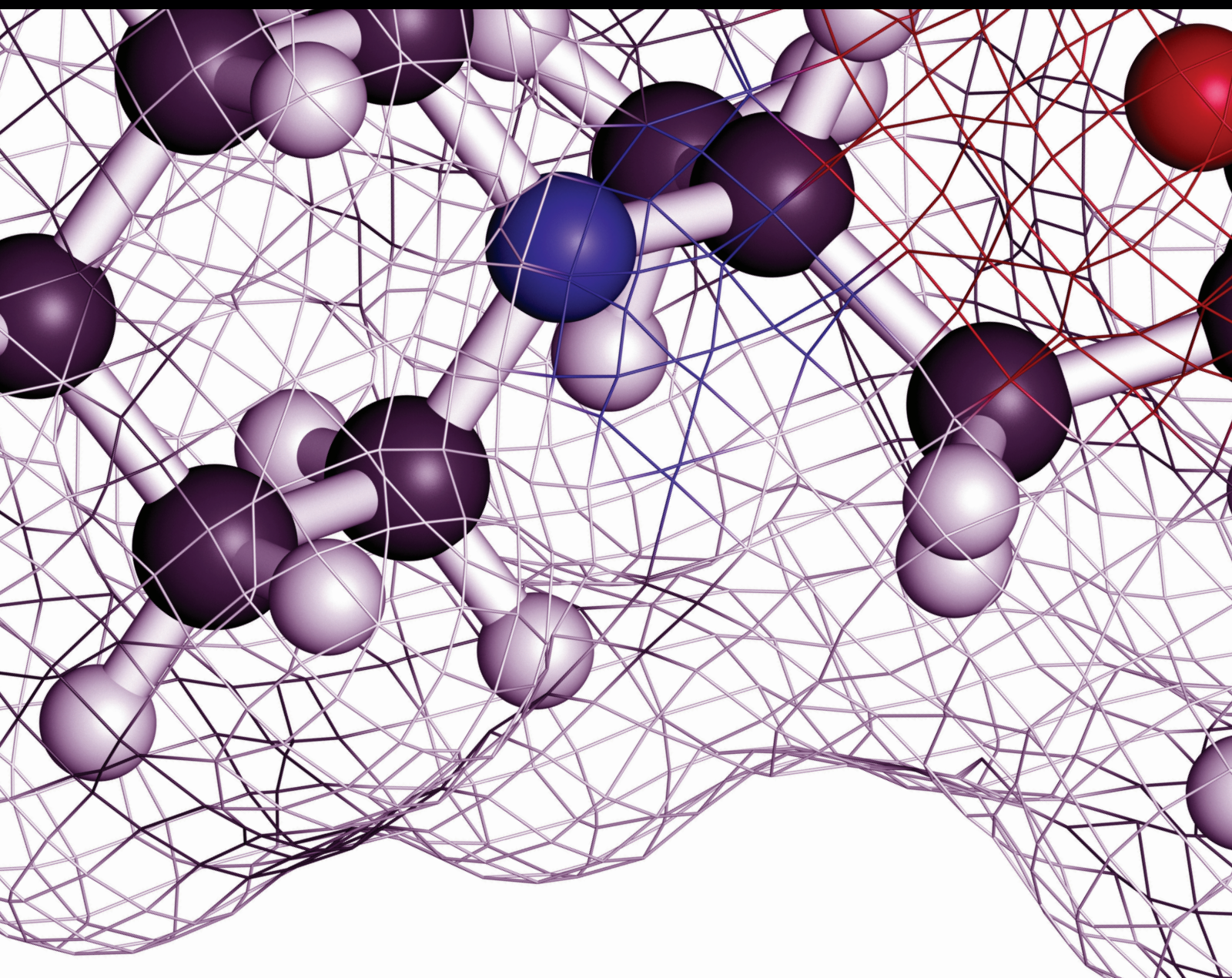
Pain Research and Management

Chronic Spinal Pain: Pathophysiology, Diagnosis, and Treatment

Lead Guest Editor: Baogan Peng
Guest Editors: Nikolai Bogduk, Michael J. DePalma, and Ke Ma



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Editorial Board

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Hindawi
Pain Research and Management
Volume 2019, Article ID 1729059, 2 pages
https://doi.org/10.1155/2019/1729059

Editorial

Chronic Spinal Pain: Pathophysiology, Diagnosis, and Treatment

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Received 28 July 2019; Accepted 29 July 2019; Published 15 August 2019

Chronic spinal pain is one of the most leading causes of disability among adults worldwide. It covers chronic neck, thoracic, and low back pain. Despite the frequency of this presenting complaint, a clear understanding of its etiologies is often elusive. Any innervated spinal structures, such as muscles, synovial joints, intervertebral discs, dura mater, and ligaments, may cause pain theoretically. Because the diagnosis of chronic spinal pain is difficult, its treatment is usually nonspecific. This special issue seeks to cover chronic spinal pain-related basic and clinical studies.

Pulsed radiofrequency (PRF) is effective in the treatment of spinal pain and neuropathic pain. The research of X. R. Xu et al. showed that microglial BDNF, PI3K, and p-ERK in spinal cord are suppressed by the treatment of PRF on DRG to ease SNI-induced neuropathic pain in rats, which provided a theoretical basis for the clinical spinal pain management. J. N. Wang et al. showed that intrathecal administration of low-concentration oxygen/ozone alleviated mechanical allodynia and attenuated radiculitis, likely by a PDE2A-cGMP/cAMP-NF-kappa B/p65 signaling pathway in chronic radiculitis rats. This study provided a new theoretical basis for the treatment of spinal radiculitis pain. The study from J. Yang et al. founded that the mice SMIR model presented a persistent pain syndrome, including evoked pain and spontaneous pain. Clonidine and gabapentin can relieve mechanical hypersensitivity dose-dependent simultaneously. However, clonidine but not gabapentin can alleviate the spontaneous pain of SMIR in the mice model. It may provide a new choice in the prevention and treatment of postoperational spinal-related pain.

Spinal pain is a kind of neuropathic pain. S. F. Husain et al. suggested that matrix metalloproteinases-12 (MMP-12) is a potential biomarker of neuropathic pain. Its detection in vivo, using IONP enhanced MRI, may be further developed as a tool for neuropathic pain diagnosis and management. Y. F. Chen et al.'s article showed that the existence of MCs (Modic changes) affects the outcomes of nonsurgical treatment in patients with LBP. However, symptoms can be improved after an additional round of treatment for Modic type I changes, while this is not confirmed for Modic type II changes.

How to diagnose and treat spinal pain effectively and safely is the key part of this special issue. The special issue accepted three consensuses from the CASP (Chinese Association for the Study of Pain): Cervicogenic headache consensus emphasized the early diagnosis of cervical headache and the appropriate time for minimally invasive interventional therapy. Osteoarthritis consensus explained the whole process management of prevention, rehabilitation, and pain diagnosis and treatment of osteoarthritis. Nonspecific low back pain consensus showed the importance of correct diagnosis and effective treatment of nonspecific low back pain. Three consensuses will provide a high-quality reference for the formulation of pain diagnosis and treatment strategies in different disciplines. P. Rigoard et al.'s study showed that the utilization of a multidisciplinary approach is emphasized to ensure that care is provided in a uniform manner to reduce variation in practice and improve patient outcomes. B. B. Wu et al.'s paper showed that the safety and effectiveness of transforaminal percutaneous endoscopic lumbar discectomy with foraminoplasty (TF PELF) are comparable to TF

percutaneous endoscopic lumbar discectomy (PELD) for LDH patients. The study from W. S. Yuan et al. suggested that there is a difference between scoliosis and nonscoliosis in the treatment of nonspecific low back pain. L. Shen et al. pointed out that the treatment of chronic pain varies from region to region in the same country.

Conflicts of Interest

The editors declare no conflicts of interest in this work.

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Nikolai Bogduk
Michael J. DePalma
Ke Ma

Hindawi
Pain Research and Management
Volume 2019, Article ID 8957847, 14 pages
https://doi.org/10.1155/2019/8957847

Review Article

The Chinese Association for the Study of Pain (CASP): Consensus on the Assessment and Management of Chronic Nonspecific Low Back Pain

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Received 14 November 2018; Revised 6 June 2019; Accepted 11 July 2019; Published 15 August 2019

Academic Editor: Jacob Ablin

Chronic nonspecific low back pain (CNLBP) is defined as pain or discomfort originating from the waist, which lasts for at least 12 weeks, but no radiculopathy or specific spinal diseases. CNLBP is a complicated medical problem and places a huge burden on healthcare systems. Clinical manifestation of CNLBP includes discogenic LBP, zygapophyseal joint pain, sacroiliac joint pain, and lumbar muscle strain. Further evaluation should be completed to confirm the diagnosis including auxiliary examination, functional assessment, and clinical assessment. The principle of the management is to relieve pain, restore function, and avoid recurrence. Treatment includes conservative treatment, minimally invasive treatment, and rehabilitation. Pharmacologic therapy is the first-line treatment of nonspecific LBP, and it is most widely used in clinical practice. Interventional therapy should be considered only after failure of medication and physical therapy. Multidisciplinary rehabilitation can improve physical function and alleviate short-term and long-term pain. The emphasis should be put on the prevention of NLBP and reducing relevant risk factors.

1. Overview

Low back pain (LBP), defined as pain or discomfort in the area between the lower ribs and the gluteal folds, is a common and potentially debilitating condition with or without leg pain. Chronic low back pain (CLBP) refers to low back pain lasting for more than 12 weeks. Patients with LBP can be placed into one of three categories, i.e., nonspecific low back pain, low back pain associated with radiculopathy or spinal stenosis, and low back pain associated with specific spinal disease [1]. Chronic nonspecific LBP (CNLBP) is defined as pain and discomfort lasting for at least 12 weeks, but no radiculopathy, specific spinal disease, or nerve root pain. The current practice of diagnosis and treatment of LBP is often empirical, but not based on scientific methodology. It is time for our experts to convene, discuss, and formulate consensus for the diagnosis and treatment of CNLBP in China. It is also necessary to refer to existing evidence on the topic and international consensus for the diagnosis and treatment of LBP. The knowledge in this field has been combined with the conclusions drawn from some good clinical studies carried out in China. We believe that the consensus will be of great significance for pain management in China and will be of great reference value for other national pain experts in the world.

2. Etiology and Epidemiology of CNLBP

2.1. Common Causes of CLBP. Based on etiology, CLBP is often classified into two categories: specific and nonspecific CLBP. Specific CLBP has obvious causes such as infection, tumor, fracture, or inflammatory disease. However, 80%–90% of CLBP is nonspecific, intractable, and difficult to cure [1–4]. It is a great challenge to clarify the specific causes of CLBP. With the development of technologies and diagnostic tests (local anesthetic injection or discography), etiologic factors can be identified in 90% of patients with CLBP [5]. A study by DePalma et al. [5] on patients with nonspecific CLBP showed that prevalence of zygapophyseal joint pain, sacroiliac joint pain, and discogenic pain was 31%, 18%, and 42%, respectively.

2.2. Discogenic LBP. Discogenic LBP is not caused by lumbar intervertebral disc herniation. It is defined as pain caused by changes in the internal structure of lumbar discs, despite intervertebral discs of normal morphology. The pathologic feature is the formation of zones of vascularized granulation tissue with extensive innervation in fissures extending from the outer part of the annulus to the nucleus pulposus [6]. Peng [7] divided discogenic LBP into two types based on discography findings: internal annular disruption (IAD) and internal endplate disruption (IED).

2.3. Zygapophyseal Joint Pain. Zygapophyseal joint pain is identified as pain arising from any structures of the lumbar facet joints, including bony articulations, hyaline cartilage surfaces, the synovial membranes, and the fibrous capsules [8, 9].

2.4. Sacroiliac Joint Pain. Sacroiliac joint pain is defined as pain originating from the region of the sacroiliac joint, exacerbated by stress and provocation tests, and relieved by sacroiliac joint injections with local anesthetic [10].

2.5. Soft Tissue-Derived LBP. Soft tissues such as ligaments and muscles around the lumbar spine play an important role in maintaining the position of the body, as well as enhancing the stability, balance, and flexibility of the spine. Diseases of the soft tissues such as ligaments, fascia, and muscles can produce pain, which is called muscle pain clinically.

2.6. Epidemiology of CNLBP. CNLBP is a serious medical and social problem, which often leads to the loss of labor force. Although many of the studies in the literature have focused on the incidence and prevalence of CNLBP, there is a lack of accurate data on the incidence of the disease because the consensus on its definition has not been established so far [11]. In 2012, a systematic survey of the global adult population showed that the point prevalence, 1-month prevalence, 1-year prevalence, and lifelong prevalence of CNLBP were 12%, 23%, 38%, and 40%, respectively [12–18]. In China, CNLBP is the most common disease in Departments of Orthopedics, Rehabilitation Medicine and Pain Medicine, accounting for 1/3 of daily outpatient visits, second only to upper respiratory tract infections. At present, the medical cost for CNLBP is greater than that of coronary heart disease, diabetes, arthritis, and cerebrovascular disease [19, 20]. CNLBP is no longer a simple medical problem, and it can cause complicated psychological problem and serious social medical economic burden on patients [21–24].

