Modified dorsal root entry zone lesioning for intractable pain relief in patients with root avulsion injury

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OBJECTIVE Dorsal root entry zone (DREZ) lesioning has been the most effective surgical treatment for the relief of intractable pain due to root avulsion injury, but residual pain and a decrease in pain relief in the follow-up period have been reported in 23%–70% of patients. Based on pain topography in the most recent studies on neuropathic pain, the authors modified the conventional DREZ lesioning procedure to improve clinical outcomes. The presumed rationale for this procedure is to eliminate the spontaneous discharges of neurons in the superficial spinal dorsal horn as well as wide dynamic range neurons in the deep spinal dorsal horn.

METHODS Ten patients with avulsion-related pain underwent surgery between 2011 and 2015. The surgical procedure was described and postoperative pain relief was assessed as follows: excellent (residual pain never exceeded 3 on the visual analog scale [VAS] without medication), good (residual pain never exceeded 5 on the VAS with medication), and poor (residual pain was greater than 5 with medication). Specific perioperative complications were assessed.

RESULTS The aim of this surgical procedure was to destroy the deeper layers of the posterior horn of spinal gray matter, which was in contrast to the procedures of Nashold and Sindou, which were to destroy the superficial layers. All patients achieved excellent (n = 7, pain relief without medication) or good (n = 3, pain relief with medication) pain relief postoperatively, and the recurrence of pain was not reported in any patients (median 29 months after surgery, range 12–64 months). Nine patients (90%) achieved complete pain relief (a score of 0 or 1 on the VAS) with or without medication. No surgical site complications such as infection or CSF leakage were noted. No motor deficit was observed in any patient. A sensory deficit was observed in 2 patients and disappeared within 1 month in 1 patient. New pain at the adjacent level of DREZ lesioning was observed in 3 patients and disappeared within 1 month in 2 patients. In the other patient, new pain persisted and required analgesics.

CONCLUSIONS These preliminary results demonstrated that total and persistent global pain relief was achieved with the modified DREZ lesioning procedure in 90% of patients without major neurological deficits. The clinical improvements achieved by this modified surgical procedure support the hypothesis that not only the superficial layers, but also deeper layers of the spinal dorsal horn are associated with intractable pain due to root avulsion injury.

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KEY WORDS neuropathic pain; central pain; dorsal root entry zone; lesions; posterior horn; substantia gelatinosa; wide dynamic range neuron

PAIN in the upper extremities due to root avulsion injury is caused by the hyperexcitability of deafferented neurons related to pain conduction in the posterior horn of spinal gray matter. Pain due to root avulsion injury is defined as neuropathic pain in the CNS and is intractable and refractory to various types of medical and surgical treatments.³ Dorsal root entry zone (DREZ) lesioning, i.e., coagulation of the DREZ by a thermocoagulation electrode^{4,8} or microsurgical bipolar coagulation,⁹

was developed in the 1970s and has been the most effective surgical treatment for relief from intractable avulsion-related pain. However, there are some limitations, such as residual pain and a decrease in pain relief in the long-term follow-up period.^{7,10,11} The aim of these traditional neurosurgical procedures is to destroy the superficial layers of the posterior horn, the cells of the substantia gelatinosa, and is based on basic research published in the 1970s on the spinal gray matter of animals.⁸ More recent findings

ABBREVIATIONS DREZ = dorsal root entry zone; MEP = motor evoked potential; VAS = visual analog scale; WDR = wide dynamic range.

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on neuropathic pain suggest that not only the superficial layers, but also deeper layers of the posterior horn in spinal gray matter are associated with pain conduction.^{1,12} Based on the most recent findings in the field, we developed a modified surgical procedure to destroy the cells of the deeper layers of the posterior horn. The aim of this study was to assess the clinical outcomes of patients who underwent the modified surgical procedure and test the hypothesis that the deeper layers of the posterior horn in spinal gray matter are associated with intractable pain due to root avulsion injury.

