful in setting the indication for treatment. The efficacy of DREZotomy for both types of BPA pain makes it the procedure of first choice. On the other hand, EMCS was moderately effective only for continuous pain; therefore, EMCS may be most appropriate for isolated continuous pain or residual continuous pain after DREZotomy. For isolated continuous pain, we had a 50% success rate (1 of 2 patients) after EMCS in our series, which is identical to the 50% success rate (5 of 10 patients) after DREZotomy in the previous report.[2] For residual pain after DREZotomy, EMCS represents one of the few viable therapeutic options.[2,18] Spinal cord stimulation is another option but is associated, in our experience and in that of others, with inconsistent results.[18,19] In our study, some patients preferred EMCS over DREZotomy as a primary option because they wished to avoid the surgical risks associated with DREZotomy such as leg weakness and sensory dysfunction.[7,8] This reflects the most attractive aspects of EMCS, which are its reversible and less invasive nature. Overall, the evidence regarding EMCS for BPA pain is still very limited, long-term follow-up is unavailable, and the cost of treatment is high.

The mechanism by which BPA pain is generated is still not completely understood.[8] Both animal and human studies suggested that neuronal hyperactivity from deafferented dorsal horn neurons is the main generator of BPA pain.[3,20,21] However, neuronal hyperactivity has been also detected in thalamic nuclei, suggesting that supraspinal mechanisms contribute to pain generation.[4] Sindou et al[2] first reported that DREZotomy was more effective for paroxysmal than continuous pain. A possible explanation of this differential effect is that paroxysmal pain originates from hyperactive neurons in the dorsal horn, whereas continuous pain originates from supraspinal structures, particularly the thalamus.[2,3,20,21] Knowing that EMCS is able to modulate the activity of supraspinal structures, particularly the sensory thalamus and cingulate gyrus, may explain its efficacy for continuous pain.[22,23] The failure of EMCS to relieve paroxysmal pain is more difficult to explain. It was reported that EMCS exerts a descending inhibitory effect on the dorsal horn neuronal activity[24]; however, that effect may be interrupted as a result of deafferentiation.[25] It seems that each procedure acted through

a distinct mechanism related to a particular type of pain: DREZotomy eliminated hyperactive neurons responsible for paroxysmal pain, whereas EMCS modulated the activity of supraspinal structures responsible for continuous pain.

Limitations

The main limitations of this study are the small sample size, particularly for subgroup analysis and retrospective design. Although the number of patients is small, it represents the largest population of patients receiving EMCS for BPA in a single center. However, our results are preliminary and should be reproduced in a larger patient population.

In 4 patients who underwent both EMCS and DREZotomy procedures, a residual effect after the first surgery, a "carryover" effect, may be argued. However, such a carryover effect is unlikely to occur after EMCS because its effects are reversible on discontinuation of treatment. Moreover, the negligible pain relief effects of the first procedure (either DREZotomy or EMCS) in those patients (Table 2) argue against such a carryover effect. However, because DREZotomy causes irreversible changes in dorsal horn, a residual effect after DREZotomy cannot be completely ruled out and remains a limitation of the present study.

Despite these limitations, our findings are of interest as the only study to describe a differential effect of EMCS on BPA pain and suggest that treatment and study of BPA pain in the future should carefully distinguish between continuous and paroxysmal pain.

CONCLUSION

We analyzed the differential effect of EMCS and DREZotomy for different types of BPA pain. EMCS was ineffective for paroxysmal pain but moderately effective for continuous pain. DREZotomy was highly effective for paroxysmal pain but moderately effective for continuous pain. It may be prudent to use EMCS for patients who continue to have intractable pain after DREZotomy.

Disclosures

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Brachial plexus injuries are classically considered a homogeneous traumatic entity, and consecutive pain is thought to be a clinical replica of experimental peripheral deafferentation. In fact, the so-called brachial plexus avulsion (BPA) syndrome has some heterogeneous aspects.