3. Pathogenesis of CNLBP

A large number of basic and clinical studies have shown that CNLBP presents not only nociceptive pain, but also neuropathic pain, usually accompanied by central and peripheral sensitization [25, 26].

3.1. Discogenic LBP. The painful disc is characterized histologically by formation of a zone of vascularized granulation tissue in the posterior part of the disc, with infiltration of macrophages and mast cells [27]. Macrophages are not only the main phagocytic cells in the inflammation but also secrete a large number of growth factors and cytokines. The aggregation of mast cells in the painful disc may be closely related to the formation of new blood vessels in the disc and the fibrosis of the disc tissue [7]. Meanwhile, discogenic LBP has also the characteristic of visceral pain [6, 28]. At present, the main pathological features of discogenic LBP are the annulus fibrosus tearing, vascularized granulation tissue gradually growing from the outer part of the annulus into the nucleus pulposus and the degenerative annulus fibrosus, and nucleus pulposus releasing inflammatory mediators. These inflammatory mediators sensitize nociceptors, which causes LBP [27]. Internal endplate disruption is a form of discogenic LBP. Endplate injury can be subdivided into two

types: formation of Schmorl's nodules and endplate degeneration. The endplate is richly innervated and the nerve density of endplate is similar to that of annulus fibrosus, which strongly suggests that the lesion in endplate is an important source of LBP [7, 29–31].

3.2. Zygapophyseal Joint Pain. Chronic inflammation caused by degeneration, repetitive stress, and/or cumulative low-level trauma leads to facet joint hyperplasia, joint effusion, and joint capsule dilatation, which stimulates nerve terminals distributed on the facet joints and thereafter produces pain response [8]. The development of zygapophyseal joint pain is often insidious with common predisposing factors including lumbar spondylolisthesis, intervertebral disc degeneration, and old age [9].

3.3. Sacroiliac Joint Pain. Sacroiliac joint pain can be divided into intra-articular causes (infection, spondyloarthropathy, and arthritis) and extra-articular causes (fracture, myofascial pain, enthesopathy, and ligament injury) [10]. The mechanism of sacroiliac joint pain is considered as the combination of axial loading and rotation [32]. The risk factors are leg length discrepancy, abnormal gait, scoliosis, trauma, sacral fixation after lumbar spinal fusion surgery, heavy manual labor, and pregnancy [10]. Histopathology reveals that there are abundant nociceptors and proprioceptors in the sacroiliac joint capsule, ligament, and subchondral bone of sacroiliac joint, which indicated that any injury to surrounding tissues could cause pain [33–36].

3.4. Soft Tissue-Derived LBP. Muscle imbalance, muscle spasm, and muscle contracture represent a three-part pathological response resulting in chronic soft tissue-derived back pain [37]. Chronic accumulation of soft tissue injury renders muscles too weak to maintain the normal function position of the waist, which strains the deep ligament [38]. Insufficiency of circulation originating from peripheral nerves and blood vessels in the muscle which are pressed, together with metabolite accumulating and inflammatory substances, forms a new point of pain and even leads to muscle atrophy and fibrosis [39]. Often ligaments and muscles are shortened on one side and loose on the other side, which leads to posture imbalance and pain spreading [40].

4. Clinical Manifestation of CNLBP

4.1. Discogenic LBP. The most important clinical feature of discogenic LBP is poor tolerance to sitting position, which often exacerbates the pain. Most patients suffer from repeated LBP attacks, aggravated by fatigue, long standing time, exposure to cold, and coughing or sneezing. Pain is relieved in bed. The pain is mainly located in the waist, and sometimes it radiates to the lower extremities. The pain can be below the knee. There is no specific sign or symptom for its diagnosis. The symptoms also include lower limbs numbness, coldness, and intermittent claudication.

4.2. Zygapophyseal Joint Pain. Zygapophyseal joint pain cannot be relieved by rest. The symptoms include low back pain, soreness, and stiffness in the morning. It can be relieved after moderate activity, but it is aggravated by excessive activity. The pain worsens at night. The pain can be relieved when lying flat or by massage. There is no obvious tenderness in the lumbar region.

4.3. Sacroiliac Joint Pain. Sacroiliac joint pain is moderate to severe pain on one side of the low back radiating to the hip or groin area. The patient is often unable/reluctant to walk or grudgingly limp. The pain can be alleviated by bending hips on bed. Serious patients cannot turn over in bed.

4.4. Lumbar Muscle Strain. Lumbar muscle strain is diffuse and dull pain in the muscles on both sides of the waist and above the iliac crests. It tends to get worse in the morning and can be alleviated with some exercise, but too much exercise can aggravate the condition. When the patient is resting, the condition is often relieved and becomes worse when the patient is tired. Pain becomes more acute with bending posture and can be relieved by stretching the back or tapping on the waist. The pain caused by lumbar muscle strain can spread to the buttocks or thighs, but not to the lower leg or foot. This pain can be associated with symptoms of autonomic nervous system disorders such as cold limbs, visceral pain, etc. Sitting tolerance decreases in the patients.

5. Signs

(1) Changes in physiological curvature of spine: scoliosis, decreased or lost physiological curvature, and kyphosis.

(2) Lumbar spinal range of motion: normal lumbar range of motion includes 75–90 degrees of flexion, 30 degrees of extension, 20–35 degrees of left and right side bending, and 90 degrees of rotation unilaterally. The range of motion is reduced in CLBP, and the activity in all directions of the lumbar spine is limited.

(3) Physical examination reveals local or extensive tenderness or percussion pain on the low back.

(4) Magnetic resonance imaging (MRI) or computed tomography (CT) scan does not display nerve root compression.

(5) Neurological examination usually does not show abnormalities in sensory, motor, and tendon reflexes.

6. Diagnosis and Differential Diagnosis

Diagnosis of CNLBP represents a challenge for clinicians because of the complexity of its etiology, which involves physical, mental, and psychosocial factors. The following are the steps to take for the diagnosis and differential diagnosis of CNLBP (Table 1).

Table 1: Differential diagnosis for nonspecific LBP.

Possible cause	Symptoms and physical examination	Imaging test	Laboratory test
Cancer	History of cancer, unexplained weight loss, and age >50 years	Lumbosacral plain radiography and MRI	ESR and tumor marker
Vertebral infection	Fever, history of recent infection, and tuberculosis	MRI	ESR, CRP, PPD, or PCT
Syndrome of cauda equina	Urinary retention, fecal incontinence, sensory disorder in saddle area, and motor deficits	MRI	None
Vertebral compression fracture	Older age, osteoporosis, and use of corticosteroids	Lumbosacral plain radiography, BMD and MRI	None
Ankylosing spondylitis	Morning stiffness, improvement after exercises, nocturnal pain, and younger age	Pelvis plain radiography	ESR, CRP, and HLA-B27
Radiculopathy	Progressive symptoms and motor weakness	CT or MRI	EMG and NCV
Symptomatic lumbar disc herniation	Back pain with leg pain in the distribution area of nerve root L4, L5, or S1 Positive for straight-leg-raise test Radicular pain present >1 month	None	None
Spinal stenosis	Older age, walking and standing worsen the symptom, pain relieved by sitting	CT or MRI	None

7. History and Physical Examination

The first step for clinical evaluation of patient includes a focused medical history and physical examination. Clinicians should inquire about the location and quality of pain as well as the stability or progression of pain and neurological symptoms (e.g., sensory and motor dysfunction). Clinicians should also inquire about history of malignancy or tuberculosis, history of previous treatment, and response to the treatment. Special attention should be paid to the patients with risk factor associated with LBP, as well as the patients with previous symptom. Clinicians should help patients with LBP enter 1 of 3 broad categories based on a focused medical history and physical examination: nonspecific LBP, LBP potentially associated with radiculopathy or sciatica, or LBP potentially associated with another specific spinal cause (red flag). It is important to conduct differential diagnosis for nonspecific LBP. The history should include assessment of psychosocial risk factors. The evaluation of LBP is shown in Table 2.

8. Auxiliary Examination

Further evaluation (e.g., imaging and electrophysiology) may be required to confirm the diagnosis. Imaging test includes plain radiography, CT, and MRI. Clinicians should not take imaging tests as routine in patients with LBP for initial evaluation. Diagnostic imaging tests should only be performed for LBP patients when severe or progressive neurologic deficits are presented or serious underlying conditions being suspected on the basis of history and physical examination, such as lumbar disc herniation or spinal stenosis which are potential candidates for surgery [41–43].

9. Functional Assessment

Functional assessment of nonspecific LBP can be achieved by valid questionnaires. Chinese version of Roland-Morris Disability Questionnaire (MDQ) and Oswestry Disability Index (ODI) is being researched to test its reliability and validity. The Chinese version of the Fear-Avoidance Belief Questionnaire (FABQ-CHI) has proved valid to evaluate the aspect of pain, health, and dysfunction in CNLBP patients. Moreover, the intelligent device for energy expenditure and activity (IDEEA) and surface electromyography (sEMG) can also be used for the functional assessment of patients with nonspecific LBP objectively.

10. Clinical Assessment

Once the diagnosis of CNLBP is made, the attending physician should conduct a clinical assessment. The goal of the evaluation is to define the cause of the disease, set up appropriate treatment strategies, and assess the efficacy of treatment objectively later. The principle of clinical assessment should be standard, quantitative, comprehensive, and dynamic [44]. The assessment includes the location, quality, intensity, frequency, and duration. Physician should also evaluate the mental and psychosocial factors of patients [45]. The method of evaluation consists of self-assessment and Behavior Rating Scale (BRS). For the assessment of pain level, Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), and pain questionnaires can be adopted. Functional assessment is usually achieved using ODI, Quebec Back Pain Disability Scale (QBPDS) [46], Short Form (36) Health Survey, and Roland-Morris Disability Questionnaire (RMDQ) [47]. One way to evaluate the back muscle function objectively and in real time is to apply surface

Table 2: Diagnostic protocol for nonspecific LBP.

Measures	Key points
(A) History inquiry	
Duration of LBP	Acute pain: within 4 weeks; subacute pain: 4 to 12 weeks; chronic pain: >12 weeks
Location of pain	Lumbosacral region
Characteristic of pain	Localized pain, radiating pain, burning sensation
Duration of pain attack	Consistent pain, intermittent pain, and night time episode
Sensory change	Numbness, stiffness, hypoesthesia, and noseresthesia
Other aspects	Education, occupation, BMI, infection, cancer, osteoporosis, endocrinopathy, history of trauma, and spine surgery
(B) Physical examination	
Inspection	Spine deformity, local condition
Palpation	Tenderness
Percussion	Percussion pain
(C) Accessory examination	
Signs	Lasegue test, Bragard sign, Gaenslen test, and Waddell test
Imaging test	Plain radiography, CT, and MRI
Electrophysiology	Electromyography and somatosensory evoked potential
Laboratory test	Erythrocyte sedimentation rate, C reactive protein, and HLA-B27

electromyography (sEMG) [48]. Physicians can evaluate the psychosocial factors through Fear-Avoidance Belief Questionnaire (FABQ) and Tampa Scale for Kinesiophobia (TSK).

11. Treatment of CNLBP

11.1. Principle of Treatment. The aim of the treatment is to relieve pain, restore function, and avoid recurrence. Treatment includes conservative treatment, minimally invasive treatment, and rehabilitation. Surgical treatment is not introduced here. Figure 1 is the flow chart of the treatment.

12. Pharmacologic Therapy

Pharmacologic therapy is the first-line treatment of nonspecific LBP, and it is most widely used in clinical practice. Physicians should formulate individualized treatment plans according to each patient's condition and modify them if necessary. The combination of different treatments may improve the clinical efficacy.

12.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). NSAIDs can provide reliable pain relief for the patients with CNLBP [49–51]. Taking more than one NSAID at the same time is not recommended. If one NSAID prescription fails to provide sufficient pain relief within two weeks of treatment, the attending physician may consider a different kind of NSAIDs prescription for such patients. Physicians should also remain alert for the ceiling effect of NSAIDs. In addition, there is association between exposure to NSAIDs and increased risk for myocardial infarction [50, 52]. Clinicians should therefore assess cardiovascular and gastrointestinal risk factors before prescribing NSAIDs and recommend continuous taking of NSAIDs for no more than 3 months. Nonselective NSAIDs include ibuprofen, diclofenac, etc. Selective Cox-2 inhibitors include etoricoxib and celecoxib, which have the effect of alleviating gastrointestinal complications.

