

equipment for more than 5 min preoperatively; removal of volatile agents from the equipment; and having a fresh carbon dioxide absorbent in the canister or nonbreathing system.³³ We found three MH patients without exposure to suxamethonium and any volatile anesthetics. It is possible that they might have been accidentally exposed to residual volatile agents in the anesthesia equipment.

Limitations

Several limitations should be acknowledged. The first limitation is related to the use of an administrative claims database. Generally, the recorded diagnoses in such databases are less well validated than those in planned prospective surveys. However, several advantages of the data submission processes in the DPC database, such as physician-dependent diagnosis reporting, requirement of data entry *via* a strict data format, and mandatory submission linked with reimbursement, maximized the accuracy and consistency of reporting. Second, given the anonymous nature of the database, it is not possible to determine whether the same individual has been noted to have MH more than once during multiple admissions. Third, the database does not include information on patients' signs and symptoms or laboratory data; thus, we could not evaluate the validity of MH diagnosis and the severity of each individual MH episode. Underreporting or biased reporting (withholding sensitive cases) could lead to underestimation of MH events. Fourth, although the database included 40% of acute-care inpatients in Japan, participation in the DPC system was voluntary for each hospital, and patient selection was not based on a random sampling method. The database only included data between July and December, and such a time restriction will cause inaccurate estimation of the incidence of several diseases that show seasonal variation. However, to our knowledge, the occurrence of MH is unlikely to show seasonal variation, and this time restriction should have little effect. Finally, it was not possible to perform a multivariate analysis to examine the concurrent effect of multiple factors, including patient characteristics and drugs used, because of the extreme rarity of MH occurrence. Data should be continuously compiled, and further analysis with larger numbers of cases is necessary.

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Case Report

Complex Regional Pain Syndrome Revived by Epileptic Seizure Then Disappeared Soon during Treatment with Regional Intravenous Nerve Blockade: A Case Report

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Received 20 December 2010; Accepted 3 March 2011

Academic Editor: Masahiko Kawaguchi

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We present a case of complex regional pain syndrome (CRPS), in which symptoms, including burning pain and severe allodynia, were alleviated by using a regional intravenous nerve blockade (Bier block) combined with physiotherapy, but reappeared following an epileptic seizure. Symptoms disappeared again following control of epileptic discharges, as revealed by single-photon emission computed tomography (SPECT) and electroencephalography (EEG) results. Although systemic toxicity of a local anesthetic applied by Bier block was suspected as a cause of the first seizure, the patient did not present any other toxic symptoms, and seizures repeatedly occurred after Bier block cessation; the patient was then diagnosed as having temporal symptomatic epilepsy. This case suggests that symptoms of CRPS may be sustained by abnormal brain conditions, and our findings contribute to the understanding of how the central nervous system participates in maintaining pain and allodynia associated with CRPS.

1. Introduction

Complex regional pain syndrome (CRPS) causes extreme pain. Dysfunctions of the peripheral nervous system, including the sensory and sympathetic nervous systems, are typically considered to sustain CRPS. The central nervous system (CNS) has also been reported to play an important role in CRPS emergence and maintenance [1]. Although many clinical studies on CRPS and studies using animal models have been conducted, the pathophysiological mechanism of CRPS is not yet clear [2–5]. Here, we report a case of a CRPS patient whose pain was improved by a regional intravenous nerve blockade combined with physiotherapy; however, CRPS relapsed into intolerable pain and severe allodynia following an epileptic seizure. Recurrent CRPS then rapidly improved through the control of epileptic discharges. During epileptic episodes, we investigated the CRPS patient using single-photon emission computed tomography (SPECT) and electroencephalography (EEG). Our findings may contribute

to the understanding of how the CNS participates in maintaining CRPS-related pain and allodynia.

2. Case Report

A 65-year-old woman with aortic regurgitation following infectious endocarditis had undergone twice aortic valve replacement procedures within 2 months. After the second operation, more than 3 weeks were required before she could be weaned from intensive treatment, including artificial ventilation and sedative drug administration. Following recovery from heart failure, sedative drug administration was discontinued. The patient's clouded consciousness persisted for several days, but she did not show signs of epilepsy. At that time, a computed tomography (CT) scan of the brain showed a diffuse lacunar infarction but no distinct lesion. As the patient's consciousness increased, she complained of intense pain and allodynia originating from the neck and radiating to

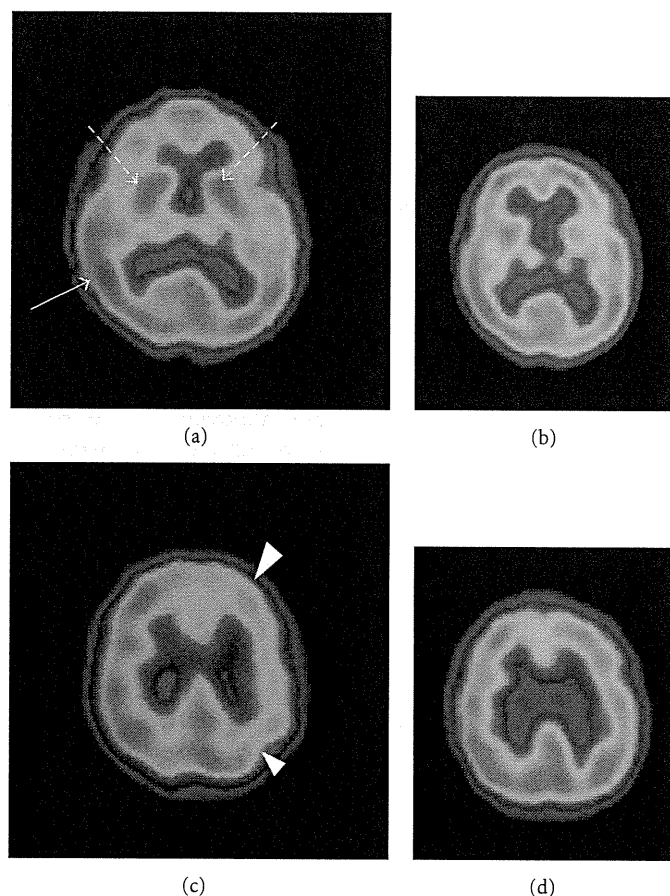


FIGURE 1: ^{99m}Tc -HMPAO-SPECT images acquired during a seizure and 10 days later. (a) and (c) show relative hyperperfusion in the right parietal lobe (arrow) and both thalami (dotted arrows) and relative hypoperfusion in the left prefrontal and parietal lobes (arrow heads) during a seizure. (b) and (d) are the same axial slices as (a) and (c), respectively, obtained 10 days after the final seizure. In (b) and (d), relative hyperperfusion and hypoperfusion are not noted, as bilateral symmetrical cerebral perfusion has been normalized.

her left hand. The patient was treated with oral nonsteroidal anti-inflammatory drugs, but no favorable effects were observed. Her pain worsened, and she consulted our pain clinic 3 months after the second operation. She showed no signs and symptoms of neurological complications, except for pain and allodynia, before and after the cardiovascular surgeries.

During the first examination at our pain clinic, she complained of spontaneous burning pain and severe allodynia from her neck to her hand; her left hand was swollen, pale, and hot. We diagnosed her condition as complex regional pain syndrome (CRPS) [6] and began treatment, although the initiating injury was unknown. Because she was being administered anticoagulant therapy, many of the available neural blockades could not be used, except for a regional intravenous nerve blockade (Bier block, with 20 mL of 0.5% lidocaine). This neural blockade was performed 4 times per week concurrently with oral administration of a tricyclic antidepressant, nortriptyline (20 mg); this treatment resulted in the gradual reduction of pain and allodynia, which allowed the patient to receive physiotherapy. One month after treatment, pain and allodynia symptoms were nearly eliminated

and swelling had also diminished. Additionally, her upper limb motor disturbance was significantly improved.

