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Case Report

PULSED RADIOFREQUENCY APPLICATION AT SOME DORSAL ROOT GANGLIONS COULD CAUSE DRASTIC NEUROMODULATION THROUGHOUT THE WHOLE BODY

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Background: The modified technique, pulsed radiofrequency (PRF) procedure, applied to nervous tissue has been providing anecdotal benefits for the management of chronic and intractable pain conditions. Although PRF has a neuromodulatory effect instead of thermally lesioning nervous tissue, the mechanism underlying the analgesic effect of PRF has not been fully clarified yet.

Objectives: To see the *changes of* electrically-evoked responses of peripheral A-δ and A-β nerve fibers and the analgesic effect induced by PRF.

Study Design: Case series.

Setting: Inpatient.

Methods: This study investigated how dorsal root ganglion (DRG) PRF influenced electrically-evoked responses of peripheral A-δ and A-β nerve fibers at the treated root ganglion dominating areas in five patients with intractable vertebral metastatic pain.

Results: DRG PRF provided sound pain relief for patients with intractable vertebral metastatic pain. PRF application at DRGs had a different effect on electrically-evoked responses of peripheral A-δ and A-β nerve fibers at not only the treated root ganglion dominating areas but also the non-treated root ganglion dominating areas far from the treated root ganglion dominating areas in each patient.

Limitation: This report is a case series.

Conclusions: PRF application at some peripheral nerves could cause drastic neuromodulation throughout the whole body.

Key words: Pulsed radiofrequency, dorsal root ganglion block, neuromodulation

Radiofrequency (RF) has been used for pain management for a long time. There are 2 types of RF procedures, continuous and pulsed stimulation (1-3). The modified technique, pulsed radiofrequency (PRF) procedure, delivers short pulses of RF energy. In recent years, PRF applied to nervous tissue has been providing anecdotal benefits for the management of chronic and intractable pain conditions such as neuropathic pain and vertebral metastatic pain (2-6).

Although PRF has a neuromodulatory effect, instead of thermally lesioning nervous tissue (1,7), the mechanism underlying the analgesic effect of PRF has not been fully clarified yet. We report here how dorsal root ganglion (DRG) PRF influenced electrically-evoked responses of peripheral A-δ and A-β nerve fibers at the treated root ganglion dominating skin areas (dermatomes supplied by the nerves) in 5 patients with intractable vertebral metastatic pain.

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CASE PRESENTATION

The present case series study was performed on 5 patients suffering from intractable vertebral metastatic pain, who visited the pain center at a university hospital. All patients were referred from other departments to the pain center because of intractable pain. They were confirmed to have vertebral metastases by bone scintigraphy, computerized tomography (CT), and magnetic resonance imaging (MRI) (Fig. 1-3). Treatment protocols used in the present report were based on institutional policy and clinical guidelines approved by the IRB of the university. The treatment

Fig. 1. Typical bone scintigraphic image of vertebral metastasis.

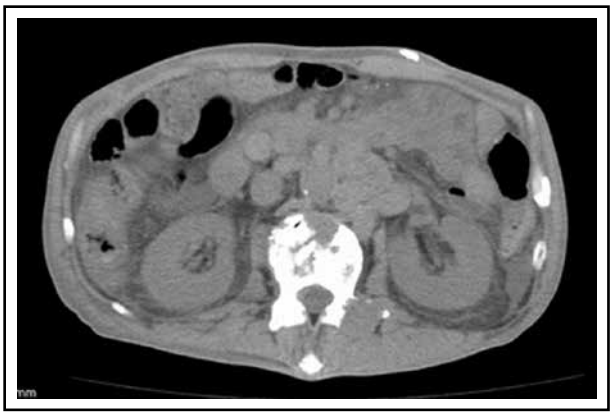

Fig. 2. Typical CT image of vertebral metastasis.

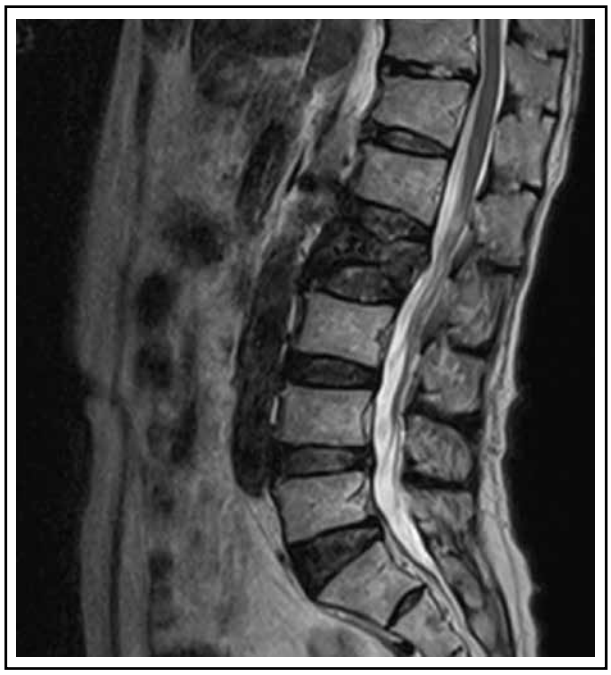

Fig. 3. Typical MRI image of vertebral metastasis.