12.2. Skeletal Muscle Relaxants. Antispasmodic muscle relaxants play a role in reducing muscle spasm associated with lower back pain [53, 54]. The possible mechanism of antispasticity of α 2-adrenergic receptor agonist (e.g., tizanidine) is to increase the proportion of gamma-aminobutyric acid (GABA) compared to glutamate in presynaptic level [55]. Additionally, they may provide pain relief, antidepression, and gastrointestinal protection. Combination therapy of skeletal muscle relaxants and NSAIDs can reduce nonspecific LBP effectively and improve the motor function in general. The gastrointestinal protective effect of skeletal muscle relaxants can offset the gastrointestinal damage induced by other drugs [56]. The possible mechanism of antispasmodic action for eperisone is to inhibit the activity of gamma motor neuron [57]. Chlorzoxazone and baclofen are also commonly used for relieving the spasm of LBP patients.

12.3. Opioids. Use of opioids is an option for nonspecific LBP patients who are uncontrolled when other drugs are being treated [58–60]. Physicians should start with prescription of weak opioids with extended-release such as tramadol hydrochloride extended-release tablets [61, 62]. Patients should be maintaining the opioid intake for management of pain, not only when pain is severe [63]. Early use of opioids can prevent early pain, which makes early

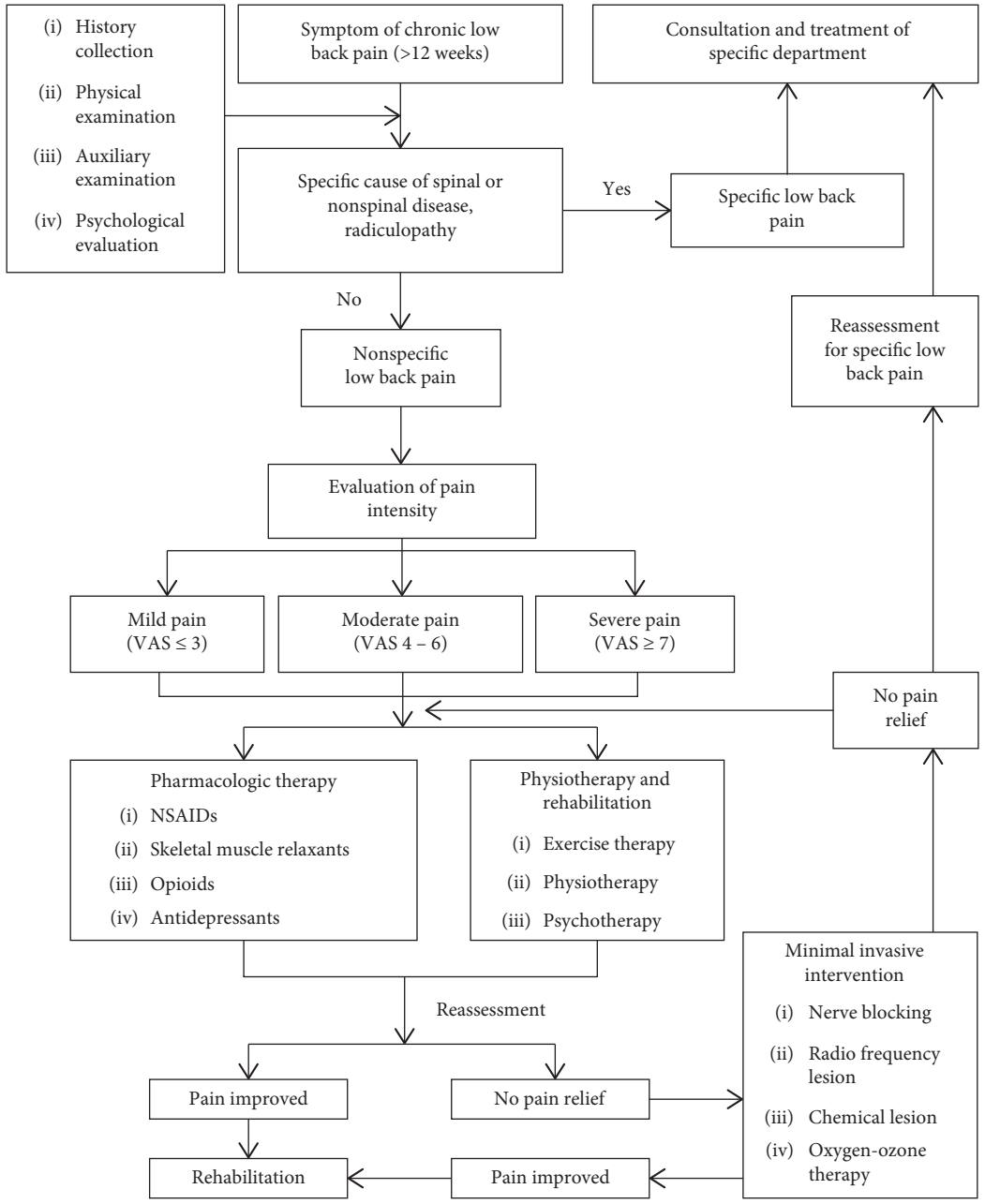

Figure 1: Flow chart of the treatment.

functional training possible. Also, one of the main purposes of opioids treatment in CLBP patients is to facilitate functional rehabilitation [64].

12.4. Antidepressants. Patients with chronic pain often suffer other affective disorders like depression and anxiety [65]. Use of antidepressants is an option for pain relief in patients with CLBP. Physicians can choose amitriptyline, duloxetine, or venlafaxine to attenuate the depression associated with chronic pain. To avoid the withdrawal symptoms of antidepressants, patients should withdraw from antidepressants gradually according to the prescription of physician [66–68].

12.5. Other Medications. 85 percent of patients with LBP display hyperalgesia [69, 70]. CNLBP is often associated with neuropathic pain [4]. Use of anticonvulsants is effective treatment for the LBP patients with pain hypersensitivity. Gabapentin and pregabalin can restore the function of excitatory neurons by blocking the voltage-dependent calcium channel which can reduce the excitatory input [66, 71]. The dysfunction of sodium ion channel plays an important role in the development of chronic pain [69]. Bulleyaconitine provides sufficient relief of pain hypersensitivity induced by chronic pain by selectively blocking the overactive sodium ion channel [71]. Recent clinical data have demonstrated the effect of traditional patch, e.g., Tibetan medicine pain relief patch, relieving pain in muscles and joints [72, 73].

13. Minimally Invasive Interventional Therapy

The right diagnosis and precise identification of the pain generator is the prerequisite for a successful interventional therapy. Interventional therapy should be considered only after failure of medication and physical therapy. In order to give patients a precise and targeted treatment, ultrasound, X-ray, or CT-guided imaging is highly recommended for the intervention.

13.1. Epidural Injection

13.1.1. Route of Epidural Injection. Epidural injections have been used extensively to treat back and leg pain. Among the routes of transforaminal, caudal, and interlaminar approaches, transforaminal epidural injections have gained wide acceptance for the treatment of lumbar and lower extremity pain. The potential advantage of transforaminal approach over interlaminar or caudal approach is targeted delivery of small volume steroid to the site of pathology, presumably to an inflamed nerve root [74].

13.1.2. Drug Choices and Frequency for Epidural Injection. Drugs used in epidural injections are usually compounds of steroid and local anesthetics. Methylprednisolone acetate and betamethasone are recommended for the epidural injection [75]. As long-acting particulate steroid accidentally into bloodstream may cause serious complications, nonparticulate steroid is recommended [76]. As for the local anesthetics, 0.5% lidocaine or 0.25% bupivacaine is recommended. The recommended volume of liquid is 7–10 ml for interlaminar route, 1-2 ml for transforaminal route, and 20–50 ml for caudal route. For those patients getting incomplete pain relief from an epidural injection, repeated injections may be required with the interval of 1–3 weeks. No more than three procedures is recommended within one year [77].

13.2. Medial Branch Block. Medial branch nerve block is mainly applied as the diagnostic test for the facet joint-mediated LBP [9]. Each facet joint is innervated by the medial branches of the spinal nerve roots from the same level and upper level; therefore, the diagnostic test should be given at the two levels at the same time. To avoid false-positive results from the spread of the anesthetic into the epidural space, 0.5 ml of test volume is recommended [9].

13.3. Sacroiliac Joint Injection. Limited high-quality RCT data support the effectiveness of sacroiliac joint injection in the treatment of sacroiliac joint pain. It is mainly performed as the diagnostic test. Due to the irregular sacroiliac joint surface, the sacroiliac joint is difficult to be injected by palpation [78]. The success rate of palpation-guided sacroiliac joint injection was reported to be merely 12%. Therefore, imaging-guided injection is recommended [79]. The needle should be inserted into the inferior one third of the joint. As the joint cavity is small, no more than 1 ml of injectant is recommended [79].

13.4. Intradiscal Injection of Methylene Blue. Injection of methylene blue into the painful disc is a minimally invasive procedure for the treatment of discogenic LBP. However, there have been few reports [80, 81]. Diagnostic discography with positive result is required before proceeding with the treatment [81]. The recommended injectant is 1-2 ml of 1% methylene blue.

13.5. Radiofrequency Treatment for CNLBP

13.5.1. Radiofrequency Ablation of Medial Branch of Spinal Nerve. Radiofrequency ablation of medial branch nerve is applied for the treatment of zygapophyseal LBP verified by positive diagnostic test. Moderate evidence exists for the short-term pain relief, but the effect after one year is controversial [82]. The puncture target is the junction of superior articular process and transverse processes. To avoid nerve root injury, the tip of the needle should be away from the intervertebral foramen under lateral fluoroscopy. Nerve stimulation test is essential during the procedure. During the stimulation process, pain within the target area should be elicited with sensory stimulation of less than 0.5 V. No lower limb muscle twitch is observed with motor stimulation of more than 1.0 V.

13.5.2. Pulsed Radiofrequency of Dorsal Root Ganglion. Pulsed radiofrequency of dorsal root ganglia was used for treatment of radiating lower extremity pain. Several case reports have reported that the benefits of such treatment are short term, but rigorous evidence is lacking [83]. For those patients getting more than 50% of pain relief with pulsed radiofrequency of dorsal root ganglion, repeated procedures for 2–5 times may be considered. For those with less than 50% of pain relief, repeated procedures are not warranted. Local anesthesia is not recommended at the beginning of the procedure.

13.5.3. Sacroiliac Joint Radiofrequency Ablation. Sacroiliac joint radiofrequency ablation is performed for treatment of sacroiliac joint pain. Diagnostic sacroiliac joint injection is required to confirm the pain generator. As sacroiliac joint is innervated by multiple lumbar and sacral nerves and the relevant nerves are diffusely distributed, bipolar radiofrequency ablation is recommended [84], although the related reports are scarce [85, 86].

13.5.4. Low-Temperature Plasma Disc Decompression for Spinal Disc Herniation. The use of low-temperature plasma disc decompression to treat spinal radiculopathy due to a contained disc herniation is supported by prospective controlled trials [87]. The indication for plasma disc decompression is contained disc herniation causing LBP with or without radiating leg pain for more than 3 months, and the disc height reduction is less than 50% [88]. The

contraindication of plasma decompression includes spinal disc prolapse, huge contained herniated disc with herniation taking over one third of sagittal distance of the spinal canal, herniated disc calcification, severe lumbar canal stenosis, lumbar instability, and neurologic function impairment [89].

13.5.5. Percutaneous Intradiscal Radiofrequency Thermocoagulation. Percutaneous intradiscal radiofrequency thermocoagulation is a treatment option for contained herniated disc. But no evidence is available for the treatment of contained herniated lumbar disc. Different reports utilized different inclusion criteria and different parameter settings in radiofrequency procedures, and the reported efficacy differed dramatically [90].

13.6. Intradiscal Electrothermal Therapy (IDET). IDET is mainly applied for low back pain originating from lumbar disc degeneration. However, the reported efficacy was mixed [91, 92]. It is recommended as a therapeutic option for recalcitrant patients with conservative treatment. Some of the literature demonstrated the efficacy of IDET for LBP superior to radiofrequency thermocoagulation [91].

13.7. Oxygen-Ozone Therapy. Oxygen-ozone therapy is widely applied in the context of pain management. Ozone may be injected into the spinal disc or the muscles, or administered through the transforaminal route [93]. Ozone can stimulate the repairing system of the body, activate inhibitory interneurons, and generate analgesic effects through the release of enkephalin and endorphin [94]. Ozone can also oxidize the proteoglycan of nucleus pulposus, destroy nucleus pulposus cells, and play an anti-inflammatory role [95]. It also generates analgesic effect by directly acting on the inflammatory tissues around the nerves [96]. The local oxidation and analgesic effect could result in muscle relaxation and vasodilatation and expedite metabolism of muscles [97]. The injection of ozone into the disc or the paravertebral space should be imaging-guided. 5–10 ml of ozone of 40~60 μg/ml is recommended for intradiscal injection, and 3~5 ml of ozone of 35 μg~40 μg/ml is recommended for trigger point injection. Trigger point injection could be performed at 3–5 points in one treatment. Four consecutive treatments could be repeated twice per week. The therapy is contraindicated for patients with hyperthyroidism and glucose-6-phosphate dehydrogenase deficiency [98].