One hour after the 18th Bier block, the patient suddenly experienced a major epileptic seizure and lost consciousness during physiotherapy. This was the first time in the patient's life that a seizure episode had occurred. Intravenous administration of diazepam followed by thiamylal was used to control the seizure. An emergency CT scan of the brain showed no distinct lesions, which was confirmed by magnetic resonance imaging (MRI). The following day, the patient regained consciousness and complained of burning pain and severe allodynia localized in her left upper limb; subsequently, there was a recurrence of other CRPS symptoms (swelling, skin temperature escalation, and paleness). Despite regular intravenous administration of phenytoin, seizures occurred several times over the following 3 days, which occasionally required additional administrations of intravenous diazepam or thiamylal, and consciousness was again lost. When the patient was partially asleep due to intravenous anticonvulsants, she executed escaping movements for noxious stimulations on various healthy body parts but did not respond to noxious and tactile stimulations

on the left upper limb, suggesting an absence of hyperalgesia and allodynia. After 3 days, her consciousness was fully recovered and no seizure episodes occurred. The patient had no further complaints of burning pain or allodynia. SPECT examinations, using ^{99m}Tc -hexamethyl-propylene amine oxime (HMPAO), were performed during the seizure period and 10 days later (Figure 1). The first image, obtained during a seizure, showed relative hyperperfusion in the right parietal lobe and both thalami and relative hypoperfusion in the left frontal and parietal lobes (Figures 1(a) and 1(c)), which improved after 10 days (Figures 1(b) and 1(d)). Electroencephalography (EEG) examinations were also carried out immediately following a seizure and 2 weeks later. EEG readings immediately following a seizure showed irregular and sporadic spiked waves in the left temporal lobe, followed by spikes in both the temporal lobes. Clinically, the patient showed an intermittent left upper limb spasm, although obvious epileptic discharges were not noted on EEG readings after the 3-day seizure episodes. Although postictal EEG readings occasionally displayed irregular spiked waves in the left posterior parietal and temporal lobes, the patient did not show epileptic symptoms. Clinical symptoms suggested that spiked waves were not related to the intermittent left upper limb spasm. On the basis of the SPECT and EEG findings, our neurologist diagnosed the patient as having temporal symptomatic epilepsy focused in the right parietal lobe. Her recovery was uneventful, and pain and allodynia nearly disappeared, although her skin color remained pale and her hand remained hot.

We obtained her consent to report her progress in accordance with the Declaration of Helsinki.

3. Discussion

The initiating injury causing CRPS symptoms in our patient was unknown. We speculated that an unconfirmed brachial plexus injury induced by a median sternotomy [7] and/or prolonged immobilization by sedative drug administration [8, 9] may have been a trigger. Furthermore, pain and allodynia may have been derived from disturbed cerebral function, possibly related to the use of heart-lung machines on 2 occasions and for many hours, and infectious endocarditis, which can induce epileptic seizures. Ictal pain related to an epileptic seizure has been noted in approximately 3% of reported epilepsy cases, typically involving an entire limb, a part of a limb, or hemibody [10–12]. Ictal allodynia-related epileptic seizures have been reported in only 2 cases, and both were in children [13, 14].

This is the first known case of successfully treated CRPS revived by an epileptic seizure. Following the first seizure, we suspected systemic toxicity of the local anesthetic (lidocaine, 100 mg) applied by Bier block. However, the anesthetic may not have been responsible for the seizures because the first seizure occurred one hour after Bier block, and the patient did not present symptoms of systemic toxicity to local anesthetics (e.g., change in speech pattern, lightheadedness, dizziness, or agitation) before the seizure, and seizures recurred several times for 3 days following Bier block

cessation. The patient's SPECT and EEG abnormal findings were primarily concentrated to the temporal and parietal lobes, whereas epileptic discharges induced by systemic toxicity of local anesthetics are known to generally originate from nonspecific regions of the brain. The patient was therefore diagnosed with temporal symptomatic epilepsy.

A previous report of a brain tumor case suggested that epileptic discharges involved in the main pain pathways (i.e., primary and secondary somatosensory cortices (SI, SII), insula, and amygdala) can cause ictal pain and allodynia [13]. A congenital epilepsy case report suggested that deregulation of pain control established by relative hypoperfusion in the thalamus may play an important role in causing ictal pain and allodynia [14]. Furthermore, acute CRPS is reported to be related to hyperperfusion in the thalamus [15]. On the basis of these findings, we considered that the epileptic discharges noted on the EEG readings and subsequent hyper- and hypoperfusion in the specific brain regions, as revealed by ^{99m}Tc -HMPAO SPECT, originated from the right parietal lobe, which includes the two main pain pathway regions (i.e., SI and SII); hyperfusion and hypofusion then spread over the entire brain, including other regions in the pain pathways (i.e., thalamus, anterior cingulate cortex, insula, and amygdala), during the seizure. This abnormal brain condition likely resulted in pain and allodynia. Further, recent advancements in functional brain imaging revealed that the anterior insula, which is strongly associated with autonomic nervous function, is reorganized in CRPS patients [16]. For our patient, abnormal autonomic-like symptoms (i.e., edema, skin discoloration, and skin temperature asymmetry) were revived by epileptic seizures. This may be related to reorganization of autonomic cerebral regions. In the present case, the second episode of CRPS symptoms occurred immediately after the first epileptic seizure episode and then rapidly disappeared with the control of epileptic discharges, although we administered antiepileptic medications, which has little potential to improve neuropathic pain. We therefore concluded that epileptic discharges relapsed into CRPS. Alternatively, we speculate that repeated seizures contributed to improvement of the second bout of CRPS symptoms. For epileptic seizure and pain relief, it has been reported that electroconvulsive therapy (ECT) can be used as an alternative treatment for chronic neuropathic pain [17]. In ECT, epileptic seizures are necessary for pain relief, as fewer seizures are related to a reduced analgesic effect. A possible mechanism of ECT for pain relief may involve alteration of neurotransmitter levels in cerebrospinal fluid, resulting in pain perception modulation. Therefore, we cannot completely rule out the possibility that repeated seizure episodes may have improved the second occurrence of CRPS symptoms.

In conclusion, the present case suggests that a pathophysiological condition(s), such as epileptic discharge and/or abnormal brain perfusion, can repeatedly trigger ictal pain, allodynia, and other signs and symptoms of CRPS when brain regions participating in pain perception have been sensitized. However, why abnormal autonomic-like symptoms of CRPS remain after controlling epileptic discharges and improvement of pain and allodynia is unclear.

4. Conclusion

We present a case of CRPS in which the symptoms of burning pain and severe allodynia were once resolved but returned following an epileptic seizure. These symptoms disappeared following the control of epileptic discharges. This suggests that CRPS symptoms may be sustained by abnormal brain conditions, and our results contribute to the understanding of how the CNS participates in maintaining pain and allodynia associated with CRPS.

Acknowledgments

This paper was partially funded by the New Energy and Industrial Technology Development Organization (no. 08C46216), Health Labour Sciences Research Grant "Third Term Comprehensive Control Research for Cancer" (398-49) and the Ministry of Education, Science, Sports and Culture (Young (B) no. 22791420). The authors declare no conflict of interests.

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Human brain activity associated with painful mechanical stimulation to muscle and bone

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Received: 8 February 2010 / Accepted: 12 May 2011 / Published online: 2 June 2011
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Abstract

Purpose The purpose of this study was to elucidate the central processing of painful mechanical stimulation to muscle and bone by measuring blood oxygen level-dependent signal changes using functional magnetic resonance imaging (fMRI).

Methods Twelve healthy volunteers were enrolled. Mechanical pressure on muscle and bone were applied at the right lower leg by an algometer. Intensities were adjusted to cause weak and strong pain sensation at either

target site in preliminary testing. Brain activation in response to mechanical nociceptive stimulation targeting muscle and bone were measured by fMRI and analyzed.

Results Painful mechanical stimulation targeting muscle and bone activated the common areas including bilateral insula, anterior cingulate cortex, posterior cingulate cortex, secondary somatosensory cortex (S2), inferior parietal lobe, and basal ganglia. The contralateral S2 was more activated by strong stimulation than by weak stimulation. Some areas in the basal ganglia (bilateral putamen and caudate nucleus) were more activated by muscle stimulation than by bone stimulation.