BPA is followed by chronic pain in the deafferented area in 60% of the cases on average (30% to 90% according to the published series). Incidence is quite different in relation to location of the disruptive lesion:

< 33% for postganglionic location, ie, distal to the dorsal root ganglion, as opposed to 90% for predominantly preganglionic locations.[1-4]

Classically, pain after BPA appears in a standard clinical manner: a continuous background of pain described as burning, throbbing, and/or aching sensations or pain with electric shooting–like violent paroxysms. These 2 components may coexist with equal intensity; 1 type may predominate over the other; or, rarely, 1 of the 2 may exist in isolation.

In a previous article devoted to outcome after dorsal root entry zone microsurgical lesioning (DREZotomy) for pain resulting from BPA,[5] we suggested that the 2 distinct types of pain be considered the clinical expression of 2 different mechanisms. There are strong arguments that paroxysmal pain arises from deafferented hyperactive neurons in the dorsal horn.[6–10] Continuous pain might rather be in relation to supraspinal generators, particularly at the thalamus, as the consequence of destruction of the neurons at origin of the ascending spinoreticulothalamic pathways.[11]

So, as pointed out by the Japanese team, to study independently the effects of surgery on the 2 components of pain is wise and of practical importance. We have shown that microsurgical DREZotomy, although effective on both components, had better effectiveness on the paroxysmal component. Pain relief was obtained, in all the patients with paroxysms only, in 75% of the patients suffering from both pain components and in 50 % of the patients who had continuous background only ($P = .04$).[5]

Like us, the authors of the present article found a differential effect by the DREZ procedure: 70% of the patients with paroxysmal pain had favorable outcomes compared with 20% with continuous pain. In addition, they carried out motor cortex stimulation and compared the results; 42% with continuous pain had favorable outcomes compared with no patients with paroxysmal pain. Our experience with motor cortex stimulation for pain after BPA is quite similar.

Because the pain after BPA is almost constantly unbearable and is resistant to all classes of analgesic agents (including opioids), anticonvulsants, and antidepressants, neurosurgery is the only recourse. When patients are referred to the neurosurgeon, the majority have already undergone attempts to nerve repair. According to literature and our experience, spinal cord stimulation is not particularly effective, especially when preganglionic lesions predominate. The reason is that most of the fibers targeted by stimulation underwent degeneration up to the brainstem. Lack of corresponding valid fibers in the dorsal column can be ascertained by somatosensory evoked potentials. It has been shown that impairment in central conduction time, ie, between dorsal root ganglion cells and brain: N13 to N20 for upper limb and N22 to P39 for lower limb, is a valuable predictor of failure of SCS.[12] Thalamic deep brain stimulation, although quite logical from an anatomical/physiological point of view, has not been confirmed as effective on pain after BPA. As proposed by the Japanese authors, DREZotomy has to be considered the first option, at least when paroxysmal pain predominates; motor cortex stimulation[13] may be proposed when the continuous pain component persists after completion of DREZ-lesioning surgery.

The authors have to be acknowledged for adding useful insights to pain surgery. This article shows how surgery for neuropathic pain can be effective if the neurosurgical method precisely targets the appropriate anatomical site(s) and accurately corrects the various pathophysiological mechanisms (and therefore components) of the pain.

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脳卒中後疼痛に対する脊髄電気刺激療法

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要　旨

脊髄電気刺激療法（SCS）は末梢性神経障害性疼痛の治療に有効であるが，中枢性疼痛である脳卒中後疼痛に対しての有効性は確立されていない．われわれの施設での30症例の難治性脳卒中後疼痛に対するSCSの経験を述べる．すべての症例にSCS試験刺激を施行し，一旦は抜去して，患者が希望すればSCSを埋め込んだ．疼痛の程度は，疼痛尺度（VAS）とpatient global impression of change（PGIC）で行った．SCS試験刺激では9症例（30%）でgood（50%≦VAS低下），6症例（20%）でfair（30～49%），15症例（50%）でpoor（30%＞）と判定された．10症例が埋め込みを希望し，うち9症例が長期（mean 28カ月，6～62カ月）フォローされ，うち7症例で有意な疼痛軽減が得られた（5症例がgood，2症例がfair）．PGICでは，この7症例中6症例がrank 2（much improved），1症例がrank 3（minimally improved）と判定され，残りの2症例はrank 4（no change），rank 5（minimally worse）と判定された．9症例のVAS中間値は86 mmから45 mmに有意に低下した（p＝0.007）．明らかな合併症はなかった．SCSは，難治性脳卒中後疼痛の一部において，良好な疼痛コントロールを提供することが示され，治療法としての可能性が示唆された．