13.8. Neuromodulation Techniques

13.8.1. Spinal Cord Stimulation (SCS). SCS is reported to be an effective treatment for failed back surgery syndrome (FBSS) and complex regional pain syndrome [99]. The effective rate was 50%–70% throughout follow-up period of 6 months to 2 years [100]. The treatment of lower extremity pain is better than that of LBP [101]. SCS is recommended to be the last resort for LBP patients who failed in various conservative therapies, epidural injection, endoscopic transforaminal discectomy, or even open surgery. Strict selection of patients is vital. All cases require SCS testing prior to permanent implantation. The test takes about 3–10 days.

13.8.2. Intrathecal Drug Delivery Systems (IDDSs). IDDS is applied mainly for cancer pain. Occasionally, it can be utilized for FBSS according to anecdotal case presentations reported [102]. Long-term usage of intrathecal drug might lead to uncertain efficacy, drug resistance, and complicated postoperative management; therefore, it is only recommended for FBSS and nonspecific LBP refractory to drug therapy, interventional treatments, or surgeries. Drugs frequently used in IDDS are opioids and local anesthetics. Other drugs such as baclofen and dexmedetomidine could also be used [103]. Trial administration of drug intrathecally is required to observe the analgesic effect and side effects before IDDS surgery.

13.9. Silver Needle Thermoconduction Therapy. Silver needle thermoconduction therapy is indicated for soft tissue originated pain, especially for myofascial pain syndrome in the lumbar and buttock region and muscle spasm [104]. In addition, silver needle thermoconduction therapy can also be applied for lumbar disc herniation, lumbar discogenic pain, and FBSS [105–107].

13.10. Acupotomy. Acupotomy is indicated for soft tissue originated pain. It was reported that acupotomy can effectively treat the third lumbar transverse process syndrome, iliolumbar ligament injury, and lumbar gluteal myofasciitis [108, 109]. In contrast to silver needle thermoconduction therapy, acupotomy is especially applicable to localized soft tissue originated pain [108, 110].

14. Rehabilitation

14.1. Exercise. Appropriate exercises can relieve pain to some extent. There is no evidence that exercise therapy improves dyskinesia in short term or medium term (6 months); however, there is evidence of significant improvement in the long term (over 12 months). Exercise therapy mainly includes pilates, tai chi, and yoga [111–113].

14.2. Acupuncture. Acupuncture can relieve pain immediately, and its effect can be maintained for up to 12 weeks. However, its long-term efficacy is unknown [114].

14.3. Massage. Massage can relieve the subacute and chronic LBP in short term and improve the patients' function. Massage combined with exercise can achieve better therapeutic effect.

14.4. Manipulation. Spinal manipulation therapy alleviates pain in a short time and improved the functional status of patients (1 month), but the long-term effect was poor [115].

14.5. Physical Therapy

14.5.1. Ultrasound. Due to the inconsistency in evaluation methods, ultrasound has not been shown effectiveness on pain relief or functional improvement in the current literature [116].

14.5.2. Transcutaneous Electrical Nerve Stimulation (TENS). Systemic review found no significant difference between TENS and acupuncture in short-term or long-term improvement of pain [117, 118].

14.5.3. Low-Level Laser Therapy. Compared with sham laser group, low-level laser therapy may relieve pain, but the effect is limited [118].

14.6. Lumbar Support Therapy. There is no evidence that lumbar support therapy is effective for LBP [119].

14.7. Traction Therapy. Compared with placebo, sham traction, or no traction, traction therapy has no significant effect on pain relief or improving physical function. However, this technique is effective for patients with radiation pain [120].

14.8. Psychological Therapy. The treatment of CNLBP cannot ignore psychological treatment. Progressive relaxation can relieve the posttreatment pain [121, 122] and promote functional improvement. Electromyographic biofeedback and operant therapy can relieve pain but is ineffective in improving physical function. Cognitive therapy for LBP has no significant benefits [123, 124].

15. Multidisciplinary Rehabilitation

Multidisciplinary rehabilitation includes physical, biological, psychological, and social therapy, involving experts from different disciplines. Studies have shown that multidisciplinary rehabilitation can improve physical function and alleviate short-term and long-term pain. With rehabilitation, patients may have the chance to resume their normal work [125].

16. Efficacy of Treatment Evaluation Criteria and Follow-Up

The efficacy should be evaluated at 2, 4, 8, and 12 weeks and 6 months after treatment. Evaluation indicators and tools include VAS, ODI, surface EMG, psychological assessment, spinal flexion and extension, shuttle walking test, and patient satisfaction and expectation [126]. The assessment should also include working state after back to work, sick leave days, medication, and side effects.

17. Prevention and Health Education

17.1. Risk Factors. There are many factors related to CNLBP, including age, occupation, psychological factors, heredity, sex, pregnancy, bodyweight, and unhealthy lifestyle. Some occupations (such as manual workers, typists, and taxi drivers), obesity, a sedentary lifestyle, and frequent bending are important risk factors for CNLBP. Psychological and genetic factors and pregnancy are closely related to the incidence of LBP [127] (Table 3).

17.2. Prevention. To prevent LBP, special attention should be paid to supporting the back, maintaining good posture, changing the habits which may lead to LBP, and maintaining ideal bodyweight [131].

Protection measures: they include minimizing bending; adjusting the height of working chair to a suitable level to avoid bending; and when lifting, using leg strength as much as possible to reduce the stress on the waist [132].

Sitting posture: it includes keeping waist straight, abdomen straight, and feet on the ground; using a soft cushion on your back to relax your lumbar muscles; and reducing tension.

Sleeping posture: it includes lying on the side with knees bent and sleeping on a firm mattress with less cushioning to support a neutral-spine position (sleeping on a soft mattress may gradually deform lumbar spine curvature resulting in injury to lumbar muscles and soft tissue).

Walking posture: it includes standing up straight, with chin up, eyes forward, without leaning forward or backward. Women with LBP should not wear high heels. High heels (>3 cm) can put a lot of stress on the waist and back muscles, increasing the risk of LBP.

Obese patients should try to lose weight. Weight gain will bring burdens on the back. Pregnancy is also a heavy burden on the lumbar spine. Pregnant women should maintain correct posture and rest before giving birth.

18. Statement

(1) Nonspecific low back pain has a long diagnostic cycle, high treatment difficulty, and high incidence.

(2) Pathogenesis includes discogenic LBP, internal endplate disruption, zygapophyseal joint pain, sacroiliac joint pain, and soft tissue-derived LBP.

(3) Auxiliary examination may confirm the diagnosis and is helpful for differential diagnosis.

(4) Pharmacologic therapy is the first-line treatment. Individualized treatment plans should be formulated to obtain clinical efficacy.

(5) Interventional therapy should be considered only after failure of medication and physical therapy which gives patients a precise and targeted treatment.

Table 3: Risk factors for CNLBP.

Risk factors	Description
Age [20]	Age is positively associated with the incidence.
Psychology [128]	Stress, anxiety, and depression may increase the incidence of LBP.
Occupation [129]	Long-term spinal heavy burden, excessive rotation, or vibration increases the risk of LBP; high-risk occupations are miners, drivers, farmers, and caregivers.
BMI [130]	Obesity is positively correlated with LBP incidence.
Gender	Women are more than men.
Genetics	LBP has familial aggregation.
Pregnancy	More than 50% pregnant women in the early pregnancy have LBP. This may be related to elevated levels of estrogen and progesterone.
Lifestyle	Smoking and sedentary lifestyle increase the risk of LBP.

(6) Rehabilitation includes exercise, acupuncture, massage, manipulation, lumbar support therapy, physical therapy, and psychological therapy and could relieve pain.

(7) Disease prevention and health care can effectively improve the prognosis of CNLBP.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Hindawi
Pain Research and Management
Volume 2019, Article ID 6528528, 9 pages
https://doi.org/10.1155/2019/6528528

Research Article

Skin/Muscle Incision and Retraction Induces Evoked and Spontaneous Pain in Mice

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Received 7 November 2018; Accepted 11 July 2019; Published 31 July 2019

Guest Editor: Ke Ma

Background. Surgery is a frequent cause of persistent pain. Unrelieved chronic postsurgical pain causes unnecessary patient suffering and discomfort and usually leads to psychological complications. The rat model of skin/muscle incision and retraction (SMIR) with decreased paw withdrawal thresholds developed by Flatters was usually used to investigate the underlying mechanism of chronic postsurgical pain. *Objectives*. The aim of our study was to develop a new mice model of SMIR for further investigation with transgenic mice and so on and to evaluate the analgesic effects of clonidine and gabapentin on pain behavior with this new mice model. *Methods*. Male C57BL/6 mice were anesthetized, and a 1.0–1.3 cm incision was made in the skin of the medial thigh approximately 3 mm medial to the saphenous vein to reveal the muscle of the thigh. The paw withdrawal threshold (PWT) to mechanical stimuli and the paw withdrawal latency to heat stimuli were measured before and after SMIR. Furthermore, the PWT to mechanical stimuli and conditioned place preference (CPP) was measured before and after the systemic injection of clonidine and gabapentin. *Results*. SMIR-evoked mechanical hypersensitivity in mice began on day 1 after the procedure, prominent between days 1 and 10 after the procedure, persisted at least until day 14, and disappeared on day 18 after the procedure. However, the mice model of SMIR did not evoke significant heat hypersensitivity. Systemic injection of clonidine and gabapentin raised the PWT in the SMIR mice dose-dependently. Compared with the mice that underwent the sham operation, mice of SMIR spent a longer time in the clonidine-paired chamber than those of NS, while the gabapentin-paired chamber has no difference with that of NS in the CPP paradigm. *Conclusion*. These data suggested that the mice model of SMIR demonstrated a persistent pain syndrome, including evoked pain and spontaneous pain. Clonidine and gabapentin could relieve mechanical hypersensitivity dose-dependently simultaneously. However, clonidine but not gabapentin could alleviate the spontaneous pain of SMIR in the mice model.

1. Introduction

Since the first definition of chronic postsurgical pain (CPSP) by Macrae [1] in 1999, the phenomenon has been recognized increasingly. About 10–50% of patients suffer such persistent postsurgical pain, despite advances in surgical techniques and perioperative analgesic strategies [1–5]. It has been well reported that spontaneous pain, allodynia, and hyperalgesia are major problems for patients with persistent pain [6–9]. Unrelieved CPSP causes unnecessary patient suffering and discomfort and leads to psychological and pathophysiological complications. The CPSP has become a separate

category in the latest IASP classification of pain, to be included in the ICD-11.

All of these procedures involve essential and prolonged tissue retraction, which could account for the persistent nature and high incidence of postsurgical pain. A new model of persistent postsurgical pain evoked by skin/muscle incision and retraction (SMIR) in rats invented by Flatters [10] was used widely for investigating the underlying mechanism of CPSP [11–13]. Therefore, developing a new SMIR model in mice is necessary for further investigation with transgenic mice and so on. Clonidine, a specific alpha-2 adrenergic receptor agonist, has a well-established analgesic profile. It has been found to have a wider application as an adjunct to anesthetics and analgesics in perioperative settings [14–17]. It can relieve mechanical allodynia in oxaliplatin-induced neuropathic mice model [18, 19]. Gabapentin, an antiepileptic drug and structural analogue of the neurotransmitter gamma-aminobutyric acid, was developed as an anticonvulsant and subsequently used for various chronic pain conditions [20–22]. However, the effects of the clonidine and gabapentin on the spontaneous pain, allodynia, and hyperalgesia in the model of SMIR have not been investigated until now.

The aim of this study was to characterize a mice model of CPSP through skin and muscle incision and retraction with pain behavior including conditioned place preference (CPP) paradigm to assess spontaneous pain. We also evaluated the different analgesic effects of clonidine and gabapentin on the new model.

2. Methods

2.1. Animals and Surgery. Adult C57/BL6 mice (8 weeks, 25–30 g) were purchased from the Experimental Animal Center of Zhejiang University. All animal procedures in this study were performed according to the guidelines of the International Association for the Study of Pain and were approved by the Animal Care and Use Committee of Zhejiang University.