Methods

This study protocol was approved by the Institutional Review Board at the Tokyo Metropolitan Neurological Hospital. Because this was a retrospective and noninvasive study, written patient informed consent was not obtained. A public notice that provided information on this study was instead given on the Tokyo Metropolitan Neurological Hospital website.

The study population comprised 10 consecutive patients with intractable pain in the upper extremities due to root avulsion injury who underwent the modified DREZ lesioning procedure by the senior author (M.T.) at the Tokyo Metropolitan Neurological Hospital between 2011 and 2015. The surgical procedure was described in detail, including patient position and approach, relevant surgical anatomy, and modified microsurgical lesioning of the posterior horn.

The anteroposterior diameter of the spinal cord and depth of DREZ lesioning were measured at the C4–5, C5–6, and C6–7 intervertebral disc levels (i.e., C-6, C-7, and C-8 spinal segments) on postoperative T2-weighted MR images of the spine from 9 patients. The other patient did not undergo MRI because of a spinal cord stimulation device that had been implanted at another hospital.

The degree of postoperative pain relief was assessed on discharge, at the first outpatient visit (3 months after surgery), and at the last follow-up evaluation (a median of 24 months after surgery) according to the following 3 levels, as described by Sindou et al.¹⁰ 1) excellent, residual pain never exceeded 3 on the visual analog scale (VAS) without medication; 2) good, residual pain never exceeded 5 on the VAS with medication including Class I analgesics, anti-convulsants, and/or tricyclic antidepressants; and 3) poor, residual pain was greater than 5 with medication including Class II analgesics or opioids. Perioperative surgical site and neurological complications and the length of the hospital stay were assessed.

Surgical Procedure

Patient Positioning and Approach

The patient was placed prone, and transcranial motor evoked potentials (MEPs) in the ipsilateral lower extremity were monitored intraoperatively to detect damage in the corticospinal tract in the posterolateral funiculus. In patients who underwent reconstructive surgery for the function of the upper-extremity muscles, the MEPs of the corresponding muscles were also monitored. Cervical multilevel laminotomy was performed using a diamond

T-saw. At the end of surgery, the laminae were fixed with titanium plates.

Relevant Surgical Anatomy

Gray matter in a healthy spinal cord is divided into 10 layers of major neurons, namely the laminae of Rexed I–X (Fig. 1).⁶ The posterior horn of gray matter comprises 6 layers, the laminae of Rexed I–VI. The major neuron in the lamina of Rexed I is the posteromarginal nucleus, while that in lamina II is the substantia gelatinosa, both of which receive peripheral pain afferents. Major neurons in the lamina of Rexed V are wide dynamic range (WDR) neurons and were recently suggested to be associated with pain.¹ In a healthy spinal cord, the lamina of Rexed II is located at a depth of 2–3 mm from the surface of the DREZ. The lamina of Rexed VI reaches a depth of 4–5 mm from the surface of the DREZ.

Modified Microsurgical Lesioning of the Posterior Horn

Under the operating microscope, the pia mater of the posterolateral sulcus was incised in the sagittal direction.

FIG. 1. Illustrations showing the anatomy of the posterior horn (A) and primary and secondary afferent pathways in the posterior horn of healthy spinal gray matter (B). The posterior horn of spinal gray matter comprises 6 layers, the laminae of Rexed I–VI (A). The thick C-fibers of nociceptive neurons (red) project to cells in the laminae of Rexed I and II, and connect with the secondary afferent neurons of the contralateral spinothalamic tract (yellow). The narrow A-fibers of the nonnociceptive neurons (green) project to cells in the laminae of Rexed III–VI. Secondary neurons in the deeper lamina of Rexed V (purple) are called WDR neurons because they receive synaptic inputs from A-fibers, connect with the contralateral spinothalamic tract, and are associated with pain conduction. Copyright Keisuke Takai. Published with permission. Figure is available in color online only.