Conclusions The putamen and caudate nucleus may have a more significant role in brain processing of muscle pain compared with bone pain.

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Keywords Pain · Muscle · Bone · Neuroimaging · fMRI

Introduction

Physical pain originating from deep tissues—including sprains, fibromyalgia, rheumatic polymyalgia, and other muscle-derived pain, and bone-derived pain such as fractures, spondylosis, and bone tumors—is very commonly encountered. Consequently, understanding how these conditions come to be painful through brain processing is clinically important. Recent imaging research using the blood oxygen level-dependent-based (BOLD) functional magnetic resonance imaging (fMRI) method successfully revealed cognitive mechanisms in response to painful stimulation.

In the field of anesthesiology, fMRI has been on trial as a tool for investigating cerebral pain processing [1–5]. Previous reports, however, have mainly been studies of

heat stimulation to skin [6, 7]. More recently, studies targeting brain activation when muscle pain is caused using electric stimulation or hypertonic saline have successfully demonstrated that some areas are differently activated, including the contralateral primary somatosensory cortex (S1), the ipsilateral anterior insula, the contralateral motor cortex, the cingulate motor area, and the perigenual cingulate [8–10]. However, there are few studies of the brain processing activated by mechanical stimulation to deep tissues [11]. To elucidate the central processing of painful mechanical stimulation to deep tissues (muscle and bone), we compared the brain activation induced by two different intensities of stimulation (strong and weak) at two different targets (muscle and bone), using fMRI.

Materials and methods

Subjects

All the procedures were approved by the Osaka University Hospital Institutional Review Board. Twelve healthy volunteers (7 men, 5 women; aged 24–56 years) agreed to receive painful stimulation while their brain activation was evaluated. They had no neurological disorders or detectable MRI abnormalities in the brain and were free from any medication within 24 h before the study. In written informed consent, each acknowledged that they were willing to receive experimental painful stimulation. Before the protocols were carried out, each volunteer was familiarized with the experimental protocol, the types of stimulation, and the tasks performed.

Painful stimulation

To determine suitable stimulation intensities for each subject, a preliminary testing was performed immediately

before the fMRI study. Perpendicularly applying a round 10-mm solid tip of an algometer probe (Pressure Algometer NPA-1, Shinko, Japan) on the surface (skin) at the medial point of the right tibia (Fig. 1), the experimenter gradually increased the pressure until the subject verbally indicated that the stimulation was painful. At that point, the pain intensity was taken to be ‘3’ on a subjective 10-point numerical rating scale (NRS). The three median values of five trials were averaged to determine the weak stimulation to be applied to the tibia of particular volunteers. Similarly, the subject was asked to verbally indicate when the pain was such that it would probably be intolerable for more than 20 s without withdrawal movement. At this point, pain intensity was scored as ‘8’ on the volunteer’s subjective 10-point NRS. Similar grading of muscle pain was also carried out [12]. Here the tip of the probe was applied to the skin on the gastrocnemius muscle at a medial point 3–5 cm from the stimulation point of the tibia (Fig. 1). For each volunteer, as in the bone protocol, subjective NRS pain scores of ‘3’ and ‘8’ were obtained. These procedures were conducted by one experimenter (M.S.) who, in each instance and so far as possible, endeavored to consistently apply the required level of pressure perpendicularly.

Protocol

Each subject participated in a trial comprising 12 fMRI task sessions. At each right-leg site that was evaluated in the preliminary testing, three trials of 20 s of strong or weak stimulation were applied in each session. The site and strength of stimulation were pseudo random for each series. After each series of three stimulations (in a session lasting 3 min; Fig. 2), there was a pause of 1 min before the next session. MRI scans were acquired throughout the 36-min period. The subjects were asked to rate, using NRS, the overall pain at the end of each series of three stimulations (mean of three periods of 20-s stimulation). Before the



Fig. 1 Photograph showing how a digital algometer was used to apply stimulation to muscle (*left*) and bone (*right*). Bone stimulation was applied to the surface (skin) at the midpoint of tibia. Muscle stimulation was applied to the surface of gastrocnemius 3–5 cm

posterior from bone stimulation point. Intensities of stimulation (muscle vs. bone, strong vs. weak) were decided for each subject by averaging the values of the median of three of five trials

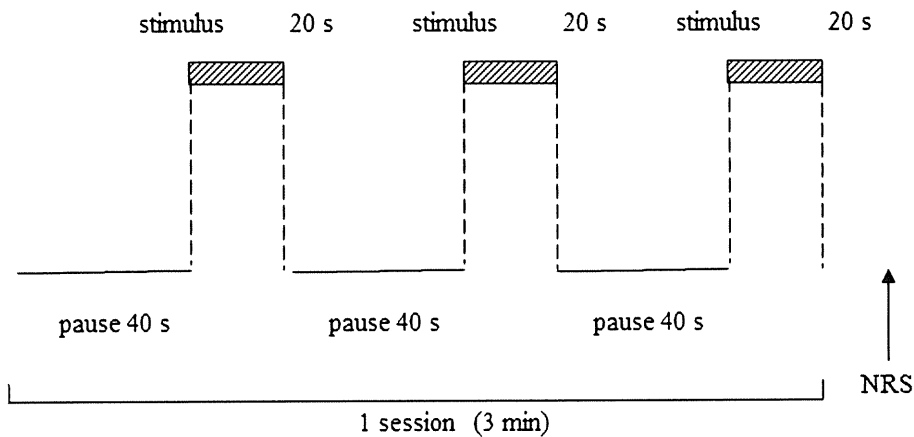


Fig. 2 Schematic representation of the experiment. Each subject underwent one trial comprising 12 sessions with a 1-min interval between sessions. Each session, lasting a total of 3 min, started with 40-s pause, and then a 20-s strong or weak stimulation to either

muscle or bone. Weak and strong stimulations for each volunteer were decided in the preliminary testing. The order of stimulation was pseudo randomized. After each session, volunteers were asked to score the perceived pain. *NRS* numerical rating scale

commencement of the protocol, each volunteer was informed that the site (muscle or bone) and intensity (weak or strong) of the forthcoming series of stimulation would be random.

MRI

Imaging was performed with a 1.5-T MRI scanner (Signa EXCITE XI 11.0; GE Healthcare, Milwaukee, WI, USA). Functional MR images were obtained using a multislice echo planar imaging technique (EPI) based on 30 oblique slices (repetition time, 3,000 ms; time to echo, 60 ms; flip angle, 90°; slice thickness, 5 mm; gap, 0 mm; field of view, 300 mm × 300 mm; in-plane resolution, 4.69 mm × 4.69 mm). All the subjects were positioned in the scanner with a foam rubber pad to minimize head movement and instructed simply to lie with their eyes closed without moving or speaking. Their heads were placed so that the uppermost superior aspect of brain was within the field of view. High-resolution T₁-weighted anatomic images with the same orientation as the EPI slices were collected from each subject. In the subsequent analysis, these images were used for coregistration of functional and anatomic data.

Data analysis

Psychophysics

Using paired *t* testing, we compared the stimulation intensity and the average subjective NRS scores for muscle (weak and strong) and bone (weak and strong), respectively. Effects of order of stimulus application on NRS were evaluated with two-way analysis of variance (ANOVA); $P < 0.05$ was regarded as significant. Values are given as mean ± SD.

fMRI data analysis

The fMRI data were analyzed with Statistical Parametric Mapping software (SPM99; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 6.1 (Mathworks, Sherborn, MA, USA). The functional images were realigned to correct for head movements, coregistered with each subject's anatomic MRI, and transformed to the format of the standard brain according to Talairach coordinates [13]. The functional images were spatially smoothed with an 8-mm full-width half-maximum Gaussian kernel. We fitted a linear regression model (fixed effects within subjects). Each condition was modeled with a boxcar function and convolved with a hemodynamic response function. Temporally, the voxel time series were high-pass filtered (124-s cutoff periods) to remove slow trends in the data, and low-pass filtered with a hemodynamic response filter.