guidelines for patients with intractable vertebral metastatic pain are as follows: patients who are referred to the pain center will be treated while receiving the recommended systemic analgesics, and if the systemic analgesics do not provide sound pain relief, we propose administering them with DRG PRF, but it is not indicated for patients with neurological deficit, coagulopathy, or significant cardiovascular disease. After obtaining approval from the ethics committee of the university and written informed consent, we routinely recorded demographics, symptoms, and course of pain in all patients. Information was extracted from medical records, after the patients provided written consent for their information to be used for this case series report.

According to the confirmed metastatic region, the patients underwent fluoroscopically or CT-guided selective DRG PRF therapy bilaterally for each metastatic vertebral body. Selective DRG PRF therapy was performed by one of the authors (ARAI). After sterile skin preparation with chlorhexidine, a radiofrequency needle with a 5 mm active tip (KT, Guiding needle, Hakko Co. Ltd., Japan) was inserted and guided by fluoroscopy or CT (Fig. 4, 5), and the location of the needle tip was confirmed not only by image, but also by electrostimulation. Patients were not injected with any local anesthetics or steroids prior to RF. The needle was connected to a RF generator (JK-3, Neurotherm, Morgan Automation Ltd., U.K.). The PRF consisted of an RF current of 2 Hz at 40 V with 20 ms active and 480 ms silent periods. The PRF treatment for each DRG was 2 sets of 2 minute RF current, whereby the temperature at the needle tip did not exceed 42°C. A numerical rating scale (NRS) at rest and while moving, ranging from 0 to 10 (0 = no pain, 10 = worst pain imaginable), was evaluated and recorded before 1 hour and 1 day after PRF. Electrically-evoked responses of peripheral A-δ and

A-β nerve fibers were evaluated and recorded at the treated root ganglion dominating and non-dominating areas before 1 hour and 1 day after PRF.

Nociceptive and Tactile Stimulation

For nociceptive stimulation, we used a modified method of intraepidermal electrical stimulation (IES) for the selective activation of cutaneous A-δ fibers (8-10). In this study, we used a stainless steel concentric bipolar needle electrode (Nihon Kohden, Tokyo, Japan) for IES. The anode was an outer ring 1.3 mm in diameter and the cathode was an inner needle that protruded 0.1 mm from the outer ring. By pressing the electrode against the skin gently, the needle tip was inserted in the epidermis where nociceptors are located, while the outer ring was attached to the skin surface. The electrical stimulus was 2 triangular pulses of 1.2 ms in duration (0.6 ms rise and fall) at an interstimulus interval of 20 ms. Three electrodes and double pulses were used to augment the response for temporal and spatial summation. For tactile stimulation, similar cutaneous sites were stimulated for A-β fibers distributed mainly in the cutaneous using the same electrode for A-δ fibers, but only outer ring without needle part by monopolar stimulation (transcutaneous electrical stimulation (TS)). The stimulus was 2 square pulses of 1.2 ms in duration at an interstimulus interval of 20 ms. Sensory thresholds of IES and TS were applied to the dorsum of the right hand and the affected areas (the chest or the leg), and the sensory threshold was measured before and after the treatment. For IES, we started stimulation with an intensity of 0.01 mA and gradually increased the current in 0.01 mA increments until the subject felt a pricking sensation, and then gradually reduced the current in 0.01 mA decrements to the point where the sensation disappeared. Usually, the pricking sensation disappeared with a decrease of 0.01 mA, but some subjects could feel a similar, but weaker sensation at this intensity. Under the pain threshold, no sensations occurred in any subject. The upper limit of the intensity of IES was set at 1.0 mA. The threshold of tactile sensations for TS was measured similarly.