FIG. 2. Illustrations showing the depth of DREZ lesioning of the procedures of Nashold (A) and Sindou (B), as well as our procedure (C). Nashold's and Sindou's procedures aimed at destroying cells in the substantia gelatinosa in the laminae of Rexed I and II. In contrast, our procedure aimed at destroying the deeper layers of the posterior horn of spinal gray matter, including the lamina of Rexed V. In the healthy spinal cord, the depth of the lamina of Rexed II is 2–3 mm (A and B), whereas that of the lamina of Rexed VI is 4–5 mm (C) from the surface of the DREZ. Copyright Keisuke Takai. Published with permission. Figure is available in color online only.

The range of lesioning in the posterior horn of spinal gray matter in the sagittal plane was defined by the segmental levels of the spinal cord in which root avulsion was observed. When a small portion of the avulsed roots remained, the pia mater was incised on the medial side of the residual roots to minimize the risk of damage to the lateral funiculus. Arteries (radiculopial and posterior spinal arteries) and veins (radicular and posterior spinal veins)

FIG. 3. Illustrations showing the sagittal range of DREZ lesioning (A) and relevant vascular anatomy (B) in a case of root avulsion injury at the level of C6–8. The pia mater of the posterolateral sulcus is incised between the healthy spinal roots (black double-headed arrow). The proximal portions of posterior nerve roots are located within the DREZ. The upper and lower limits of lesioning are at the proximal portion of intact C-5 and T-1 posterior nerve roots in the DREZ (blue double-headed arrow). A radiculopial artery courses along the spinal root, turns a hairpin curve, and joins the posterior spinal artery (B). The radiculopial artery is observed in some cases of root avulsion injury. When the posterolateral sulcus is divided, the radiculopial and posterior spinal arteries are preserved intact as much as possible. Copyright Keisuke Takai. Published with permission. Figure is available in color online only.

adjacent to the posterolateral sulcus were preserved intact by cutting the arachnoid trabeculae around the vessels. The goal of DREZ lesioning was to destroy the laminae of Rexed from layers I to VI of the posterior horn in spinal gray matter (Figs. 2 and 3). The spinal cord was divided into the posterior and lateral funiculi using a microsurgical probe according to the fiber bundles of the spinal tracts (Fig. 4). When the posterior and lateral funiculi were completely divided, they spread easily and the posterior horn of spinal gray matter was observed. The posterior horn was lesioned using a microsurgical tumor forceps with a blunt dissection technique at a depth of 4–5 mm from the surface of the DREZ. The depth of DREZ lesioning was measured using a small paper ruler. Bipolar coagulation was avoided to prevent heat injury to the spinal tracts because bipolar coagulation may spread over the posterior or lateral funiculus, resulting in the occlusion of the perforating branches of pial arteries. Gliotic tissues are commonly

FIG. 4. Operative photographs showing our DREZ lesioning procedure. The posterior (asterisk) and lateral (double asterisks) funiculi are divided according to the fiber bundles of spinal tracts (A). During dissection, radiculopial and posterior spinal arteries are preserved intact as much as possible (B). After dissecting the posterior and lateral funiculi, the posterior horn is lesioned by microsurgical tumor forceps with a blunt dissection technique (C). Abnormal gliotic tissues are commonly observed in the deeper layers of the posterior horn (arrow). The gliotic tissues potentially associated with neuropathic pain are resected as much as possible. Figure is available in color online only.

observed in the deeper layers of spinal gray matter and are resected using a tumor forceps where possible.