We compared image data for each group—weak muscle stimulation, strong muscle stimulation; weak bone stimulation, strong bone stimulation—against the data from each resting condition, respectively. All the data were pooled for group statistical comparisons. Across the subjects, random effect analysis was performed to determine the significant activation associated with different sites and intensities of stimulation ($P < 0.001$ uncorrected; minimum cluster size, 20 voxels). To investigate the brain network related to painful stimulation intensity, we calculated the difference in the areas activated by strong stimulation minus weak stimulation (paired *t* test; $P < 0.005$ uncorrected; minimum cluster size, 20 voxels). To identify the brain areas that are differently activated by muscle and bone stimulation, we also analyzed the data separately (strong muscle minus strong bone; weak muscle minus weak bone; and all

together) (paired *t* test; $P < 0.005$ uncorrected; minimum cluster size, 20 voxels).

Results

Stimulation and pain intensity

The mean intensity of muscle stimulation was 21.1 ± 8.4 N for weak stimulation and 40.7 ± 7.8 N for strong stimulation; the mean intensity of bone stimulation was 14.2 ± 5.7 N for weak stimulation and 30.1 ± 7.9 N for strong stimulation. The NRS scores with strong muscle and strong bone stimulation were significantly higher than those with weak muscle and weak bone stimulation, respectively ($P < 0.05$ for both) (Table 1). All the volunteers clearly distinguished the two intensities of stimulation because the weaker stimulation was always scored lower. Although the volunteers found weak muscle stimulation trials more painful ($P < 0.05$) than weak bone stimulation, no similar difference was found for strong stimulations. Comparing the data among the three trials of the same intensity at the same site, no differences in NRS scores were found; this indicates that repeated mechanical stimulation did not sensitize or desensitize the volunteers ($P > 0.05$).

fMRI

In response to painful muscle stimulation, brain activation was apparent within the bilateral anterior cingulate cortex (ACC), insula cortex, the secondary somatosensory cortex (S2), the inferior parietal lobule (IPL), the posterior cingulate cortex (PCC), putamen, the ipsilateral dorsolateral prefrontal cortex (DLPFC), thalamus, caudate, and the contralateral claustrum (Fig. 3a,b; Table 2). In response to painful bone stimulation, brain activation was also apparent within the bilateral ACC, the IPL, the S2, the PCC, the ipsilateral DLPFC, and the contralateral claustrum (Fig. 4a,b; Table 2). Peak coordinates (*x*, *y*, *z*) in Montreal

Neurological Institute (MNI) space and Z-scores (>6.00) for the activated brain regions by muscle and bone pain are shown in Table 2. Differences in the areas activated by strong versus weak muscle stimulation were mainly found in the contralateral S2 and the bilateral thalamus (Fig. 3c). For strong versus weak bone stimulation, the difference was found in the contralateral S2 (Fig. 4c). With weak stimulations, the activation differences between muscle and bone stimulation were apparent in the bilateral caudate nucleus and contralateral Brodmann areas 22 and 45 (Fig. 5a). With strong stimulations, the activation differences were apparent in the bilateral putamen, the ipsilateral ACC, and the contralateral claustrum (Fig. 5b). Analyzing the sum of the differences between muscle- and bone-related pain revealed that activation was different in the bilateral caudate and contralateral putamen (Fig. 5c; Table 3).

Discussion

In this study, as an initial step toward elucidating the brain activation associated with mechanically induced deep tissue pain, we found that the contralateral S2 was more activated by stronger stimulations to muscle or bone. We also found that parts of the basal ganglia (putamen and caudate nucleus) were more activated by muscle stimulation than by bone stimulation.

Psychophysics

The NRS scores measured during fMRI were higher than those determined in the preliminary testing. Although the reason is not clear, the difference of the rate of pressure increase between preliminary testing and the fMRI session may be a cause.

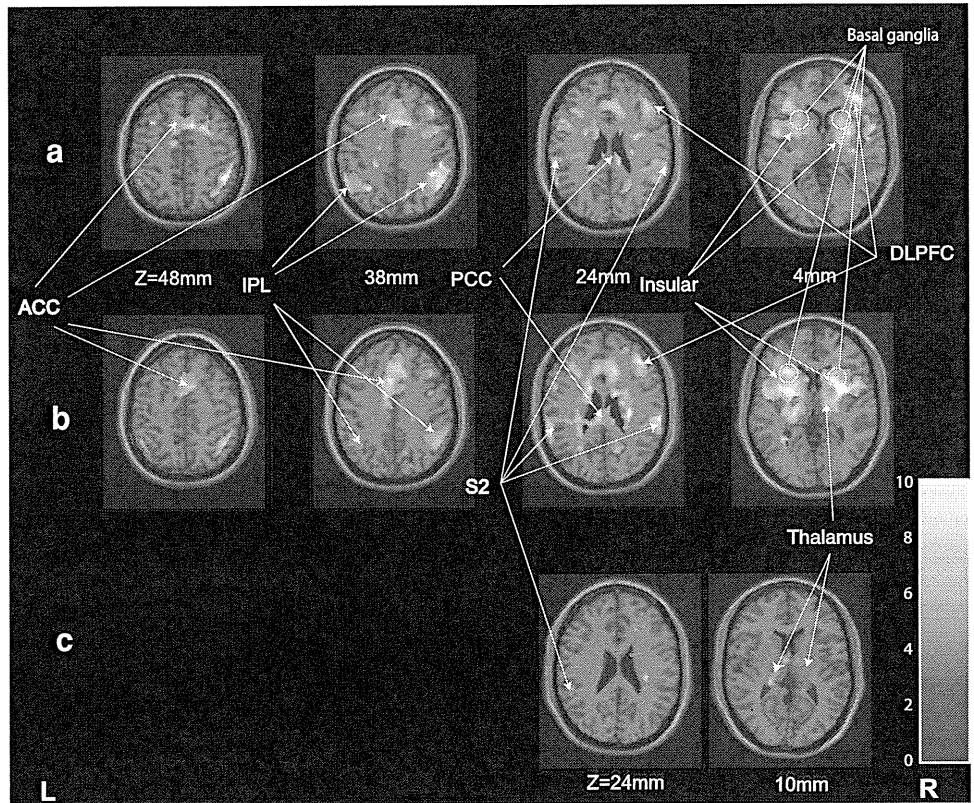
On the other hand, the NRS scores for the two sets of three stimulations at each site did not change during the protocol (see Table 1), suggesting that no further change in sensitivity occurred. Nie et al. [14] have reported that after

Table 1 Numerical rating scale (0–10 NRS) by mechanical stimulation

	1st stimulation	2nd stimulation	3rd stimulation	mean	
weak muscle stimulation	4.83±1.99	4.67±1.88	4.5±1.98	4.67±1.90	* **
strong muscle stimulation	8.17±1.34	8.5±1.17	8.25±1.42	8.31±1.28	
weak bone stimulation	4.25 ±2.14	3.25 ±1.14	3.92 ±1.78	3.81±1.74	* **
strong bone stimulation	8.83 ±1.03	8.25 ±1.36	8.17 ±1.70	8.42 ±1.38	

NRS with strong muscle and strong bone stimulation were significantly higher than those with weak muscle and weak bone stimulation ($*P < 0.05$). In weak stimulations, NRS with muscle stimulation was higher than with bone stimulation ($**P < 0.05$). There were no differences between strong muscle and bone stimulations among NRS with 1st, 2nd, and 3rd stimulation in the same study groups

Fig. 3 Brain activation induced by muscle stimulation: weak stimulation (a), strong stimulation (b), and contrast of strong and weak stimulation (c). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (left) to ventral (right). Statistical map thresholds are $P < 0.001$ (a, b, uncorrected), and $P < 0.005$ (c, uncorrected, paired test). Minimum cluster size is 20 voxels. Right (R) and left (L) sides are indicated. ACC anterior cingulate cortex; IPL inferior parietal lobule; S2 secondary sensory cortex; DLPFC dorsolateral prefrontal cortex; PCC posterior cingulate cortex



ten stimulations with 30-s intervals between stimulations, subjects gave higher VAS scores, increasing to $192\% \pm 71\%$ for stimulation of the tibia and to $117\% \pm 42\%$ for stimulation of the tibia anterior muscle. In the present study, the protocol specified a 60-s interval during all the sessions. This interval was apparently long enough to prevent temporal sensitization. To evoke equivalent pain in muscle and bone, greater stimulation had to be applied largely to the muscle; this may be because nociceptive nerve density is greater in the periosteum than in muscle [15].