PRF Effects

The pathophysiological characteristics and therapeutic management of the patients are described in Table 1. Patient 1 underwent selective DRG PRF

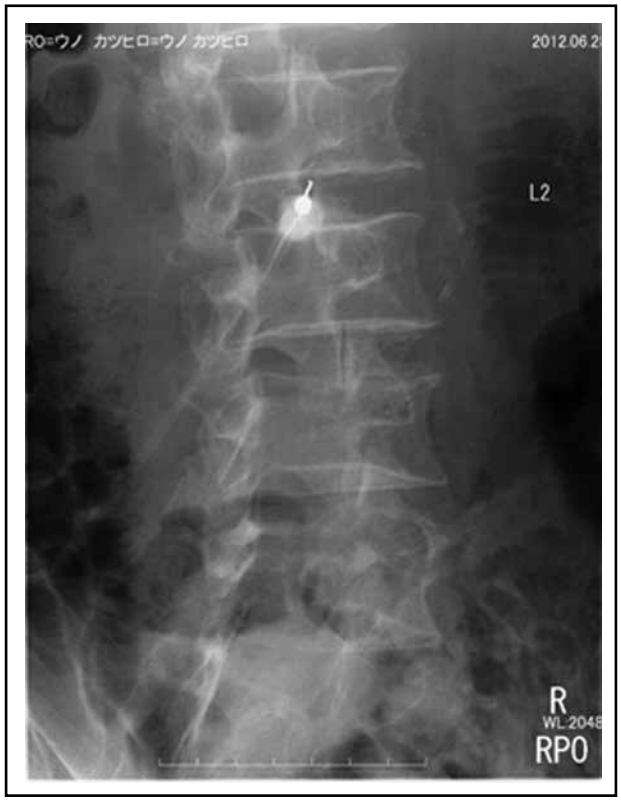

Fig. 4. Typical fluoroscopic images of RF needle placement.

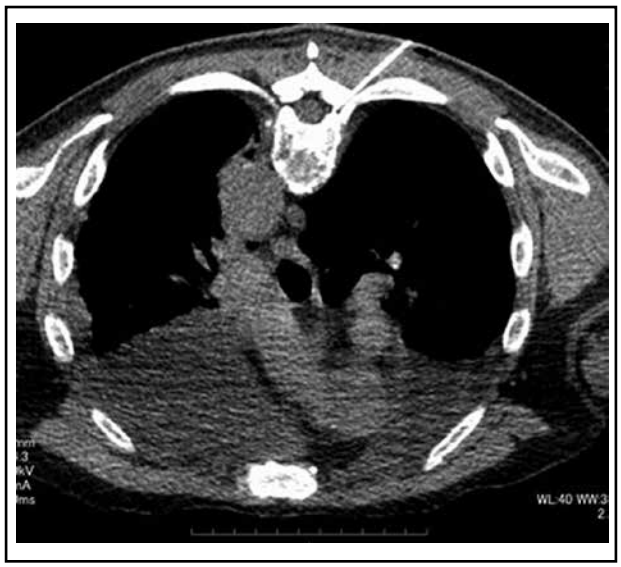

Fig. 5. Typical CT guided Image of RF needle placement.

therapy bilaterally for T7 vertebral body. Patient 2 underwent selective DRG PRF therapy bilaterally for L1 and 2 vertebral bodies. Patient 3 underwent selective DRG PRF therapy bilaterally for L1, 2, and 3 vertebral bodies. Patient 4 underwent selective DRG PRF therapy bilaterally for L4 vertebral body. Patient 5 underwent selective DRG PRF therapy bilaterally for L2, 3, and 4 vertebral bodies. Table 2 shows the individual changes of NRS, the pain threshold of IES, and tactile threshold of TS. All patients experienced sound pain relief after DRG PRF. In a part of our preliminary study using 12 healthy subjects (10), the pain threshold of IES for the right hand, right foot, right chest, and right leg was 0.07 - 0.13, 0.09 - 0.14, 0.09 - 0.15 and 0.07 - 0.14 mA respectively, and the tactile threshold of TS for the right hand, right foot, right chest, and right leg was 0.36 - 0.55, 0.40 - 0.65, 0.38 - 0.65 and 0.40 - 0.65 mA respectively.