Results

Patient Characteristics

The 10 patients consisted of 9 men and 1 woman, with a median age of 51 years (range 39–67 years; Table 1). The cause of the root avulsion injury was a motorbike accident in 6 patients, a car accident in 2, and a fall in 2. The time interval between the accident and the worsening of pain varied from immediately after the accident to 18 years (median 1 month). The quality of pain was of a spontaneous and paroxysmal nature. The paroxysm of pain was greater than spontaneous paresthesia and intolerable in all patients, described as “clamping,” “stabbing,” or “boring.” All patients regularly received analgesics, 1 patient was receiving an anticonvulsant, 2 patients were prescribed tricyclic antidepressants, and 2 patients were receiving opioids before surgery. The intensity of paroxysmal pain was a median of 9.5 on the VAS (range 5–10) in spite of the different analgesics or even opioids used. The frequency of paroxysmal pain was 1–3 times per hour all day, with most patients awoken by pain at night. The paroxysm of pain occurred suddenly without a trigger. Of the 10 patients examined, 2 had a previous history of DREZ

lesioning and residual or recurrent pain, and 1 (Case 2) underwent DREZ lesioning using the thermocoagulation electrode at our hospital 14 years ago, but pain recurred 1 year after the first surgery and gradually worsened thereafter. Another patient (Case 8) underwent DREZ lesioning by microsurgical bipolar coagulation at another hospital, but pain recurred 3 weeks after the first surgery.

Depth of DREZ Lesioning

The mean anteroposterior diameter of the spinal cord was 7.3 ± 0.9 mm at C4–5, 6.8 ± 0.9 mm at C5–6, and 6.4 ± 1.1 mm at C6–7 intervertebral disc levels (C-6, C-7, and C-8 spinal segments). The depth of DREZ lesioning was 4.0 ± 1.2 mm at C4–5, 4.1 ± 1.3 mm at C5–6, and 4.2 ± 1.0 mm at C6–7 intervertebral disc levels (Fig. 5).

Pain Relief

All patients, including 2 who underwent repeat surgery, achieved excellent ($n = 7$, relief without medication) or good pain relief ($n = 3$, pain relief with medication) postoperatively (Table 1). All patients continued to be free of paroxysmal pain at the first outpatient visit (3 months after surgery) as well as at the last follow-up evaluation (median of 29 months after surgery, range 18–70 months). Nine patients (90%) achieved complete pain relief (0 or 1 on the

TABLE 1. Clinical characteristics of 10 patients who underwent the new DREZ lesioning procedure

Case No.	Age (yrs), Sex	Etiology	Time Btwn Accident & Pain	Pain Duration (yrs)	Pain Distribution	VAS Score		Postop Analgesics	Pain Relief	FU (mos)
						Preop	Final FU			
1	59, M	Motorbike accident	Immediate	31	Rt C7–8	9	5	Yes	Good	70
2	39, M	Motorbike accident	Immediate	22	Lt C6–8	10	0	No	Excellent	47
3	63, F	Fall	4 mos	8	Lt C5–T1	10	0	Yes	Good	38
4	49, M	Car accident	3 mos	6	Rt C7–8	10	0	No	Excellent	38
5	52, M	Motorbike accident	Immediate	7	Rt C6–8	10	0	No	Excellent	29
6	44, M	Motorbike accident	1 mo	6	Rt C6–8	5	1	No	Excellent	28
7	46, M	Motorbike accident	1 mo	12	Rt C6–8	10	0	No	Excellent	27
8	41, M	Fall	3 wks	4	Rt C6–7	7	0	Yes	Good	23
9	67, M	Car accident	15 yrs	24	Lt C6–8	8	0	No	Excellent	20
10	65, M	Motorbike accident	18 yrs	20	Lt C6–8	5	0	No	Excellent	18

FU = follow-up.

FIG. 5. A representative postoperative axial T2-weighted MR image of the cervical spine (A). The arrow indicates the site of the DREZ lesioning procedure. A representation of parameters to be measured for each patient in axial imaging is shown (B). AP = anteroposterior.

VAS) with or without medication. Among the 9 patients, 7 did not require any analgesic postoperatively, while 2 required half the amount of analgesics because of mild persistent spontaneous paresthesia, but did not require other drugs such as anticonvulsants, tricyclic antidepressants, or opioids postoperatively. The 1 remaining patient achieved good pain relief but required analgesics because of postoperative new pain.