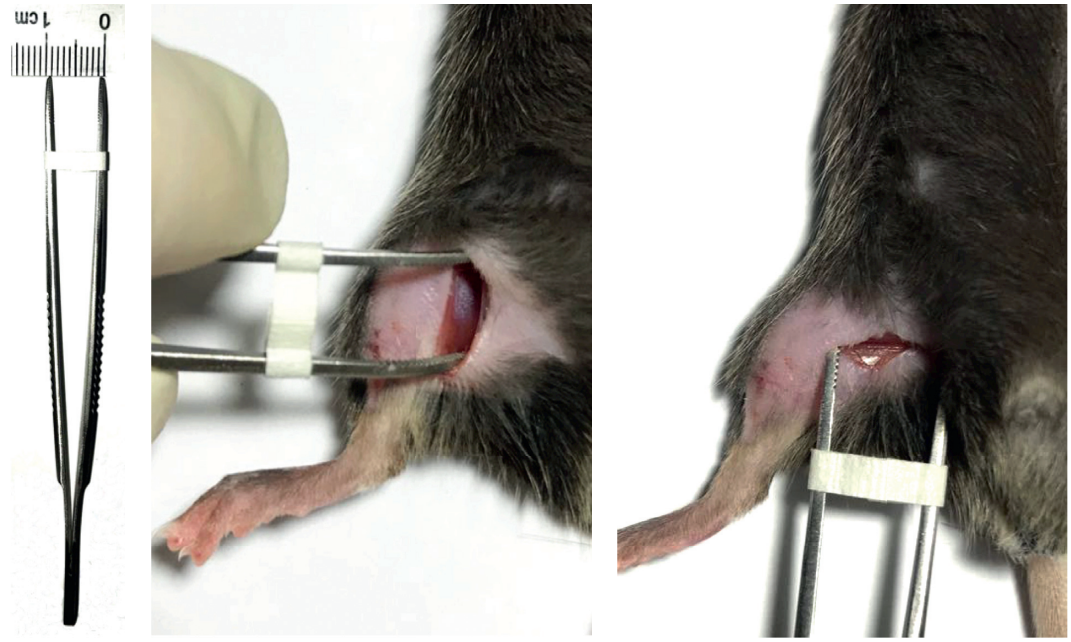
To produce SMIR, animals were anesthetized with sodium pentobarbital (40–50 mg/kg, intraperitoneally (i.p.)), laid on their back, and the medial thigh on the right side was shaved. The shaved skin was then repeatedly swabbed with sterile alcohol wipes to sterilize the area and to allow visualization of the saphenous vein. A 1.0–1.3 cm incision was made in the skin of the medial thigh, approximately 3 mm medial to the saphenous vein, to reveal the muscle of the thigh. An incision (about 1 cm long) was then made in the superficial (gracilis) muscle layer of the thigh, approximately 3 mm medial to the saphenous nerve. The superficial muscle was then parted further, by spreading blunt scissors into the muscle incision site, to allow the insertion of a custom-made dissecting retractor. The skin and superficial muscle of the thigh were then retracted by 1 cm, revealing the fascia of the underlying adductor muscles; this retraction was maintained for 1 hour. Sham-operated mice underwent the same procedure with the exception of the skin/muscle retraction (Figures 1(a)–1(c)). Following recovery from anesthesia, all animals could ambulate normally and rise up on their hindpaws to reach food and water.

2.2. Mechanical Allodynia Test. On the experimental day, the von Frey behavioral test was performed according to the up-down algorithm described by Chaplan et al. [23]. To determine evoked reflex responses to mechanical stimuli, animals were placed on a raised mesh grid and covered with a clear plastic box. Calibrated von Frey filaments were applied to the middle of the plantar surface of the right paw until the filament bent. Brisk withdrawal or paw flinching was considered as a positive response. Lifting of the paw due to normal locomotor behavior was ignored. In the absence of a response, the filament of the next greater force was applied. If a response was obtained, the filament of the next lower force was applied. The tactile stimulus producing a 50% likelihood of withdrawal response was calculated and treated as the paw withdrawal threshold (PWT).

2.3. Heat Allodynia Test. Animals were placed in individual Perspex boxes on a glass floor. Nociceptive responses to a noxious heat stimulus were examined by measuring the hindpaw withdrawal latency (PWL) from a focused beam of radiant heat projected to the plantar surface (Ugo Basile Plantar Test apparatus, Gemonio, Italy). The withdrawal latency to this stimulus was measured in seconds, and the apparatus had a built-in cutoff latency of 20 seconds. The operated hindpaw of each mouse was tested three times and then the average of these three readings was taken. The heat sensitivity on separate days and then on days 1, 3, 7, 10, 14, and 18 after surgery was determined.

2.4. Conditioned Place Preference Protocol. CPP was adapted from the behavioral paradigm established by King et al. in adult rats [24, 25]. CPP testing was conducted using three Plexiglas chambers separated by manual doors. The two end chambers were connected via one center chamber. The walls of one chamber were white with horizontal black stripes and the walls of the other chamber were white with vertical black stripes. We used the chambers with striped walls to ensure that mice would not strongly prefer one chamber to the other.

Habituation was performed across 2 days for 30 minutes each day; mice were permitted to move freely to all chambers. On day 3, a preconditioning preference test was conducted to determine whether a chamber bias existed. Mice were placed into the middle chamber and permitted to move freely in all chambers for 15 minutes, and the time spent in each end chamber was recorded. The mice that spent more than 80% or less than 20% of the total time in a single chamber were eliminated from further study. On day 4, mice received vehicle (e.g., saline) chamber pairing and drug pairing 4 hours later. During conditioning, mice were allowed to stay only in the paired chamber, without access to other chambers for 15 minutes immediately following the vehicle or drug injection, including clonidine and gabapentin. Clonidine and gabapentin were purchased from Sigma-Aldrich (St Louis, MO, USA). Chemicals were dissolved in sterile saline. Different volumes of stock solution were administered to the animals i.p. with a 1 ml syringe. Twenty hours after drug pairing, mice were placed in the middle chamber of the CPP box with all doors open, so that



(a) (b) (c)

Figure 1: Photograph of injury site during the 1-hour retraction period of skin/muscle incision and retraction (SMIR) surgery. (a) Custom-made retractor with a spreading distance of 1 cm. (b) Revealing the fascia of the underlying adductor muscles. (c) The muscles were parted by the custom-made retractor for 1 hour.

the animals could have free access to all chambers. The time spent in the drug-paired chamber and saline-paired chamber was calculated. The preference index was calculated as the time spent in the drug-paired chamber subtracted from the time spent in the saline-paired chamber.

2.5. Statistical Analyses. GraphPad Prism 7.0 was used to plot and fit the data. Statistical comparisons were made using Student's *t*-test, paired *t*-test, and two-way repeated-measures ANOVA (Student–Newman–Keuls test was used for post hoc comparison). All data are presented as the mean ± SEM. In all cases, $P < 0.05$ was considered statistically significant.

3. Results

3.1. Mouse Model of Persistent Postsurgical Pain Evoked by SMIR. SMIR was performed on the right hindpaw of mice (Figures 1(a)–1(c)), and PWTs and PWLs of the ipsilateral hindpaw plantar surface were tested. As compared to the sham-operated mouse, SMIR treatments decreased PWTs on postsurgical day 1 and lasted to day 10, while it recovered at day 18 after SMIR surgery (Figure 2(a)). Sham treatments did not change the PWTs. These data suggested that the SMIR treatments induced mechanical allodynia in mice.

The effect of SMIR surgery on hindpaw responses to thermal stimuli was also investigated. Figure 2(b) illustrates the PWL to a noxious heat stimulus prior to and up to 18 days after SMIR or sham surgery. Withdrawal latencies of ipsilateral paws in SMIR-operated mice were not significantly altered up to postsurgical day 18. The same findings were made in the sham-operated group.

3.2. Clonidine Relieves Evoked Pain and Spontaneous Pain after SMIR. Clonidine is an agonist of alpha-2 adrenergic receptor; it has had marked analgesic effects on both evoked pain and spontaneous pain in basic research studies; we therefore evaluated the analgesic effects of clonidine on SMIR-induced persistent pain. As shown in Figure 3(a), the injection of saline had no effects on PWTs, while application of clonidine increased the PWTs of mice with SMIR in a dose-dependent manner (Figures 3(b)–3(d), i.p.). More specifically, clonidine increased PWTs at doses of 0.1 mg/kg (Figure 3(c)) and 0.5 mg/kg (Figure 3(d)), but it had no effect at 0.02 mg/kg (Figure 3(b)). Interestingly, clonidine also elevated the PWTs of mice with sham treatments at 0.5 mg/kg, but not at other doses.

We further evaluated the effects of clonidine on place preference by using the CPP behavioral paradigm. As shown in Figure 4, mice that received sham treatments did not show place preference to the clonidine-paired chamber during the habitation or testing period (Figures 4(a) and 4(b)), and no difference was detected on the preference index (Figure 4(b)). Mice that underwent the SMIR operation spent a similar amount of time in the two chambers during the habitation period; interestingly, they spent a longer time in the drug-paired chamber during the testing period (Figures 4(c) and 4(d)). These data suggested that SMIR could cause spontaneous pain to occur, which could be relieved by 0.5 mg/kg clonidine.

3.3. Gabapentin Relieved the Evoked Pain but Not Spontaneous Pain after SMIR. Gabapentin is the first-line medicine for the treatment of neuropathic pain. We further evaluated the

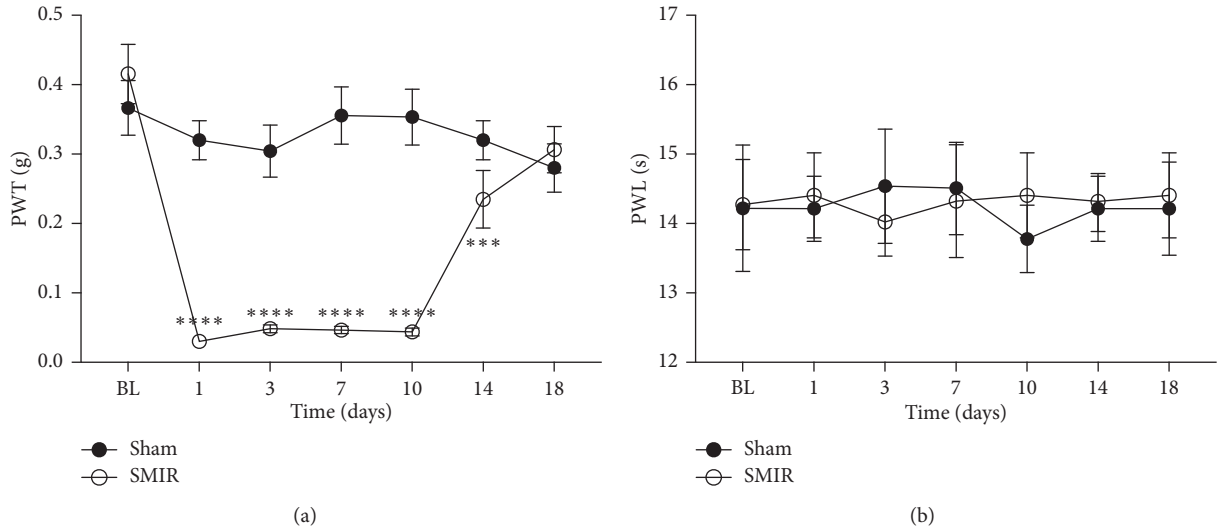
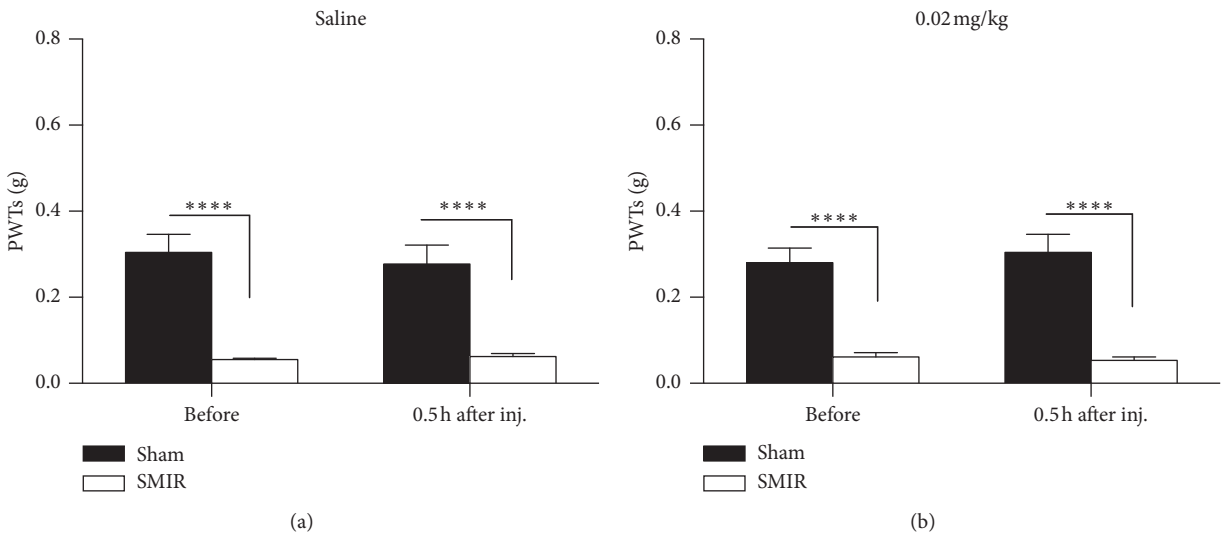


Figure 2: Paw withdrawal threshold (PWT) for mechanical stimulation and paw withdrawal latencies (PWLs) to noxious heat stimulation evoked by skin/muscle incision and retraction (SMIR) surgery. (a) The sham treatment group did not demonstrate significant mechanical hypersensitivity as compared to baseline, to von Frey stimulation in the ipsilateral paw. SMIR surgery evoked a persistent significant mechanical hypersensitivity. SMIR-evoked mechanical hypersensitivity in the ipsilateral paw (two-way RM ANOVA, sham versus SMIR: F1; 16 = 50.6, $P < 0.0001$; time: F6; 96 = 15.42, $P < 0.0001$, interaction: F6; 96 = 15.48, $P < 0.0001$; $n = 9$ for the sham group, $n = 9$ for the SMIR group; $^{***}P < 0.001$, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (b) Paw withdrawal latencies in the sham-operated group were unaltered throughout the time course. SMIR surgery also did not evoke significant heat hypersensitivity. Withdrawal latencies of the ipsilateral paws in the SMIR-operated mice were not significantly altered up to post-operative day 18 (two-way RM ANOVA, sham versus SMIR: F1; 17 = 0.013, $P = 0.91$; time: F6; 102 = 0.07, $P = 0.999$, interaction: F6; 102 = 0.23, $P = 0.97$; $n = 9$ for the sham group, $n = 10$ for the SMIR group, under Sidak's multiple comparisons test). ANOVA, analysis of variance; RM, repeated measures; BL, presurgery baseline.