Imaging

A previous positron emission tomography (PET) study and event-related fMRI study using noxious electronic stimulation of muscle showed activation in the ACC, S2, and anterior insula [8, 10]. Also, PET and fMRI study using injection of hypertonic saline into muscle evoked the activation in contralateral insula and putamen [9, 16]. In our study, the results for mechanical stimulation are consistent with the previous muscle pain studies, which have shown that the different types of stimulation (hypertonic saline, electrical stimulation, and mechanical stimulation) applied to muscle induce equivalent activation patterns [8, 10, 16]. We found that stronger muscle stimulation resulted in greater activation in the contralateral S2, the bilateral

thalamus (contralateral > ipsilateral), and that stronger bone stimulation caused greater activation in the contralateral S2. In each case, the contralateral S2 was more activated by strong stimulation. However, caution is needed in interpreting these results because greater application of the force to skin is also involved during strong stimulation. The activation of the contralateral S2 may also come from greater cutaneous stimulation. In a PET study investigating thermal stimulation to skin, Coghill et al. [17] have shown that the ipsilateral cerebellum, the contralateral S1, the supplementary motor area, the bilateral S2, the lentiform nucleus, the insular cortex, and the thalamus and ACC are more activated depending on perceived pain intensity. In an fMRI study, using mechanical phasic stimulation on the skin, Ringler et al. [18] have shown that the contralateral S2 is more activated by stronger stimulation. The contralateral S2 may take part in processing pain intensity derived from both skin and deep tissues.

Comparison of the activation associated with muscle and bone stimulation revealed that caudate nucleus and putamen were more activated by muscle than by bone stimulation. No activation existed that was evoked by (bone > muscle) stimulation (data not shown). The activation in these areas is supposed to be related to stimulated sites (muscle or bone), not to stimulation or pain intensity, because these areas were not included as a contrast when we stimulated the single target (muscle or bone) with the

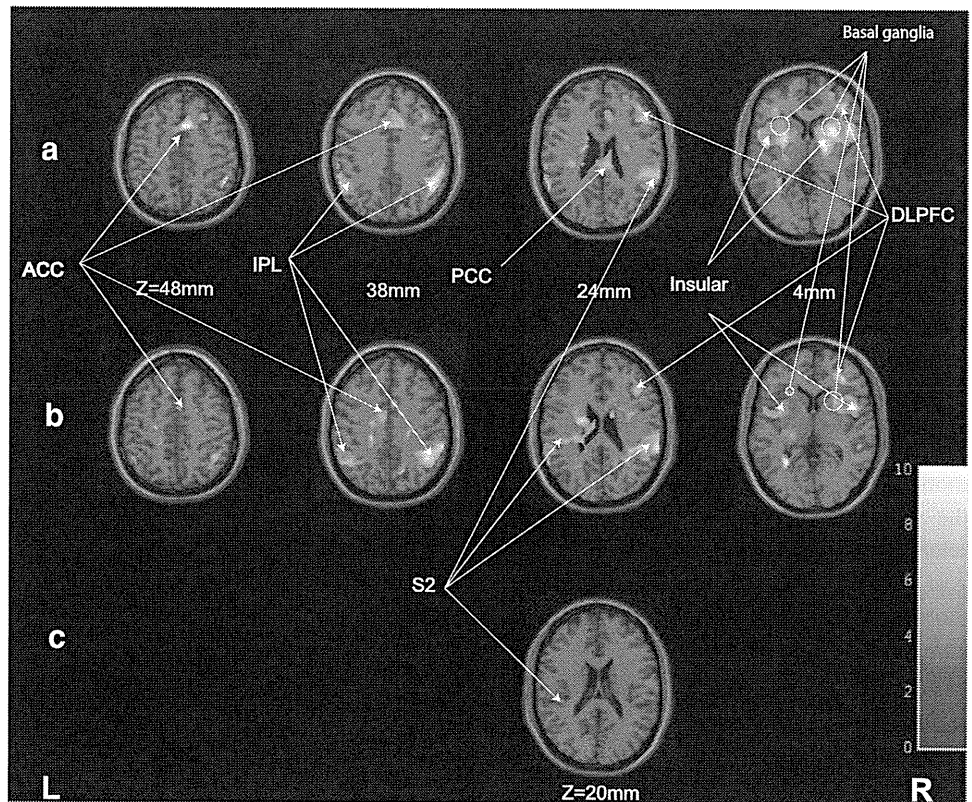
Table 2 Peak coordinates (*x*, *y*, *z*) in Montreal Neurological Institute (MNI) space and Z-scores (>6.00) for the activated brain regions by muscle and bone pain

Region	BA	Muscle pain				Bone pain				
		Peak voxel coordinate			Z-score	Peak voxel coordinate			Z-score	
		<i>x</i>	<i>y</i>	<i>z</i>		<i>x</i>	<i>y</i>	<i>z</i>		
ACC	32	-8	12	44	7.07					
	32	-6	18	32	6.42					
	32	-12	26	30	6.42					
Insula right	13	28	26	2	6.33					
		34	4	8	6.09					
Insula left		-34	6	8	6.25	44	-48	10	6	6.27
	47	-28	24	-8	6.05					
S2 right	40	62	-32	30	6.32					
S2 left	40	-60	-32	28	6.39					
IPL left						40	-48	-52	40	6.57
	40	-48	-58	42	6.33	40	-48	-40	28	6.48
	40	-44	-48	42	6.13	40	-62	-36	32	6.27
Thalamus right		20	-18	10	6.04					
Putamen right		26	2	6	6.16					
		20	-4	8	6.10					
Putamen left		-32	6	6	6.54					
Clastrum left		-26	12	10	6.39	-30	10	6	6.18	
Caudate right		16	12	8	6.13					

Brodmann areas are given where available

BA Brodmann area, ACC anterior cingulate cortex, S2 secondary sensory cortex, IPL inferior parietal lobule

Fig. 4 Brain activation induced by bone stimulation: weak stimulation (a), strong stimulation (b), and contrast of strong and weak stimulation (c). In millimeter elevations relative to a line through the anterior-posterior commissure (AC-PC line), brain slices are shown in superior-inferior sequence. The axial slices are arranged from dorsal (left) to ventral (right). Statistical map thresholds are $P < 0.001$ (a, b, uncorrected), and $P < 0.005$ (c, uncorrected, paired test). Minimum cluster size is 20 voxels. Right (R) and left (L) sides are indicated. ACC anterior cingulate cortex; IPL inferior parietal lobule; S2 secondary sensory cortex; DLPFC dorsolateral prefrontal cortex; PCC posterior cingulate cortex



different intensities. Additionally, pain intensities were identical between strong muscle and strong bone pain. Reports of the previous pain imaging studies have

suggested that the putamen is activated by nociceptive stimulation [17, 19], including muscle pain with hypertonic saline [16]. Basal ganglia are reported to have a role in

Fig. 5 Contrast of brain activation induced by muscle and bone stimulation: contrast of weak stimulation to muscle and bone (a), contrast of strong stimulation to muscle and bone (b), and contrast of all the stimulations to muscle and bone (c). In millimeter elevations relative to a line through the anterior–posterior commissure (AC–PC line), brain slices are shown in superior–inferior sequence. The axial slices are arranged from dorsal (left) to ventral (right). Statistical map thresholds are $P < 0.005$ (uncorrected, paired test). Minimum cluster size is 20 voxels. Right (R) and left (L) sides are indicated. BA Brodmann area; ACC anterior cingulate cortex