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はじめに

脳卒中後疼痛は，難治性求心路遮断痛の中でも，特に難治であり，脳卒中の1～8%に発症する[1,2]．脳卒中で障害された脳部位に一致した知覚障害と疼痛が体表面に現れる[3]．一旦，疼痛が生じると長期にわたって日常生活レベルを低下させる[4]．投薬治療としてアミトリプチリン，ガバペンチンが，通常，第一選択だが有効性が高いとはいえない[5]．脳深部刺激療法の有効性はばらつきがあり[6]，大脳一次運動野電気刺激療法（MCS）が約50%に有効であるが，高額医療であり，開頭術を必要とする[7,8]．

一方，SCSはfailed back surgery syndrome（FBSS），CRPS，末梢性虚血性疾患，帯状疱疹後疼痛，脊髄損傷後疼痛に対し，その有効性が報告されているが[9]，脳卒中後疼痛に関してはまとまった報告はない[4]．われわれの施設では，脳卒中後疼痛に対して積極的に脊髄電気刺激の試験刺激を行って，有効な症例には刺激装置の埋め込みまで勧めている．そこで，その有効性について報告したい．

1．症例（Table 1）と方法

大阪大学脳神経外科で，2002年5月から2009年7月までに，87症例の脳卒中後疼痛患

〈Special Article〉 Electrical spinal cord stimulation for chronic pain
Efficacy of spinal cord stimulation on post-stroke pain
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者に対して何らかのニューロモデュレーション治療を施行した（大脳一次運動野電気刺激術：13症例，反復経頭蓋磁気刺激療法：59症例，SCS：30症例，一部の症例はオーバーラップ）．SCS 30症例は男性21症例，女性9症例，平均年齢は64.8±7.4（歳±SD），平均疼痛罹病期間は44.8±35カ月である．脳卒中後疼痛の診断は，i）脳卒中後に疼痛を発症，ii）脳血管障害に伴う知覚障害，iii）知覚障害部位に疼痛がある，iv）侵害性または末梢性神経障害性疼痛などの原因が排除できる，の4項目がそろっていることを条件とした[10]．また，心因性疼痛や認知症のある症例，脳卒中後の肩手症候群は除外した．全症例が6カ月以上にわたる疼痛期間がある．視床出血が9症例，被殻出血12症例，他である（Table 1，Figure 1）．すべての患者が半身の痛みを訴え，一肢から半身，全体まで様々である．Allodyniaが18症例（60%），知覚過敏が11症例（37%）にみられた．軽度の運動障害がある症例が20症例，中等度が3症例であった．

腹臥位で透視を使用して，脊髄硬膜外腔を穿刺して，4極電極（Medtronic社，PISCES-Quad®）を挿入して，通電しながら疼痛部位に電気刺激感がくるように留置し[11]，約2日間試験刺激を行い，パラメータを変えて除痛効果を判定した後，効果の有無に関わらず一旦抜去している．上肢痛の場合はC_{4-7}に留置し，下肢痛の場合はT_{9-12}に留置した．抜去した後，患者の希望があれば，再度，電極を脊髄硬膜外腔に挿入して，コネクターを接続，皮下に埋没して，試験刺激を施行して有効性が認められれば，刺激装置（Medtronic社，ITREL III® またはSYNERGY®）を前胸部か腹部に埋め込んでいる．

疼痛の評価はVAS（visual analogue scale）で行い，除痛効果はexcellent（VASでの痛みの低下率80%以上），good（VASでの痛みの低下率50～79%），fair（VASでの痛みの低下率30～49%），poor（VASでの痛みの低下率30%未満）に分類し，6カ月ごとに評価した．Patient global impression of change（PGIC）を最終フォローアップ時に評価した．Rank 1：very much improved，2：much improved，3：minimally improved，4：no change，5：minimally worse，6：much worse，7：very much worse．Rank 1，2は臨床的に有意な改善と判断した[12]．