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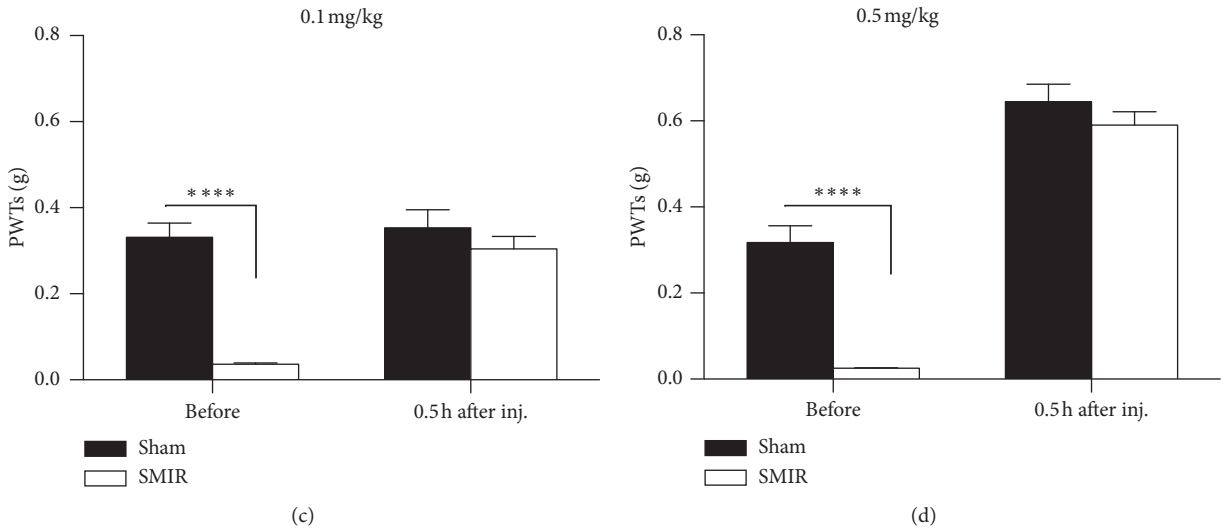
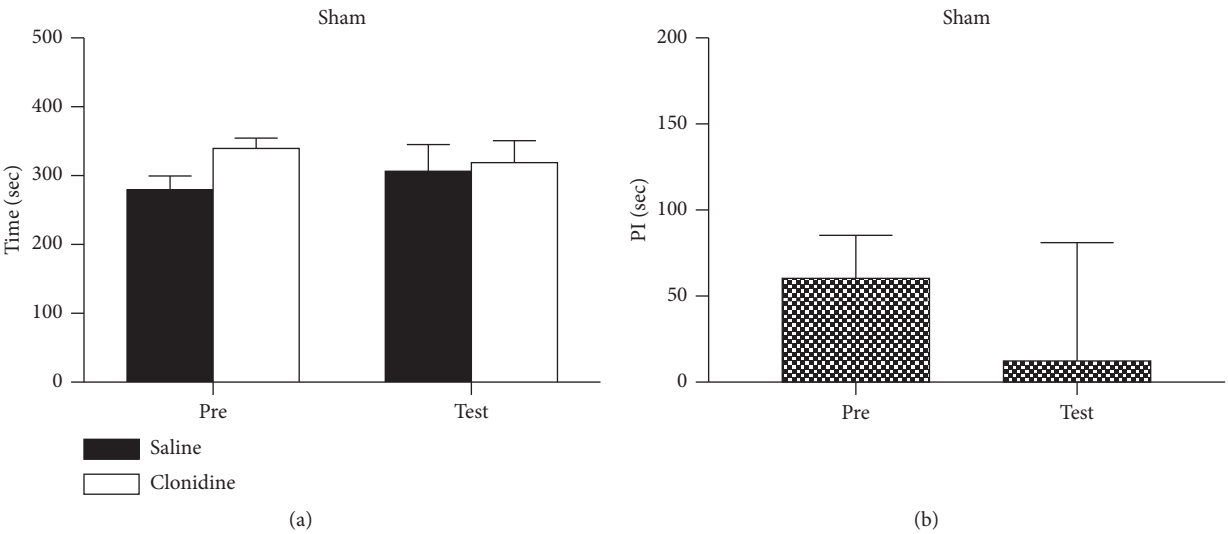


Figure 3: Systemic administration of clonidine raised the paw withdrawal threshold (PWT) in skin/muscle incision and retraction (SMIR) mice. (a) Saline had no effect on the PWTs in the sham and SMIR groups injected at day 4 after SMIR (two-way RM ANOVA, sham versus SMIR: F1; 17 = 35.83, $P < 0.0001$; treatments: F1; 17 = 0.55, $P = 0.47$, interaction: F1; 17 = 1.74, $P = 0.20$; $n = 7$ for the sham group, $n = 8$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (b) SMIR decreased the PWTs, which was not changed by the application of clonidine at 0.02 mg/kg (two-way RM ANOVA, sham versus SMIR: F1; 17 = 87.23, $P < 0.0001$; treatments: F1; 17 = 0.08, $P = 0.78$, interaction: F1; 17 = 0.33, $P = 0.57$; $n = 9$ for the sham group, $n = 10$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (c) Clonidine at 0.1 mg/kg increased the PWTs of the SMIR group (two-way RM ANOVA, sham versus SMIR: F1; 17 = 24.07, $P = 0.0001$; treatments: F1; 17 = 37.01, $P < 0.0001$, interaction: F1; 17 = 26.54, $P < 0.0001$; $n = 9$ for the sham group, $n = 10$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (d) Clonidine at 0.5 mg/kg increased the PWTs of both the SMIR group and the sham group (two-way RM ANOVA, sham versus SMIR: F1; 17 = 24.04, $P = 0.0001$; treatments: F1; 17 = 273.3, $P < 0.0001$, interaction: F1; 17 = 19.53, $P < 0.0004$; $n = 9$ for the sham group, $n = 10$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). ANOVA, analysis of variance; RM, repeated measures.



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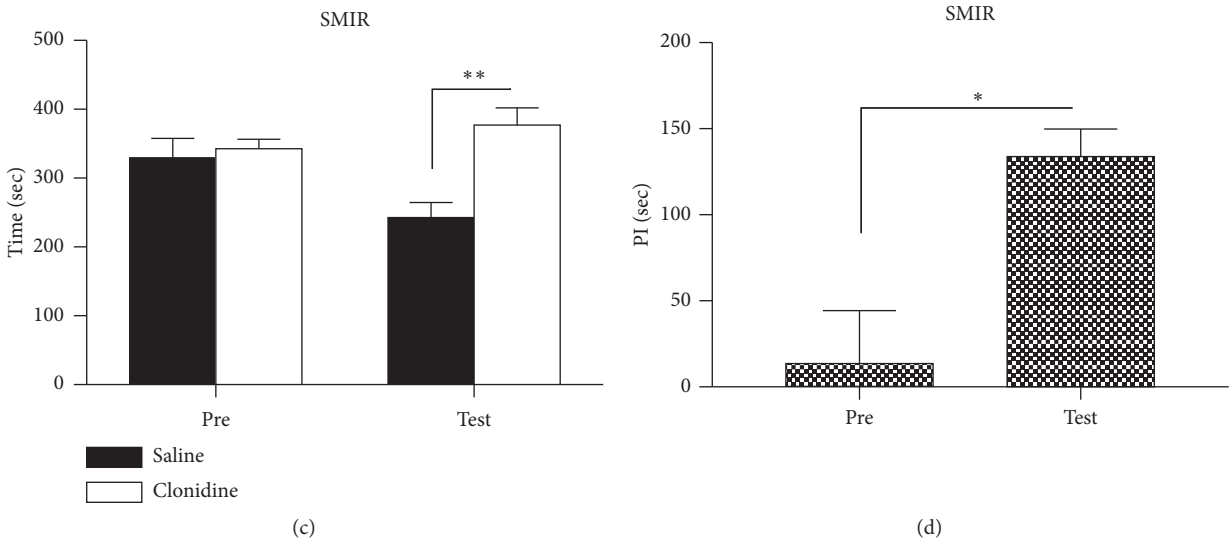

Figure 4: Systemic administration of clonidine induced the place preference to the drug-paired chamber. (a) Mice that received sham treatments spent equal amounts of time in the chambers during the preconditioning and testing periods (two-way RM ANOVA, pre versus test: F1; 23 = 0.06, $P = 0.76$; drug versus saline: F1; 23 = 7.54, $P = 0.44$, interaction: F1; 23 = 3.29, $P = 0.43$; $n = 6$). (b) No difference was detected in the preference times of the sham group (t-test, $P > 0.05$). (c) Preference was detected after the application of clonidine (0.5 mg/kg) to the mice of SMIR (two-way RM ANOVA, pre versus test: F1; 23 = 3.41, $P = 0.04$; drug versus saline: F1; 23 = 26.81, $P = 0.001$, interaction: F1; 23 = 17.99, $P = 0.04$; $n = 6$). (d) A significant difference was detected in the preference times of the SMIR group (t-test, $P < 0.05$). ANOVA, analysis of variance; RM, repeated measures; PI, preference index.

analgesic effects of gabapentin on both evoked pain and spontaneous pain induced by SMIR treatments. As shown in Figure 5(a), saline application had no effect on the PWTs; the PWTs of mice remained unchanged after application of gabapentin at 10 mg/kg (Figure 4(b)), while the PWTs increased at 20 mg/kg (Figure 4(c)) and 50 mg/kg (Figure 4(d)), tested at 0.5 hours after the injection. This suggested that evoked pain could be relieved by gabapentin at doses of 20 mg/kg and 50 mg/kg. Similarly, we evaluated the analgesic effects of gabapentin on spontaneous pain after SMIR. As shown in Figures 6(a) and 6(b), the mice exposed to sham treatments did not show place preference to the gabapentin-paired chamber. Unlike our previous observations, the application of gabapentin at 50 mg/kg did not induce a preference for its paired chamber (Figure 6(c)); consistently, no difference was detected in the preference time (Figure 6(d)), which indicated that the gabapentin treatment failed to induce place preference. These data suggested that the spontaneous pain was not relieved by 50 mg/kg gabapentin on day 4 after SMIR.

4. Discussion

As mice are used for various gene knockout/down models, which allow further study of the mechanism underlying of pain. Our results demonstrated that the SMIR model in mice was developed and characterized by a significant decrease in withdrawal threshold to von Frey filaments for 14 days after the procedure and a spontaneous pain measured by CPP. Clonidine and gabapentin could relieve mechanical hypersensitivity dose-dependently. Moreover, clonidine but not gabapentin could alleviate the spontaneous pain of SMIR in the mice model. To our knowledge, this is the first study expanding the SMIR model from rat to mice successfully and investigating the effects of clonidine and gabapentin on spontaneous pain and mechanical allodynia simultaneously in mice SMIR model.