Perioperative Complications

No surgical site complications such as infection or CSF leakage were noted (Table 2). No motor deficit was noted postoperatively in any of the patients, although the amplitude of intraoperative MEPs decreased to less than one-half at the end of surgery in 4 patients. Sensory deficits were noted postoperatively in 2 patients. A permanent sensory deficit was observed at the contralateral C-7 and C-8 dermatomes in 1 patient. This new sensory deficit occurred in the first patient and was presumed to be due to damage to the anterior funiculus, located at the ventral side of the spinal cord. The depth of DREZ lesioning was deeper than expected (6 mm) in this patient. In the other patient, a transient slight hemisensory deficit was observed at the ipsilateral lower extremity. New pain in the cervical dermatome adjacent to DREZ lesioning occurred in 3 patients. New pain disappeared on discharge in 2 patients and did not recur thereafter. In 1 of these 2 patients, the

intravenous administration of *N*-methyl-D-aspartate acid receptor antagonists was effective.⁵ In 1 patient, new pain persisted and required analgesics. Morphine withdrawal syndrome occurred in 1 patient to whom a large amount of opioids was administered preoperatively. The cessation of morphine was eventually achieved in this patient due to excellent global pain relief. The median length of hospital stay was 22 days (range 15–40 days).

Case Illustration

A 39-year-old man (Case 2) was injured in a motor-bike accident when he was 18 years old. Immediately after the accident, severe pain developed in the C6–8 dermatomes of the upper left extremity. The quality of pain was the paroxysmal type, which has been described as being equivalent to “being hit by a baseball bat.” The intensity of paroxysmal pain was 10 on the VAS in spite of the administration of different analgesics. The frequency of paroxysms was once every 2–3 hours all day and continued for 10 minutes each time. The patient underwent DREZ lesioning using a thermocoagulation electrode at our hospital when he was 25 years old. After the first surgery, the intensity of pain decreased to 5 on the VAS; however, a decrease in pain relief occurred 1 year later and eventually deteriorated to the same degree as the preoperative status. T2-weighted MR images showed DREZ lesioning at the C5–8 segmental levels of the cervical cord but the depth of DREZ lesioning was limited to the superficial layers of the posterior horn of spinal gray matter (Fig. 6). Therefore, the patient underwent a second surgery in which the deeper layers of the posterior horn were lesioned using our modified method. After the second surgery, the complete disappearance of paroxysmal pain was achieved and it was possible to discontinue analgesics. A transient slight sensory deficit was observed on the left side, but improved within 1 month. The recurrence of pain was not reported in the 42-month follow-up period.

Discussion

In the present study, we described a modified DREZ lesioning procedure for the relief of intractable pain due to root avulsion injury. The target of DREZ lesioning in the procedure is deeper than that of conventional surgery

TABLE 2. Complications in 10 patients who underwent the new DREZ lesioning procedure

Case No.	Neurological Complications	Outcome
1	New pain at C-6; sensory deficit at contralateral C-7, C-8	New pain persisted & required analgesics; sensory deficit also persisted
2	Hemisensory deficit	Sensory deficit disappeared on discharge
3	None	
4	None	
5	New pain at C-5	New pain disappeared on discharge
6	Morphine withdrawal syndrome	Cessation of morphine was achieved
7	None	
8	None	
9	New pain at T-1	New pain disappeared on discharge
10	None	

None of the patients experienced surgical site complications.

FIG. 6. Case 2. Axial T2-weighted MR images showing a comparison between the results of Nashold's procedure (A–C) and the modified DREZ lesioning procedure (D–F) at the C-6 (A and D), C-7 (B and E), and C-8 (C and F) segmental levels of the spinal cord. Note the difference between the 2 procedures: the depth of DREZ lesioning (arrow) is limited to the superficial layers with Nashold's procedure, whereas it reaches deeper layers with our procedure.