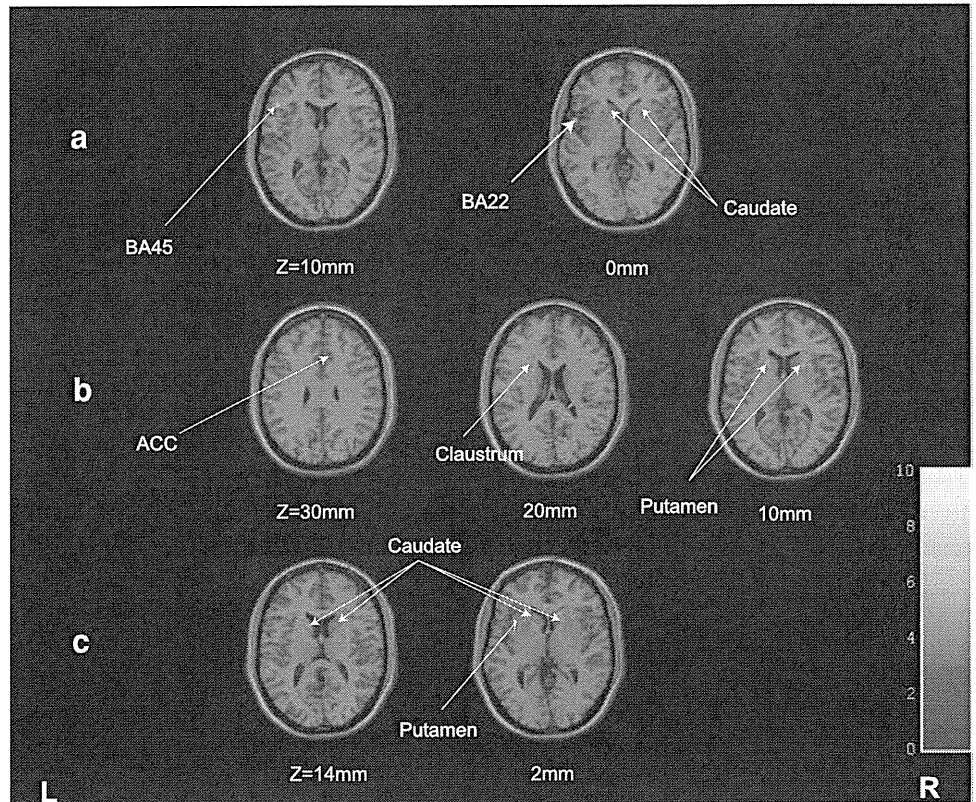


Table 3 Peak coordinates (x, y, z) in Montreal Neurological Institute (MNI) space and Z-scores for activated brain regions by muscle–bone pain

Region	(Muscle–bone) pain			
	Peak voxel coordinate			Z-score
	x	y	z	
Putamen left	–24	12	24	4.12
Caudate left	–18	16	8	4.01
Caudate right	16	22	0	3.95

motor preparation, movement control, and emotional, motivational, and cognitive function [20–22]. Processing in the putamen and caudate nucleus is also reported to be related to pain-avoidance behavior [23]. Our results suggest that the putamen and caudate nucleus may have a more significant role in the brain processing of muscle pain compared with bone pain.

Conclusion

In conclusion, the putamen and caudate nucleus may have a more significant role in the brain processing of muscle pain compared to bone pain.

Acknowledgment We thank Syoji Kobashi and Tamotsu Nomura for helping in imaging procedures, Tateo Iwakura for help with image analysis, and Sho Karl Shibata and David Eunice for editing. Scans were performed at Ishikawa Hospital. This work was supported by a Grant-in-aid for community health and medical care from the Ichou Association for Promotion of Medical Science.

Conflict of interest None.

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Case Report

Oral Local Anesthesia Successfully Ameliorated Neuropathic Pain in an Upper Limb Suggesting Pain Alleviation through Neural Plasticity within the Central Nervous System: A Case Report

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Received 20 December 2010; Revised 3 March 2011; Accepted 25 March 2011

Academic Editor: Kouichiro Minami

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Neural blockades are considered an alternative to pharmacotherapy for neuropathic pain although these blockades elicit limited effects. We encountered a patient with postbrachial plexus avulsion injury pain, which was refractory to conventional treatments but disappeared temporarily with the administration of the local anesthetic lidocaine around the left mandibular molar tooth during dental treatments. This analgesic effect on neuropathic pain by oral local anesthesia was reproducible. Under conditions of neuropathic pain, cerebral somatotopic reorganization in the sensorimotor cortices of the brain has been observed. Either expansion or shrinkage of the somatotopic representation of a deafferented body part correlates with the degree of neuropathic pain. In our case, administration of an oral local anesthetic shrank the somatotopic representation of the mouth, which is next to the upper limb representation and thereby expanded the upper limb representation in a normal manner. Consequently, oral local anesthesia improved the pain in the upper limb. This case suggests that pain alleviation through neural plasticity within the brain is related to neural blockade.

1. Introduction

Neuropathic pain typically appears following peripheral nerve injury due to neuropathies, plexopathies, and trauma to selected sites within the central nervous system (CNS). Recently, evidence-based recommendations of pharmacological treatments for neuropathic pain have been proposed based on both positive and negative results from multiple randomized controlled trials. However, approximately 10–15% of all neuropathic pain patients are refractory to pharmacotherapy. For these cases, more invasive pain-management interventions, such as intrathecal drug delivery, neurostimulation, or neural blockade, may be used. Ideally, blocking neural transmission, either temporarily by using local anesthetics or permanently by surgical nerve ablation, can reduce neuropathic pain; however, no neural blockades

have been found to be consistently successful [1]. Here, we report on a case of a patient with postbrachial plexus avulsion injury pain whose neuropathic pain had been refractory to several evidence-based pharmacotherapies and interventions, such as spinal cord stimulation, cervical epidural blockade, and brachial plexus blockade. His pain could be well controlled by oral local anesthesia, suggesting pain alleviation through neural plasticity within the CNS.

2. Case Report

A 49-year-old man, who had a left brachial plexus avulsion injury 10 years before, experienced severe neuropathic pain in his left upper limb immediately after the trauma. The patient complained of continuous burning, pressing, and

tingling pain in the upper limb. From the beginning of the perception of the pain in his upper limb, he felt illusory perceptions of fingers touching his face although he did not perceive pain or any other sensory deficits in the face. He had been treated several times for the pain through left brachial plexus blockades and cervical epidural blockades, with no success. His neuropathic pain decreased slightly when taking pregabalin and with the application of cervical spinal cord stimulation (SCS), but it remained severe. He did not have any pain or trigger areas in the face getting caries of the teeth. He once underwent a dental treatment for his left mandibular molar tooth. When local anesthesia was applied around the left mandibular molar tooth (3 mL, 0.5% lidocaine), he felt the enlargement of that region, which was followed by an immediate disappearance of his neuropathic pain. At that time, the illusory finger sensations in the face disappeared. Approximately 2 hours after the dental treatment, the neuropathic pain returned and gradually increased to pre-dental treatment levels. A nonsteroidal anti-inflammatory drug, loxoprofen, completely ameliorated the dental pain but was not effective against the neuropathic pain. Since then, the patient had 3 dental treatments, and local anesthesia around the left molar tooth consistently ameliorated his neuropathic pain. Analgesic effects consistently lasted for several hours following the administration of the local anesthesia. His neuropathic pain was able to be mildly controlled by a combination of pregabalin, SCS, and local anesthesia around the left molar tooth although the molar tooth had completely improved. The use of oral local anesthesia for breakthrough neuropathic pain had been especially effective.

We obtained the patient's consent to report his progress, in accordance with the Declaration of Helsinki.