A rat model of SMIR developed by Flatters [10] was usually used for investigating the underlying mechanism of postsurgical pain [11–13]. Our study expanded this model from rat to mouse. Similar to the rat model by Flatters, our mice model showed hypersensitivity to mechanical stimulation but not heat stimulation. However, the two main differences between the two models were the summit and duration of pain behavior. Mechanical hypersensitivity evoked by SMIR in the rat model was observed by postoperative day 3, most prominent between postoperative days 10 and 13, lasted until at least postoperative day 22, and had dissipated by postoperative day 32. SMIR-evoked mechanical hypersensitivity of our mice model began on day 1 after the procedure, prominent between days 1 and 10 after the procedure, persisted at least until day 14, and disappeared on day 18 after the procedure. Another main difference between the two models was spontaneous pain behavior measured by CPP in our mice model. Allodynia and hyperalgesia, but not spontaneous pain, are frequently used to evaluate pain stages in animal models [10]. However, it has been reported that spontaneous pain is a major problem for patients with persistent pain [6–9]. Castel et al. developed a porcine model of postoperative pain with spontaneous behavior score [26]. However, a porcine model for studying the underlying mechanism is not commonly accepted. The presence of spontaneous pain has previously been reported and evaluated using the CPP behavioral assay [24]. Critical to such a study paradigm is the selection of drugs that do not possess rewarding properties in naive

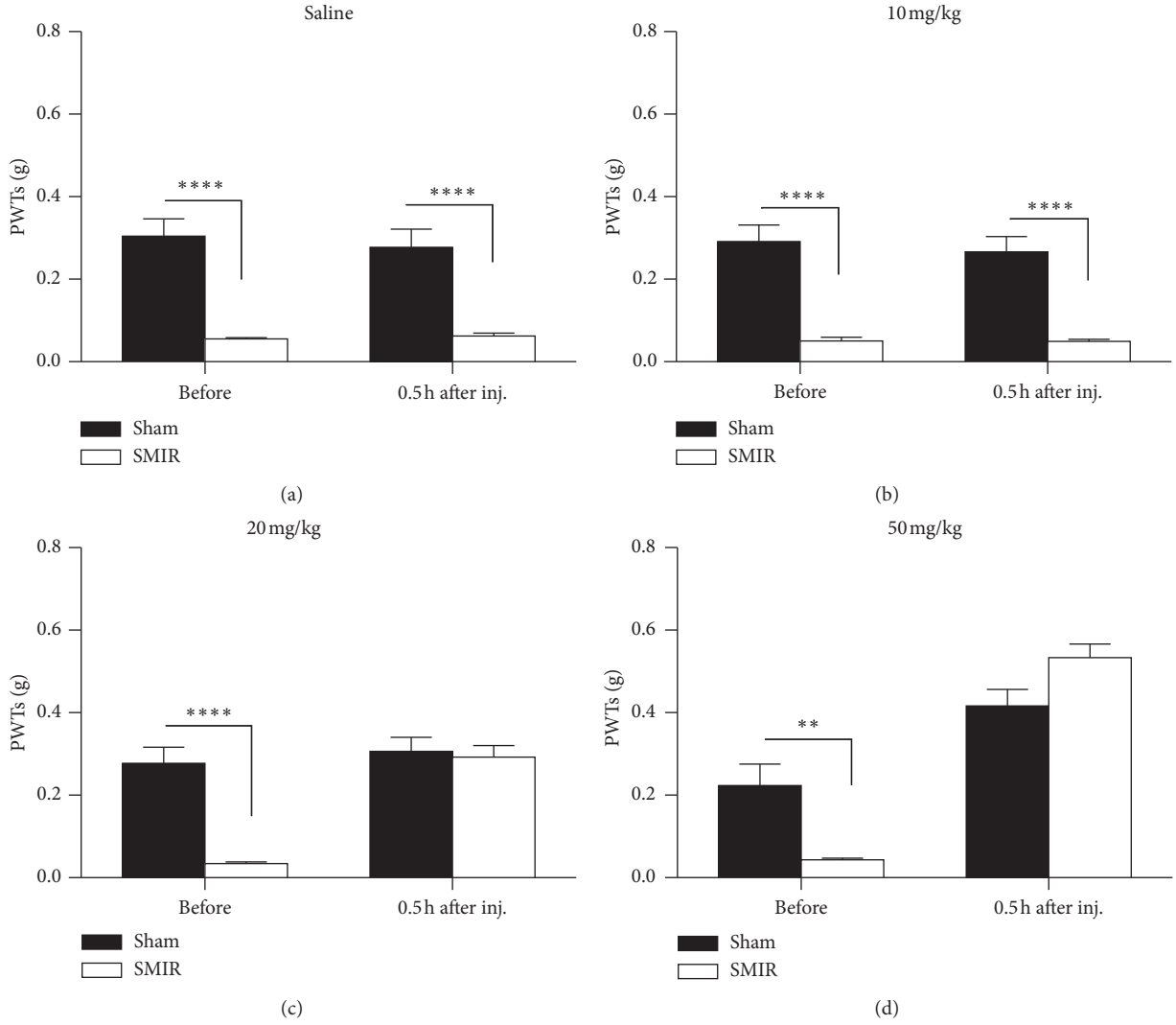

Figure 5: The application of gabapentin systemically raised the paw withdrawal threshold (PWT) in skin/muscle incision and retraction (SMIR) mice. (a) Saline had no effect on the PWTs in the sham and SMIR groups injected at day 4 after SMIR (two-way RM ANOVA, sham versus SMIR: F1; 17 = 35.83, $P < 0.0001$; treatments: F1; 17 = 0.55, $P = 0.47$, interaction: F1; 17 = 1.74, $P = 0.20$, $n = 7$ for the sham group; $n = 8$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (b) SMIR decreased the PWTs, which were not changed by the application of gabapentin at 10 mg/kg (two-way RM ANOVA, sham versus SMIR: F1; 17 = 71.68, $P < 0.0001$; treatments: F1; 17 = 0.25, $P = 0.63$, interaction: F1; 17 = 0.19, $P = 0.67$; $n = 9$ for the sham group, $n = 10$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (c) Gabapentin at 20 mg/kg increased the PWTs of the SMIR group (two-way RM ANOVA, sham versus SMIR: F1; 17 = 13.41, $P = 0.0019$; treatments: F1; 17 = 57.53, $P < 0.0001$, interaction: F1; 17 = 36.69, $P < 0.0001$; $n = 9$ for the sham group, $n = 10$ for the SMIR group, $^{****}P < 0.0001$ under Sidak's multiple comparisons test). (d) Gabapentin at 50 mg/kg increased the PWTs of both the SMIR group and sham group (two-way RM ANOVA, sham versus SMIR: F1; 9 = 0.73, $P = 0.41$; treatments: F1; 9 = 102.7, $P < 0.0001$, interaction: F1; 9 = 19.41, $P = 0.0017$; $n = 5$ for the sham group, $n = 6$ for the SMIR group, $^{**}P < 0.01$ under Sidak's multiple comparisons test). ANOVA, analysis of variance; RM, repeated measures.

animals and their administration at sites that are not a part of the reward circuit. In our study, we employed clonidine, which is not known to be rewarding in naive mice. Moreover, we verified in our experiments that these agents did not produce CPP in saline-treated, sham-operated mice. On the other hand, clonidine produced robust CPP, which suggested the presence of ongoing spontaneous pain in these mouse models of persistent pain.

Recent studies have shown that some drugs have different effects on spontaneous pain and hyperalgesia, which suggested that different mechanisms may be involved in the regulation of spontaneous pain or evoked pain [27]. Our data suggested that clonidine at both 0.1 mg/kg and 0.5 mg/kg (i.p.) can relieve persistent allodynia, which is consistent with the previous report [24]. Similar to clonidine, gabapentin at both 0.1 mg/kg and 0.5 mg/kg (i.p.) can relieve persistent allodynia. However, CPP was induced by clonidine but not gabapentin in the mice model of SMIR. Our team had also found that the mechanical allodynia could be alleviated by the application of clonidine. Clonidine-induced place preference was only observed at day 7 in the mice model of common peroneal nerve [19]. Clonidine is

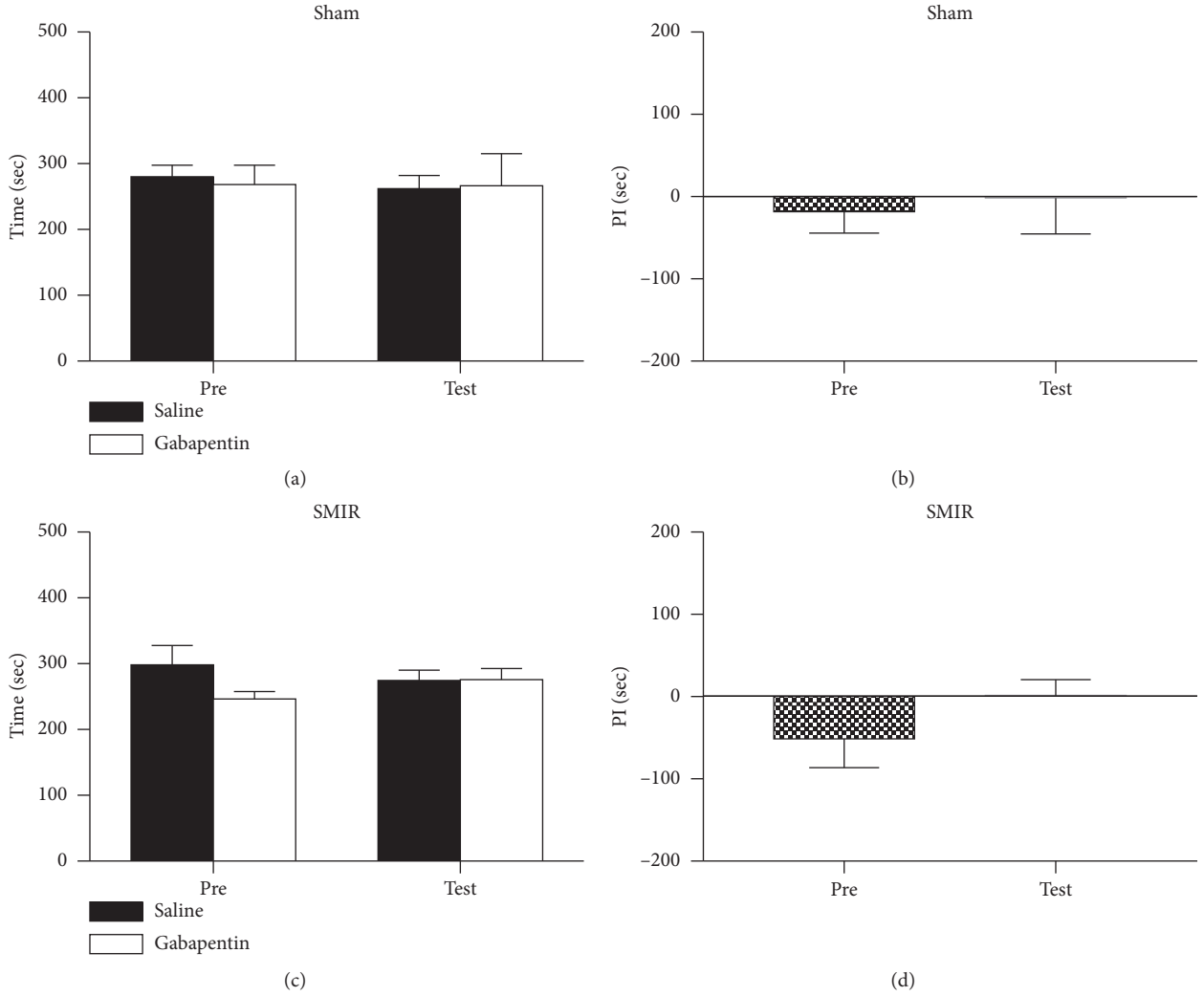

Figure 6: Systemic administration of gabapentin did not induce the place preference to the drug-paired chamber. (a) Mice that received sham treatments spent equal amounts of time in the chambers during the preconditioning and testing periods (two-way RM ANOVA, pre versus test: F1; 19 = 0.65, $P = 0.46$; drug versus saline: F1; 19 = 0.08, $P = 0.92$, interaction: F1; 19 = 0.42, $P = 0.82$; $n = 5$). (b) No difference was detected in the preference times of the sham group (t-test, $P > 0.05$). (c) No place preference was detected after the application of gabapentin (50 mg/kg) to the mice of SMIR (two-way RM ANOVA, pre versus test: F1; 31 = 0.09, $P = 0.69$; drug versus saline: F1; 31 = 7.09, $P = 0.26$, interaction: F1; 31 = 7.76, $P = 0.24$; $n = 8$). (d) No difference was detected in the preference times of the SMIR group (t-test, $P > 0.05$). ANOVA, analysis of variance; RM, repeated measures; PI, preference index.

reported to inhibit spinal LTP while gabapentin targets at voltage-gated calcium channels [28, 29]. It is likely that evoked pain and spontaneous pain are regulated by different mechanisms or by different analgesic drugs [30].