In patient 1, the thresholds of IES for the right hand and the root ganglion dominating area (the right chest) were 3 times the normal limits (0.39 and 0.36 mA, respectively), but those of TS for the right hand and the right chest were within the normal limits (0.49 and 0.40 mA, respectively). After the treatment, while the thresholds of IES for the right hand further increased twofold, the thresholds of IES for the root ganglion dominating area (the right chest) decreased to the normal limits. The threshold of TS for the right hand increased after the treatment, but the threshold of TS for the right chest did not show apparent changes. In patient 2, the thresholds of IES for the right hand and the root ganglion dominating area (the right leg) were twice as high as the normal limit (0.21 and 0.29 mA, respectively). The threshold of TS for the right hand was lower than the normal limit (0.30 mA). In contrast, the threshold of TS for the root ganglion dominating area (the right leg) was a little bit higher than the normal limit (0.75 mA). After the treatment, the threshold of IES for the right hand slightly increased (0.25 mA), but that of TS for the right hand increased twofold. In contrast, the threshold of IES for the root ganglion dominating area (the right leg) increased to 0.39 mA and then decreased to the previous value, and that of TS for the right leg obviously decreased under the normal limit (0.25 mA) and then increased to the normal limit. In patient 3, the threshold of IES for the right hand was within the normal limit (0.09 mA), but that of TS for the right hand was slightly lower than the normal limit (0.30 mA). In contrast, the threshold of IES for the root ganglion dominating area (the right leg) was about 3 times as high as the normal limit (0.31 mA), but that of TS for the right leg was much lower than the normal limit (0.12 mA). After the treatment, the thresholds of IES and TS for the right hand doubled 1 day later (0.22 and 0.57 mA, respectively). In contrast, the thresholds of IES and TS for the root ganglion dominating area (the right leg) radically went up 1 hour later (0.79 and 0.56 mA, respectively) and then went down (0.45 and 0.12 mA, respectively). In patient 4, the thresholds of IES and TS for the right hand were within the normal limit (0.08 and 0.48 mA, respectively). In contrast, the threshold of IES for the root ganglion dominating area (the right leg) was remarkably higher than the normal limit (0.50 mA). After the treatment, the threshold of IES for the right hand increased twofold (0.20 mA), but that of TS for the right hand hardly changed. In contrast, the threshold of IES for the root ganglion dominating area (the right leg) once decreased to 0.58 mA and then increased to the previous value, but that of TS for the right leg gradually increased to 0.70 mA. In patient 5, the thresholds of IES for the right hand and the root ganglion dominating area (the right leg) were 3 times as high as the normal limit (0.29 and 0.33 mA, respectively). In contrast, the thresholds of TS for the right hand and the right leg were slightly higher than the normal limit (0.68 and 0.75 mA, respectively). After the treatment, the threshold of IES for the right hand decreased to the normal limit, but that of IES for the root ganglion dominating area (the right leg) once decreased and then increased to the previous level. In contrast, the thresholds of TS for the right hand and the right leg gradually decreased to the normal limit (0.37 and 0.45 mA, respectively).

DISCUSSION

PRF is applied to not only the DRG, but also to the peripheral nerve, which provides sound pain relief for several pain conditions for 2 to 6 months (1,2,4-6). Animal studies also show the antinociceptive effects of DRG PRF (11,12). PRF applied to the DRG induces inhibition of excitatory c-fiber responses and global reduction of evoked synaptic activity. Several studies reported that the antinociceptive actions induced by PRF are partially due to the enhancement of noradrenergic and serotonergic descending pain inhibitory pathways and the inhibition of excitatory c-fibers (7). Also, a spared nerve injury model showed that after

Table 1. Characteristics and pharmacological treatment used on the patients.

Patient	Age (years)	Gender	Weight (kg)	Origin	Metastatic region	Daily opioid dose[a] (mg/day)	Pharmacological treatment
1	71	Male	58	Lung	T7	5	PGB 75 mg/day + MTP 10 mg/day
2	45	Male	55	Colon	L1-2	50	PGB 50 mg/day
3	42	Male	60	Lung	L1-3	90	PGB 50 mg/day + IPM 30 mg/day
4	61	Male	54	Liver	L4	190	-
5	78	Female	45	Lung	L2-4	5	PGB 50 mg/day

Abbreviations: PGB, pregabalin; MTP, mirtazapine; IPM, imipramine. [a]Oral morphine equivalent.

Table 2. Pain scores at rest and while moving and thresholds with each stimulus condition (TS and IES) before and after PRF.