試験刺激の時の疼痛低下の程度を2群に分けて解析した．“good”と“fair”を1群にまとめ，“poor”をもう1群とした．臨床因子である年齢，性別，疼痛部位（上肢，下肢），疼痛期間，脳卒中の原因，知覚過敏またはallodyniaの有無，運動障害の程度と試験刺激の時の有効性の2群を検定した．

2．結　果（Table 1）

1）試験刺激

試験刺激では，すべての症例で1個のリードを埋め込んだ（24症例は下肢痛の治療のための胸椎レベル，6例は上肢痛のため頸椎レベル）．テスト刺激で，goodと評価した症例は9症例（30%），fairと評価した症例は6症例（20%），poorと評価した症例が15症例（50%）存在した．VAS中間値は80mmから60mmに有意に低下した（$p<0.001$）．

試験刺激を受けた30症例のうち，20症例は埋め込みを希望せず，10症例が永久埋め込みを希望した．2症例は2個の電極（1個頸椎，1個胸椎）を埋め込みした（No. 24，30）．永久埋め込みした10症例の臨床的な特徴をTable 2にまとめた．

永久埋め込みした10症例のうち，試験刺激で，7症例はgood，2症例はfair，1症例はpoorと判定した．試験刺激でpoorと評価された1症例は永久埋め込みを希望した（No. 2 Table 2）．その患者はVASで25%の除痛効果

Table 1. Patient characteristics and results of trial stimulation

Patient No.	Age (y/sex)	Pain duration (months)	Underlying disease	Painful region treated	Motor weakness	Sensory disturbance		Baseline VAS	VAS after trial	% VAS change	Trial stimulation result	IPG implantation
						Allod	Hyperp					
1	59, M	48	Lt sc inf	Rt LL	Mild	+	−	7	7	0	Poor	−
2	54, F	12	Lt thal hem	Rt UL	Mild	+	+	10	7.5	25	Poor	+
3	59, F	97	Rt put hem	Lt LL	Mild	−	+	8	4	50	Good	+
4	65, M	30	Rt thal hem	Lt LL	−	−	−	9	4	56	Good	+
5	71, M	19	Lt thal hem	Rt UL	Moderate	+	−	10	10	0	Poor	−
6	64, F	68	Lt put hem	Rt LL	Mild	+	−	10	7	30	Fair	+
7	74, F	156	Lt put hem	Rt LL	Mild	−	−	8	8	0	Poor	−
8	75, F	24	Lt thal hem	Rt LL	Mild	−	−	7	3	57	Good	+
9	75, M	24	Rt put hem	Lt LL	−	−	−	10	7	30	Fair	−
10	58, M	60	Lt pontine inf	Rt LL	Mild	+	−	6	3	50	Good	−
11	66, F	32	Rt put hem	Lt LL	Mild	+	−	7	3	57	Good	+
12	67, M	52	Lt thal inf	Rt UL	Mild	+	+	8.5	8.5	0	Poor	−
13	57, M	80	Rt put hem	Lt LL	−	+	+	6	6	0	Poor	−
14	72, M	83	Lt thal hem	Rt LL	Moderate	−	−	8.5	7.5	12	Poor	−
15	65, M	33	Lt thal inf	Rt UL	Mild	−	−	9	6	33	Fair	+
16	48, M	11	Rt put hem	Lt LL	Mild	+	−	8.6	3	65	Good	+
17	69, M	6	Lt thal hem	Rt LL	Mild	+	+	8	8	0	Poor	−
18	66, M	81	Rt put hem	Lt LL	−	−	+	8.5	7	18	Poor	−
19	67, M	14	Brain stem inf	Rt LL	−	+	−	5	5	0	Poor	−
20	61, M	29	Lt pontine inf	Rt UL	Mild	+	−	9	6	33	Fair	−
21	72, M	16	Lt put hem	Rt LL	Mild	+	+	9	9	0	Poor	−
22	76, M	41	Lt thal hem	Rt UL	Moderate	−	−	8.5	2.5	71	Good	−
23	62, F	6	Rt sc hem	Lt LL	Mild	+	+	8	5.6	30	Fair	−
24	51, F	46	Rt put hem	Lt LL & UL	Mild	+	−	7	3	57	Good	+
25	65, F	20	Rt medullary inf	Lt LL	−	+	+	9.5	8.5	10	Poor	−
26	64, M	56	Rt put hem	Lt LL	Mild	+	+	8	8	0	Poor	−
27	56, M	6	Rt thal hem	Lt LL	−	−	−	7.8	5	25	Poor	−
28	74, M	93	Lt thal inf	Rt LL	Mild	−	−	8	5	38	Fair	−
29	62, M	19	Lt put hem	Rt LL	Mild	−	−	7	7	0	Poor	−
30	71, M	82	Rt thal hem	Lt LL	Mild	+	+	6.5	1.5	77	Good	+