3. Discussion

Under conditions of neuropathic pain, particularly for deafferentation pain following massive nerve injury, such as postamputation phantom limb pain, postbrachial plexus injury pain, or postspinal cord injury pain, cerebral somatotopic reorganization in the sensorimotor cortices of the brain is observed. Following deafferentation of an upper limb by nerve injury, the somatotopic region corresponding to the upper limb in the sensorimotor cortices shrinks, and the somatotopic region responding to the facial region, which is located next to the upper limb, expands (Figure 1(a)) [2, 3]. The degree of shrinkage of the upper limb representation correlated linearly with the severity of the neuropathic pain [4]. Further, expansion of the somatotopic representation of the affected body part correlated with pain alleviation through neurorehabilitation techniques [5–7]. Therefore, somatotopic reorganization in the sensorimotor cortices closely relates to pathophysiological mechanisms underlying neuropathic pain and its alleviation.

Concerning the somatotopic reorganization of the face and hand regions, the overlapping of these regions can sometimes induce the following illusion in patients with a deafferentation of a hand: touching the face creates obvious referred sensation of fingers in the face as if the fingers

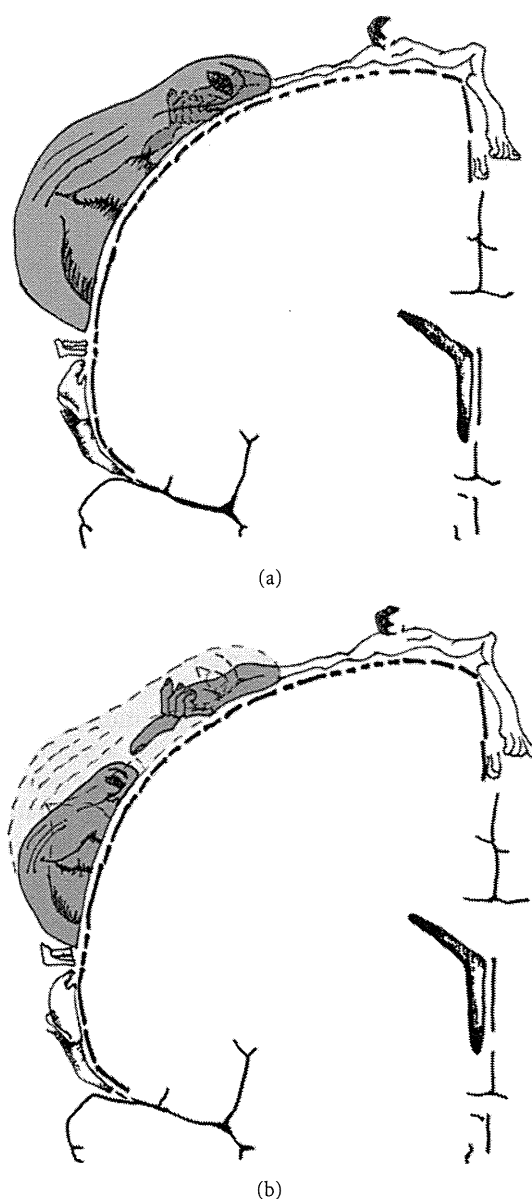


FIGURE 1: Topographical somatotopic reorganization in the sensorimotor cortices following deafferentation by a brachial plexus avulsion injury (a) and normalization of the reorganization by application of local anesthesia in the mouth (b).

are embedded in the face [8]. We consider one possibility that the analgesic effects of the oral local anesthesia in our case were derived from the neural plasticity in the sensorimotor cortices because our patient perceived a similar illusory sensation of fingers in the face. Deafferentation by local anesthesia, as well as that by nerve injury, shrinks the somatotopic representation of the exposed body part and simultaneously expands the nearby somatotopic representation in the sensorimotor cortices, and these are not associated with subcortical changes [9, 10]. On the basis of this notion, we speculated that, in our case, local anesthesia in the mouth shrank the mouth/face representation and subsequently expanded the somatotopic representation of the hand/upper

limb within the sensorimotor cortices (Figure 1(b)), resulting in amelioration of the neuropathic pain in the upper limb. The disappearance of the illusory finger sensations in the face soon after the oral local anesthesia supported the intimate relationship between analgesic effects of the upper limb pain and cerebral reorganization of hand/upper limb and face/mouth representations.

In general, neural blockades are applied to painful body parts in order to block neural transmission; however, the clinical significance of neural transmission blockades remains unclear for nerve-injured neuropathic pain because of deafferentation. Local anesthesia at an intact limb contralateral to the painful limb has been reported to display clear analgesic effects on postamputation phantom limb pain, suggesting pain alleviation through neural plasticity within the CNS [11]. Thus, several types of local anesthesia or neural blockades on unaffected body parts have distinct clinical significance compared to neural transmission blockades, whereas peripheral nerve blockades shrink the somatotopic area of the exposed body part and seem to have no analgesic effect on neuropathic pain in general. Specific analgesic effects on neuropathic pain from local anesthesia and neural blockade could be derived from CNS plasticity. In the future, functional brain imaging studies examining the relationship between neural blockade application for neuropathic pain and CNS plasticity need to be performed in order to better understand somatotopic reorganization in the sensorimotor cortices induced by neural blockades.

4. Conclusion

For neural blockades, oral local anesthesia is a novel candidate for treating neuropathic pain in the upper limb, and the analgesic effect might be derived from its effects on neural plasticity within the CNS.

Acknowledgments

This paper was partially funded by the New Energy and Industrial Technology Development Organization (no. 08C46216) and the Ministry of Education, Science, Sports, and Culture (Young (B) no. 22791420). The authors declare no conflict of interests.

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Impact of remifentanil introduction on practice patterns in general anesthesia

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Received: 16 June 2011 / Accepted: 18 August 2011 / Published online: 9 September 2011
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Abstract

Purpose The introduction of new medicine can change clinical practice patterns and may affect patient outcomes. In the present study, we investigated whether introduction of remifentanil in Japan affected the practice patterns of anesthesia.

Methods Using the Japanese Diagnosis Procedure Combination database, we extracted records of 423,491 patients who underwent surgery with general anesthesia in 243 hospitals before (2006) and after (2007) the introduction of remifentanil, and identified anesthetic agents used for each patient. A hierarchical mixed-effects logistic regression analysis was performed to analyze the factors that affected selection of remifentanil. Further, we compared

postoperative length of stay (LOS), in-hospital mortality, and total costs between 2006 and 2007.

Results In 2007, remifentanil was used for up to 41.4% of all general anesthesia, accompanied by a reduction in nitrous oxide use and an increase in total intravenous anesthesia. Female gender, increasing age, and preoperative comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with the use of remifentanil, whereas accompanying cardiac disease and co-application of epidural anesthesia were negatively associated. In 2007, a similar in-hospital death rate, similar or decreased total costs, slightly reduced duration of anesthesia, and substantially reduced postoperative LOS were seen compared to those in 2006.

Conclusions Our data revealed rapid changes in practice patterns in anesthesia after the introduction of remifentanil in Japan. Remifentanil was used more often in patients with comorbidities and without epidural anesthesia, and its introduction did not affect increase in total medical costs.

Electronic supplementary material The online version of this article (doi:10.1007/s00540-011-1221-5) contains supplementary material, which is available to authorized users.

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Keywords Remifentanil · Anesthetic practice ·
Postoperative outcome · In-patient medical cost

Introduction

The introduction of new medical devices such as the drug-eluting stent for angina pectoris [1] or new drugs such as anti-tumor necrosis factor- α antibody for rheumatoid arthritis [2] had a major impact on medical practice patterns over a short time period, affecting not only patient outcomes but also total medical costs, although published reports gave variable results [3].

In anesthesiology, only a limited number of reports show changes in practice patterns in anesthesia [4]. It is

also not clear to what extent such changes affect medical costs and patient outcome [5].