Patient		NRS		Threshold (mA)			
		Rest	Moving				
1 Male				Rt hand (IES)	Rt hand (TS)	Rt chest (IES)	Rt chest (TS)
	Before	4	7	0.39	0.49	0.36	0.40
	1 hour later	2	4	0.40	0.49	0.30	0.47
	1 day later	2	5	0.99	0.65	0.15	0.40
2 Male				Rt hand (IES)	Rt hand (TS)	Rt leg (IES)	Rt leg (TS)
	Before	3	8	0.21	0.30	0.29	0.75
	1 hour later	1	4	0.25	0.59	0.39	0.25
	1 day later	1	3	0.25	0.60	0.30	0.59
3 Male				Rt hand (IES)	Rt hand (TS)	Rt leg (IES)	Rt leg (TS)
	Before	5	7	0.09	0.30	0.31	0.12
	1 hour later	0	2	0.07	0.20	0.79	0.56
	1 day later	1	4	0.22	0.57	0.45	0.12
4 Male				Rt hand (IES)	Rt hand (TS)	Rt leg (IES)	Rt leg (TS)
	Before	3	6	0.08	0.48	0.80	0.50
	1 hour later	1	2	0.17	0.50	0.58	0.60
	1 day later	1	2	0.20	0.50	0.80	0.70
5 Female				Rt hand (IES)	Rt hand (TS)	Rt leg (IES)	Rt leg (TS)
	Before	6	7	0.29	0.68	0.33	0.75
	1 hour later	1	2	0.08	0.51	0.20	0.60
	1 day later	2	4	0.12	0.37	0.33	0.45

Abbreviations: NRS, numerical rating scale; Rt, Right

an PRF electrode was applied to the sciatic nerve proximal to the site of injury of this nerve, increased proinflammatory gene expression, such as TNF-α and IL-6, observed at the site of injury in the sciatic nerve returned to baseline values, up-regulation of GABAB-R1, Na/K ATPase, and 5-HT3r, as well as down-regulation of TNF-α and IL-6, were identified in the DRG, and up-regulation of Na/K ATPase and c-Fos were found in the spinal cord (13).

In patients 1, 2, and 5 of the present case series, their right hands were two- to threefold less sensitive to noxious stimulation, but were normal or slightly less sensitive to tactile stimulation before the PRF treatment, which means that their medication hardly influenced tactile sensation, but greatly affected nociceptive sensation. Similarly, their affected area, the right chest or right leg, were threefold less sensitive to noxious stimulation, but were normal or slightly less or more sensitive to tactile stimulation, which means that their medication and vertebral metastasis hardly influenced tactile sensation, but greatly affected nociceptive sensation. In contrast, although their right hands were almost within the normal limits for not only noxious stimulation, but also tactile stimulation

in patients 3 and 4, the affected areas, the right legs, were more than threefold less sensitive to noxious stimulation and were more sensitive to tactile stimulation, especially in patient 3. That is, their medication and vertebral metastasis caused neuromodulation.

Since all previous studies have investigated the effects of PRF on the treated nerves and DRGs per se and the related dorsal horn of the spinal cord (11-14), we at first expected PRF application at DRG would induce only a local effect. However, our findings showed for the first time that PRF application at 2 to 6 DRGs altered nociceptive and tactile sensation, not only at the treated root ganglion dominating skin areas (dermatomes supplied by the nerves), but also at the non-treated root ganglion dominating skin areas far from the treated root ganglion dominating areas right after the treatment, which indicates that PRF application at some peripheral nerves could give rise to drastic neuromodulation throughout the whole body possibly by means of neural network, thereby leading to anecdotal pain relief. Also, our findings showed marked pain reduction and changes of nociceptive and tactile sensation not only at the treated root ganglion dominating skin areas, but also at the non-treated root ganglion dominating skin areas immediately 1 hour after the treatment. Since these phenomena have not reported before the present study, we need further studies for them.

There are several limitations to the present report. The present report is a case series and not a randomized control analysis. Also, we did not investigate what happens throughout the whole central nervous system. We thus need further research by using electroencephalography and fMRI. We used 3 concentric electrodes and double pulses for the following reasons: 1) the number of needle electrodes in Aδ-fiber stimulation is crucial because expanding the area of nociceptive stimulation lowers the sensory threshold and enhances pain sensation. This effect is thought to be based on the special summation (15). Actually, although we used one concentric needle electrode in the previous study, we realized 3 electrodes could elicit more clear pain sensation than 1 electrode (16); 2) similarly, the number of electric pulses affect nociceptive sensation. One short pulse could elicit nociceptive sensation sufficiently, but double pulses are more effective for clear-cut pain sensation. This is also thought to be based on the temporal summation (17). Furthermore, we tried to use 3 or 4 electric pulses in the preliminary experiments and we found the problem of high time jittering. Thus, we adopted double electric short pulses.

In conclusion, DRG PRF procedure provided sound pain relief for patients with intractable vertebral metastatic pain. PRF application at DRGs had a different effect on electrically-evoked responses of peripheral A-δ and A-β nerve fibers at not only the treated root ganglion dominating areas, but also the non-treated root ganglion dominating areas far from the treated root ganglion dominating areas in each patient.

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