Allod : allodynia, Hyperp : hyperpathia, VAS : visual analogue scale, M : male, F : female, Rt : right, Lt : left, put : putaminal, thal : thalamic, hem : hemorrhage, inf : infarction, sc : subcortical, LL : lower limb, UL : upper limb, + : presence, − : absence. median VAS in target regions significantly decreased from 8.0 to 6.0 after trial ($p < 0.001$).

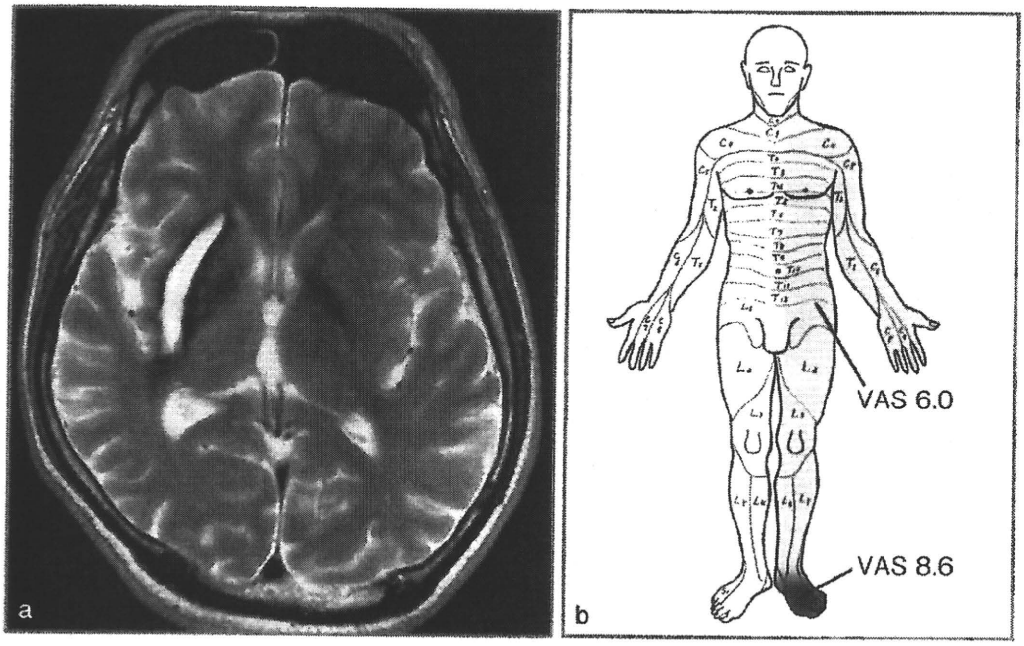

Figure 1. Illustrated case (No. 16)
MRI T2 強調画像では右被殻に陳旧性の脳出血を認める（a）．左半身の疼痛の中では左足の痛みが最も強かったので，足の領域に paresthesia がくるように胸椎レベルに電極を留置した（b）

Table 2. Patients characteristics and long-term follow-up for ten patients with permanent implantation