(Figs. 2–4). Previous studies did not provide the outcomes of the conventional surgical procedure by postoperative imaging;^{8,10} however, those of our surgical procedure were objectively confirmed by postoperative MRI (Figs. 5 and 6). With this modified neurosurgical procedure, excellent and lasting global pain relief was achieved in 90% of patients without permanent motor or sensory neurological deficits (Table 1). Our procedure was effective in patients who underwent this surgery for the first time and also in those with residual and recurrent pain who had a previous history of the conventional DREZ lesioning procedure and underwent this surgery for the second time.

In thermocoagulation DREZ lesioning described by Nashold and Ost Dahl,⁸ the depth of lesioning in the posterior horn in the axial plane was defined based on basic research published in 1973 by Denny-Brown et al.² on spinal gray matter in monkeys. Denny-Brown et al. reported that cells in the substantia gelatinosa in the monkey develop a state of prolonged tonic discharge after dorsal-root interruption. Therefore, the depth of lesioning in Nashold's procedure is 2 mm from the surface of the DREZ, which corresponds to the superficial layers of the posterior horn. The target of the superficial layers of the posterior horn is cells in the substantia gelatinosa in the lamina of Rexed II. In the microsurgical "DREZotomy" described by Sindou et al.,⁹ which is diverted from selective posterior rhizotomy for Pancoast tumors, the depth of lesioning is 2–3 mm from the surface of the DREZ, which also corresponds to the superficial layers of the posterior horn. However, in recent basic research on neuropathic pain, neurons related to pain conduction were found to be located in the superficial and deeper layers of the posterior horn in spinal gray matter (Fig. 1). These neurons are referred to as

WDR neurons because they receive direct inputs from nociceptive neurons, which project to the superficial layers of the posterior horn, as well as multisynaptic inputs from nonnociceptive neurons in the deeper layers.¹ Increased spontaneous firing in WDR neurons after nerve injury is related to the development of mechanical allodynia in animal models of neuropathic pain.¹² Based on the latest findings on neuropathic pain, we modified the depth of DREZ lesioning to 4–5 mm from the surface of the DREZ, which corresponds to the laminae of Rexed I–VI in the posterior horn. The presumed rationale for our modified DREZ lesioning is to eliminate the spontaneous discharges of neurons in the superficial spinal dorsal horn and WDR neurons in the deep spinal dorsal horn. In all patients, gliotic tissues were observed in the deeper layers of the posterior horn of gray matter. The spinal segmental levels of the gliotic tissues corresponded to the most painful area in the dermatomes of the upper extremities and may be associated with an abnormal hypersensitive neural pool due to deafferentation.

Limitations

This preliminary study was limited by the small number of patients. Assessments of the surgical outcomes of patients treated by our procedure were not compared prospectively with those of patients treated with other conventional procedures. DREZ lesioning, including our modified procedure, is limited by the development of postoperative new pain adjacent to the spinal levels of lesioning because of its destructive nature. The cause of new pain was presumed to be due to damage to the healthy posterior horn adjacent to avulsed levels or to the healthy anterior funicu-

lus during the DREZ lesioning procedure. In our patients, new pain was curable with conservative treatment. The safety of lesioning of the spinal cord needs to be evaluated in well-designed studies using a larger number of patients.

Conclusions

With the modified DREZ lesioning procedure, total and lasting global pain relief was achieved in most patients without major neurological deficits. The clinical improvements achieved by our modified surgical procedure support the hypothesis that not only the superficial layers, but also deeper layers of the posterior horn in the spinal gray matter are associated with intractable pain due to root avulsion injury.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: both authors. Acquisition of data: Takai. Analysis and interpretation of data: Takai. Drafting the article: Takai. Critically revising the article: Taniguchi. Reviewed submitted version of manuscript: both authors. Approved the final version of the manuscript on behalf of both authors: Takai. Study supervision: Takai.

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