Remifentanyl, a mu-opioid receptor agonist, has a unique pharmacokinetic profile, characterized by rapid equilibration with the central compartment, and a short half-life, independent of infusion duration [6, 7]. Although its use is common in Western countries [8], it was finally approved in Japan in December 2006, and its use in clinical practice commenced in January 2007. The unique pharmacological properties of this novel drug facilitated its rapid assimilation into Japanese clinical procedures, making a considerable impact on anesthetic practice. However, accurate data have not been reported on the expansion of remifentanyl use and the subsequent changes in practice patterns in general anesthesia. In addition, the effects of remifentanyl introduction on patient outcomes remain unclear.

In the present study, we investigated the proportion of remifentanyl use in the first year of its introduction and changes in the patterns of anesthetic drug use. Then, we analyzed factors affecting selection of remifentanyl. We also compared duration of anesthesia and total costs as well as postoperative length of stay (LOS) and in-hospital mortality before and after introduction of remifentanyl, using the nationwide Japanese administrative claims database, the Diagnosis Procedure Combination (DPC) database.

Materials and methods

DPC database and participants

The DPC is a mixed-case system, similar to the diagnosis-related groups (DRG) in the U.S. Medicare program. It was launched in 2002 by the Ministry of Health, Labor and Welfare of Japan and is linked with a lump-sum payment system. Key objectives of the DPC system are to implement a standardized electronic claims system and to provide transparency of hospital performance [9, 10]. All 82 university teaching hospitals must adopt the DPC system, and community hospitals can voluntarily adopt this system. Data are mainly used for profiling practice patterns, refining case-mix classification, and planning health policies such as resource allocation.

The DPC database comprises discharge abstracts and administrative claims, with data compiled between July 1 and December 31 each year by the DPC Research Group [10–13]. The database initially included 82 hospitals in 2003. The numbers of inpatients and participant hospitals are increasing each year, with around 3 million patients from 926 hospitals in 2007, which represented approximately 45% of all acute care inpatient hospitalizations in Japan [11]. The database includes the following data:

unique identification number of each hospital; patient age and sex; diagnoses recorded in the Japanese language together with the *International Classification of Diseases, 10th Revision*; surgical procedures coded with original Japanese codes; drugs and devices used; LOS; in-hospital mortality; and total costs (including costs for hospitalization, surgery, anesthesia, drugs and devices used).

The DPC database corresponds to the Nationwide Inpatient Sample in the United States [14] to some extent but has several advantages [10]. To optimize the validity of the recorded diagnoses, physicians in charge record the diagnoses in reference to the medical charts. Detailed data are available for the treatments administered on a daily basis (e.g., types of drugs administered, duration of anesthesia, volume of blood transfusion). Medical clerks and licensed medical information managers accurately record the dates of each surgery and other procedures and the dates of use of each drug and device. Physicians and hospitals consistently comply with data submission because it is mandatory to obtain DPC-based reimbursement of medical fees.

All patient identifiers have been removed from this database. Because of the anonymous nature of the data, obtaining informed consent from patients was unnecessary. The Institutional Review Board of the University of Occupational and Environmental Health approved this study design.

Data extraction

To compare the pre-remifentanyl period (July–December 2006) with the remifentanyl treatment period (July–December 2007), we included data from all 243 hospitals that participated in the DPC survey in both years. We extracted data on all surgical patients who underwent general anesthesia in these hospitals, including type of hospital, type of admission, patient age, sex, surgical procedures, duration of anesthesia (min), volume of blood transfusion, postoperative LOS (days), in-hospital mortality, and total costs. General anesthesia was defined as anesthesia for surgery for at least 20 min with volatile anesthetics and/or intravenous anesthetics supplemented with oxygen via a mask including laryngeal mask or endotracheal tube.

We also extracted data regarding medications used for general anesthesia, including barbiturates, nitrous oxide, volatile anesthetic agents, muscle relaxants, hypnotics, and narcotics.

Patients who underwent the following eight classes of surgery in 2007 were subdivided to evaluate differences in distribution of remifentanyl among surgical subcategories: cardiac surgery, neurosurgery, thoracic surgery, vascular surgery, general surgery, gynecology, orthopedic surgery, and otolaryngology. When a patient underwent two or more surgeries during the hospitalization, the patient was

classified into one group according to the most recent surgery. If a patient underwent multiple surgeries at the same time, we selected the one surgery that required the most medical resources. Postoperative LOS was determined as the days between the day of the surgery and that of discharge.

Descriptive statistics

The proportions of patients who received each drug were compared between 2006 and 2007. Combinations of remifentanyl and fentanyl, and of nitrous oxide and volatile agents, were also compared between the 2 years. Further, postoperative in-hospital mortality, duration of anesthesia, postoperative LOS, and total costs were compared between the 2 years for all populations and eight surgical subcategories.

Logistic regression to determine factors for selecting remifentanyl

To determine possible contributing factors for selection of remifentanyl, we extracted the data of patients who had general anesthesia with either fentanyl alone or remifentanyl and fentanyl in 2007. In the logistic regression model, the dependent variable was set as “remifentanyl use” (fentanyl alone = 0; both remifentanyl and fentanyl = 1). A hierarchical mixed-effects logistic regression analysis was performed in which age, sex, intraoperative use of epidural anesthesia, comorbidities, and surgical subcategories were set as fixed effects, and sites (described by unique identifiers for all 243 hospitals) were used as random intercepts.

Statistical analysis

We performed univariate comparisons of variables for the two groups, using the Mann–Whitney *U* test for nonparametric data and the chi-square test for categorical data as appropriate. All statistical analyses were conducted using the SAS 9.1 (SAS Institute, Cary, NC, USA), and *P* values <0.05 were considered to be significant. The exchange rate was assumed to be 100 yen to 1 U.S. dollar (USD).

Results

Patient demographics

All 243 acute care hospitals that participated in DPC in both 2006 and 2007 were enrolled in this study. A total of 423,491 patients (206,102 in 2006 and 217,389 in 2007) were identified. Overall, 59.6% of patients were admitted

to 53 teaching hospitals, while the remaining 40.4% were treated at 190 non-teaching hospitals (Supplemental Tables 1, 2).

Anesthetic drug used

Table 1 shows the use of each anesthetic drug in 2006 and 2007. Remifentanyl accounted for 41.4% of all general anesthesia usage in 2007. The proportion of cases in which either fentanyl or remifentanyl was used increased from 76.5% in 2006 to 83.3% in 2007. The proportion including remifentanyl in 2007 was higher in teaching hospitals than

Table 1 Anesthetic drugs used

Drug	2006 (<i>n</i> = 206,102) (%)	2007 (<i>n</i> = 217,389) (%)	<i>P</i> *
Narcotics			
Remifentanyl	0.0	41.4	<0.001
Fentanyl	76.5	71.2	<0.001
Morphine	13.7	13.4	<0.001
Hypnotics			
Barbiturates	18.4	14.9	<0.001
Propofol	72.8	76.9	<0.001
Midazolam	9.4	12.6	<0.001
Nitrous oxide	25.8	14.0	<0.001
Volatile anesthetic agents			
Sevoflurane	79.5	74.2	<0.001
Isoflurane	4.6	3.3	<0.001
Halothane	0.1	0.1	0.732
Muscle relaxants			
Suxamethonium	0.5	1.3	<0.001
Vecuronium	84.2	81.9	<0.001
Rocuronium	0.0	2.6	<0.001
Pancuronium	1.0	0.9	0.158
Others			
Droperidol	12.2	13.9	<0.001
Ketamine	5.1	3.8	<0.001
Diazepam	1.3	1.2	0.023
Combination of fentanyl and remifentanyl			
Neither	23.5	16.7	<0.001
Fentanyl alone	76.5	41.9	<0.001
Remifentanyl alone	0.0	12.1	<0.001
Both	0.0	29.3	<0.001
Combination of nitrous oxide and volatile agents			
Neither	14.0	21.0	<0.001
Nitrous oxide alone	2.1	1.6	<0.001
Volatile agents alone	60.1	65.0	<0.001
Both	23.8	12.4	<0.001

* *P* value for the comparison between 2006 and 2007 evaluated with the chi-square test