Patient No.	Age (y/sex)	Pain duration (months)	Underlying disease	Painful region treated	Motor weakness	Sensory disturbance		%VAS reduction during trial	Latest Follow-up		Follow-up (months)
						Allod	Hyperp		% VAS reduction	PGIC	
2	54, F	12	Lt thal hem	Rt UL	Mild	+	+	25	20	5	16
3	59, F	97	Rt put hem	Lt LL	Mild	−	+	50	50	2	62
4	65, M	30	Rt thal hem	Lt LL	−	−	−	56	50	2	60
6	64, F	68	Lt put hem	Rt LL	Mild	+	−	30	30	3	6
8	75, F	24	Lt thal hem	Rt LL	Mild	−	−	57	57	2	41
11	66, F	32	Rt put hem	Lt LL	Mild	+	−	57	57	2	24
15	65, M	33	Lt thal inf	Rt UL	Mild	−	−	33	33	2	25
16	48, M	11	Rt put hem	Lt LL	Mild	+	−	65	19	4	12
24	51, F	46	Rt put hem	Lt LL & UL[a]	Mild	+	−	57	57	2	12
30	71, M	82	Rt thal hem	Lt LL	Mild	+	+	77	ND[b]	ND[b]	ND[b]

[a]This patient had less than 6 N months follow-up at the time of latest follow-up and was therefore excluded from long-term-follow-up analysis.
[b]This patient had two electrodes implanted, but only results for the thoracic electrode are included in statistical analysis.
For PGIC：2 = much improved；4 = no change；5 = minimally worse.
VAS：visual analogue scale, PGIC：patient global impression of change, M：male, F：female, Rt：right, Lt：left, put：putaminal, thal：thalamic, hem：hemorrhage, inf：infarction, LL：lower limb, UL：upper limb, ND：not determined

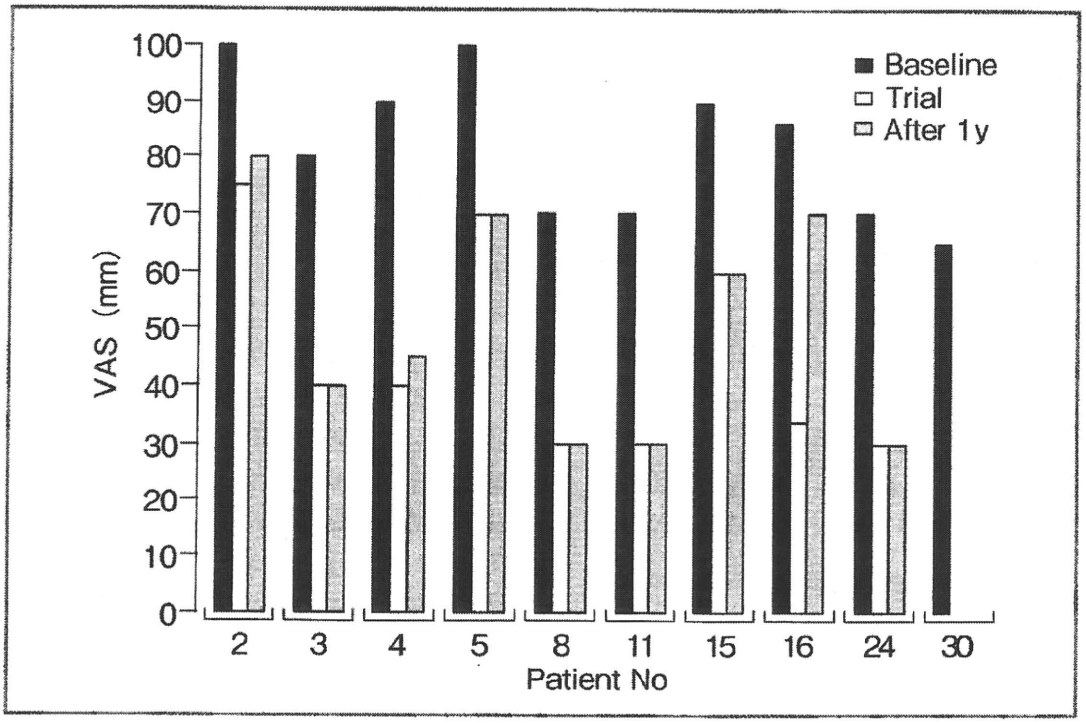

Figure 2. VAS pain scores for ten permanently implanted patients

No. 30 の患者はフォローアップが6カ月に満たないので，長期フォロー成績の解析から除外した．最新のフォローアップにおける VAS の中間値は 8.6 から 4.5 に有意に低下した（p = 0.007）．
Baseline：刺激前の VAS，Trial：試験刺激時の VAS，After 1y：SCS 埋め込み1年後のフォローアップ時の VAS

が得られ，長期効果は定かでないが永久埋め込みを希望した．

2）最新のフォローアップ結果（Figure 2）

最新のフォローアップでは，1症例（No 30）は6カ月にフォローアップが満たないので長期フォロー評価からは除外した．残りの9症例は平均28カ月（12～62カ月）のフォローアップ期間であった．最終フォローアップ時には7症例が VAS で有意な除痛効果（5症例 good，2症例 fair）が得られた．PGIC scale では6症例が rank 2（much improved），1症例が rank 3（minimally improved）であった．7症例全症例が1日2～10回の刺激を使用していた．Poor と評価された2症例のうち，1症例は rank 4（no change），もう1症例は rank 5（minimally worse）であった．9症例の VAS の中間値は 86mm（70～100mm）から 45mm（30～80mm）（p＝0.007）に低下した．9症例の平均 VAS 低下率は 41.5%（19～57%）であった．7症例の長期フォローで良好な除痛が得られている群では，平均 VAS 低下率は 46.5%（30～57%）であった．

Poor と評価した2症例のうち，1症例は試験刺激および初期には，少し除痛効果がみられた（No. 2）．長期フォロー中は，刺激に伴う paresthesia を不快と感じて，除痛効果が得られなかった．もう1人の患者（No. 16）は試験刺激および初期には good と評価されたが，徐々に SCS の効果が消失した．

使用した刺激のパラメーターは 1.5～6.0 V，パルス幅は 210 μsec，周波数は 31 Hz（10～50 Hz）のバイポーラー刺激である．

3）合併症

2症例で電極の位置がわずかに（半椎体以内）ずれたが，治療には支障がなかった．フォローアップ中に1症例（No. 4）がSCSとは無関係な原因で死亡した．

4）試験刺激の除痛効果と臨床的特徴の関係

特に試験刺激の除痛効果と臨床的特徴の間に有意な相関性は見い出せなかった．疼痛部位が知覚過敏であることがpoor群において，goodまたはfair群よりも多い印象があるが，有意差はなかった（$p=0.074$）．

3．考　察

SCSは，これまで脳卒中後疼痛に対しては報告数が少なく，効果がないと考えられてきた[6]．本研究は，薬物抵抗性の脳卒中後疼痛の患者において，SCSが除痛効果を示すことを報告した最初の研究である．試験刺激においては，約半数の患者が有意な除痛効果を示した（**Table 1**）．さらに9症例中7症例の患者で平均28カ月（6～62カ月）のフォローアップ期間中に有意な除痛効果が得られた（**Table 2**）．この7症例中，6症例はrank 2 (much improved)，1症例はrank 3 (minimally improved) とPGIC scaleで評価され，平均のVAS低下は46.5%であった．

過去の報告では，FBSS患者の80%が，試験刺激で50%以上の疼痛減弱が得られるとされている[9]．今回の脳卒中後疼痛に対するSCSでは，50%の患者が30%以上の除痛効果を示し，30%が50%以上の除痛効果を示し，過去のFBSS患者に対する治療効果の報告よりは劣る結果となった．しかし，脳卒中後疼痛は他に治療法が少なく，治療抵抗性で，疼痛が著しいことを考えると，この程度の治療効果でも重要であると考えられる．

われわれの知る限り，過去の2つの報告が脳卒中後疼痛に対するSCS効果を報告している[6]．最初の報告はわれわれの知見に近く，10症例中3症例で，長期有効性が示されているが[13]，2報目の報告は，45症例中3症例のみで60%以上の除痛効果が長期に得られた[14]．われわれの研究では，30%以上の除痛効果を成功閾値としており，30症例中6症例で（平均VAS低下率が51.5%）満足のいく除痛効果と判定された．その6症例はPGIC scaleでmuch improvedを選択した．われわれの知見とKatayamaらの知見[14]は，goodと判定する閾値の違いによるものである．慢性疼痛治療の良好と判定する定義に関するコンセンサスは存在しないが，多くの研究において30%の除痛が有意な臨床的改善として判定されている[12]，50%の除痛効果の定義はやや厳しいとも考えられる．それゆえ，過去の報告では不適切な成功の閾値設定のため，SCSの脳卒中後疼痛に対する有効性を過小評価していたのでないかと考えられる．

薬物抵抗性の脳卒中後疼痛の治療オプションは限られている．MCSは約50%に有効であると報告されている[7]．しかし，MCSは開頭が必要で特殊な施設に限られる．一方，SCS手技は比較的簡単で，低侵襲で，脳神経外科医，整形外科医の脊椎専門医だけでなく，麻酔科医，ペインクリニック医でも施行できる[15]．他の神経刺激手技に比べて，経皮的SCS試験刺激は患者が受け入れやすく，試験刺激が有効と判断されなくても電極は簡単に抜去することができる．われわれの施設では，問題となる合併症を認めていない．

脳卒中後疼痛の疼痛部位の分布は様々であるが，最も多いのは半身全体が痛む様式で，特に手や足の末梢側に強く痛むことが特徴である[16]．疼痛部位全体を刺激のparesthesiaでカバーすることが，SCS治療成功の必要条件であるので，SCSのターゲットとして限局された疼痛部位であることが望ましい[17]．今回の検

討では，被殻出血による足の疼痛が最も多く，内包後脚の一部を含む被殻出血が足に限局するひどい疼痛を起こす傾向がみられた[18]．また，足に強い脳卒中後疼痛がSCSに適していると考えられた．その理由として，頸椎よりも胸椎の方が電極留置後も電極のずれが少ないことが挙げられる[19]．加えて，足の疼痛はMCSの適応としては適しておらず，一次運動野の足の領域が半球間裂に主に存在するため，平板電極で刺激することが困難であるためである[20]．

試験刺激に対する反応性を予測する臨床因子の解析では，疼痛部位が知覚過敏になっている場合，知覚低下例に比べてSCS反応性がよくないという結果が得られた．この知見は過去の報告で，SCSは自発痛よりも誘発痛に効果が少ないという知見を裏付けている[21]．試験刺激の有効性は，永久埋め込み後の大多数で同様に継続した．SCS試験刺激は，永久埋め込み前の有効性判断の試験として，低侵襲で意味のあるものと考えられる．

今回の検討では，症例数が多いとはいえないこととと，後方視的研究であることが問題と考えられる．脳卒中後疼痛の発生頻度は低く，見過ごされていることも多いと考えられ[3]，1つの施設で多数症例を解析することは困難である．もう1つの問題点として，対照群がないことが挙げられる．SCSは刺激感があるので，2重盲験試験でシャム刺激対照を置くことも困難である[22]．未手術群を対照として設定するのも適切とはいえない．対照群がないことより，SCSの有効性の中に疼痛が自然寛快したものが含まれていると考える人もいるかもしれないが，一般に脳卒中後疼痛は長期間持続し，寛快するのは稀である[4]．これらの臨床研究の限界より，難治性脳卒中後疼痛の一部の患者ではSCSが良好な疼痛コントロールを提供するとわれわれは考えている．より強力なエビデンスを得るには，多数症例での前方視的研究が必要であると考えられる．

4．結　論

この研究はSCSが薬物抵抗性の脳卒中後疼痛の一部の患者に除痛コントロールをもたらすことを報告した最初の報告である．脳卒中後疼痛に対するSCSの効果は，成功率も除痛の程度も高いものではなかった．しかし，脳卒中後疼痛は耐えがたく，治療抵抗性であり，他の治療法がないことから，この程度の除痛効果でも重要であると考えられる．今後，前方視的研究を多数症例で行うことで，SCS治療に反応する患者群を選定することが望ましい．

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