The limitation of this study was that the underlying mechanism, including acute pain transiting to chronic pain and the different effects of clonidine and gabapentin on CPP or evoked pain, has not been investigated. Gabapentin did not induce place preference or alleviate spontaneous pain, but attenuate evoked pain with high doses. Whether gabapentin combined with other analgesic drugs could alleviate both evoked pain and spontaneous pain should be investigated further in basic research and clinical trials.

In conclusion, the SMIR model of mice was developed successfully with a postoperative persistent pain syndrome, including evoked pain and spontaneous pain. Clonidine and gabapentin can both relieve mechanical hypersensitivity dose-dependently, but have different effects on spontaneous pain in our SMIR model. The underlying mechanism should be further investigated.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

Z. F. and X. L. designed research. J. Y., F. Y., Y. W., C. W., and J. W. performed experiments. J. Y. and F. Y. analyzed data. J. Y., F. Y., and G. Y. wrote the manuscript.

Acknowledgments

This work was supported by the Chinese National Natural Science Foundation (81571068) and Department of Science and Technology of Zhejiang Province (2016C37104).

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Hindawi
Pain Research and Management
Volume 2019, Article ID 8184592, 12 pages
https://doi.org/10.1155/2019/8184592

Review Article

Optimizing the Management and Outcomes of Failed Back Surgery Syndrome: A Proposal of a Standardized Multidisciplinary Team Care Pathway

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Received 19 December 2018; Revised 29 April 2019; Accepted 27 June 2019; Published 8 July 2019

Guest Editor: Baogan Peng

Failed back surgery syndrome (FBSS) is a major, worldwide health problem that generates considerable expense for healthcare systems. A number of controversial issues concerning the management of FBSS are regularly debated, but no clear consensus has been reached. This pitfall is the result of lack of a standardized care pathway due to insufficient characterization of underlying pathophysiological mechanisms, which are essential to identify in order to offer appropriate treatment, and the paucity of evidence of treatment outcomes. In an attempt to address the challenges and barriers in the clinical management of FBSS, an international panel of physicians with a special interest in FBSS established the Chronic Back and Leg Pain (CBLP) Network with the primary intention to provide recommendations through consensus on how to optimize outcomes. In the first of a series of two papers, a definition of FBSS was delineated with specification of criteria for patient assessment and identification of appropriate evaluation tools in order to choose the right treatment options. In this second paper, we present a proposal of a standardized care pathway aiming to guide clinicians in their decision-making on how to optimize their management of FBSS patients. The utilization of a multidisciplinary approach is emphasized to ensure that care is provided in a uniform manner to reduce variation in practice and improve patient outcomes.

1. Introduction

A significant proportion of patients who have undergone lumbar spinal surgery continue to suffer from persistent pain and impaired function, referred to as failed back surgery syndrome (FBSS) [1–5]. Patients with FBSS are a heterogeneous group, with complex and varied aetiologies, and typically present with chronic back or extremity pain, often both [1]. They have a low health-related quality of life (HRQoL) and high psychological morbidity and are frequent users of health services [2–4].

Failed back surgery syndrome is a condition that is difficult to treat successfully because of (a) lack of a precise pathophysiology and complexity of presentation [4, 6–10], (b) lack of a gold standard therapy or one-size-fits-all solution [11], and (c) limited availability of clinical guidance [12]. Patients with FBSS are at risk of being confined to the care of a single discipline, and treatment recommendations

are often determined by the managing healthcare provider's experience [13]. Although repeat surgery has been shown to be less successful than the primary surgery in several studies [14–18], awareness of available, alternative treatment options is often limited among surgeons, which may lead to further treatment delay and economic inefficiencies.

There is a growing trend towards evidence-based medicine that requires clinical decisions to be based on well-documented results taking the patient's best interests and the pain physician's/surgeon's experience into account. While this approach has been very successful in other fields of medicine, limited data are available concerning many issues related to the management of FBSS despite new validated therapeutic options. This lack of good quality data not only makes it difficult to utilize an evidence-based paradigm in the routine management of FBSS but also makes the optimal choice of treatment options for patients difficult.

The complexity of FBSS suggests that a multidisciplinary team (MDT) approach is important for the optimization of outcomes [19–22]. However, the management of patients with FBSS is often complicated by limited access to specialist pain centers offering the clinical expertise of multiple professional disciplines. While there are some published treatment pathways and algorithms following this main principle, there is no standardized care pathway for FBSS based on an MDT approach to provide guidance on assessment, treatment, and long-term evaluation of patients with FBSS to clinicians in order to optimize treatment outcomes.

To address the challenges of defining a comprehensive FBSS care pathway, an international panel of physicians with a special interest in FBSS established the Chronic Back and Leg Pain (CBLP) Network with the goal to provide recommendations on the management of patients with FBSS based on a multidisciplinary input. The work is presented in a series of two papers. The first paper focused on the definition of FBSS and outlined the criteria for appropriate diagnosis, with recommendations of validated tools to improve patient assessment [23]. The goal of this paper is to present a standardized care pathway to support clinicians in their decision-making on how to assess, treat, and evaluate patients with FBSS from an MDT-based perspective.

2. Materials and Methods

2.1. The Chronic Back and Leg Pain Network Constitution and Methodology. The composition of the CBLP Network and the methodology used to develop the proposed standardized FBSS care pathway adhere to the outlines presented in our first paper on FBSS definition and guidelines for patient assessment [23]:

(i) Participants in the CBLP panel were selected based on their extensive clinical and scientific experience in managing FBSS patients with focus on representation of the three specialties that are most involved in the treatment of this patient population: orthopaedic surgery, neurosurgery, and pain medicine/anesthesiology. Invitations were sent to potential participants all over Europe and accepted prior to engagement in the panel. Formal face-to-face meetings were held on a regular basis from 2012 to 2016 with additional follow-up teleconferences. All meetings were chaired by a trained facilitator to help the consensus process. Additional input was provided on an ongoing basis by relevant clinical specialists involved in the multidisciplinary evaluation and treatment of patients with FBSS (psychologist, psychiatrist, physiotherapist, and rehabilitation physician).

(ii) Systematic literature searches in PubMed, MEDLINE, LILACS, Embase, and the National Guideline Clearinghouse were conducted by two separate reviewers (one independent reviewer = GB and one reviewer on behalf of the group = NN) on a regular basis up to September 2018, without any restrictions regarding the language or year of publication. The search strategy was developed in order to maximize sensitivity of article identification, using controlled vocabulary and title/abstract words combining variations of "Failed back surgery syndrome," "Back pain," "Chronic leg pain" with "Multidisciplinary" OR "Team," "Clinical pathway" OR "Practice guideline" OR "Algorithm" OR "Guideline" OR "Protocol" (detailed description hereafter). The literature searches in this paper focus on therapeutic strategies and algorithms. For the independent reviewer (GB), the term "Failed back surgery syndrome" was cross-referenced with terms pertaining to clinical guidelines or algorithms (i.e., "Clinical pathway" OR "Practice guideline" OR "Algorithm"). Hand-searching of reference lists of identified reports and relevant review articles was also carried out. For the group reviewer (NN), the search strategy varied according to the database as follows:

(a) MEDLINE: ("Failed back surgery syndrome" OR "Chronic Back pain" OR "Chronic leg pain") AND ("Multidisciplinary" OR "Interdisciplinary" OR "Team" OR "Clinical pathway" OR "Guideline" OR "Protocol" OR "Algorithm")

(b) LILACS: ("Failed back surgery syndrome") AND ("Multidisciplinary" OR "Interdisciplinary" OR "Team" OR "Pathway" OR "Guideline" OR "Protocol" OR "Algorithm")

All references retrieved from databases were exported to Zotero to identify and exclude duplicated studies.

The two literature searches were pooled and crossed to converge into one final diagram. Our methodology is summarized in Figure 1.

The final literature review ensured that the CBLP Network members had access to the same body of evidence during the panel discussions.

(iii) Consensus was defined as full agreement on the set goals which was achieved during the facilitated round table discussions, based on the outcomes of the literature overview, each member's personal experience, and the additional input from relevant

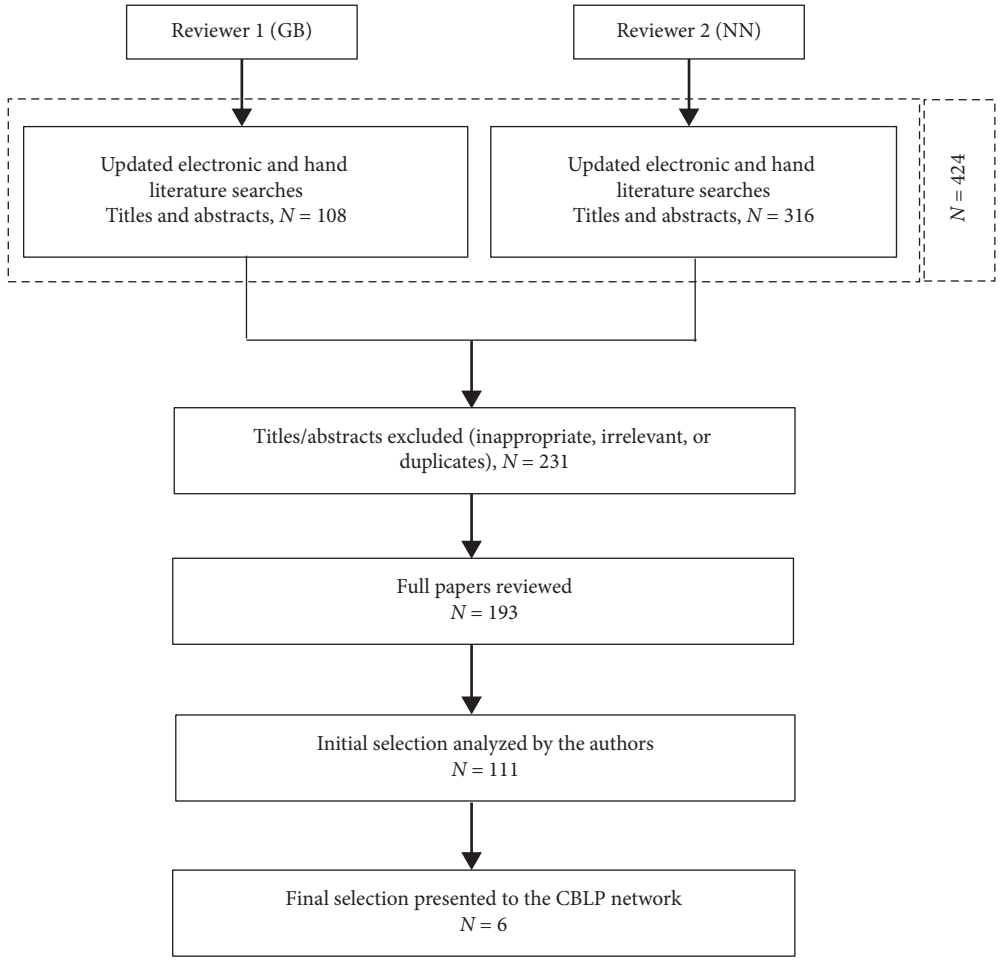

Figure 1: Diagram summarizing literature searches: FBSS management. The electronic and hand literature searches yielded 424 titles. Following a review of full-text versions of the 177 (NN) + 16 (GB) residual publications, after discarding duplicates and initial exclusion of 231 titles/abstracts, 95 (NN) + 16 (GB) papers were finally selected and 6 were retained. These are presented in Table 1.

clinical specialists. The consensus process did not include any individual (independent and anonymous) rating rounds based on the Delphi method since the number of participants was considered to be too small and the purpose of the discussions was not to measure consensus based on specific statements, but to resolve disagreements (reach full consensus) on the set task [27]. The limitations of the chosen methodology to reach consensus are discussed in our first paper on FBSS definition and patient assessment [23].

3. Results

3.1. Proposed Care Pathway in the Management of FBSS Utilizing an MDT. Six comprehensive FBSS care pathways or algorithms were identified by the literature searches (Table 1) [2, 12, 20, 24–26]. Their successful application and adoption in clinical practice have, however, been constrained by focusing on one treatment or investigation of a single FBSS subgroup, with lack of standardization. None of the algorithms met all of the following criteria for the development of an algorithm or care pathway: focus on all available aspects and means for patient evaluation and therapeutic options, emphasis on the involvement of an MDT, and evidence that a wide variety of experts provided consensus in its development.

In response to the identified limitations of current practice in the caretaking of FBSS patients, the CBLP Network developed a care pathway based on an MDT input to serve as a quick reference decision resource (Figure 2). The pathway focuses equally on (1) appropriate clinical evaluation for adequate patient selection and (2) elucidation of the full range of available treatments and diagnostic procedures and their place in the overall continuum of care using an evidence-based approach, as summarized in Figure 2.

3.2. Level One Treatment. If a specific spinal aetiology for pain has been identified without demonstrating the need for further surgery and significant psychosocial comorbidities have been ruled out, Level One treatment can be initiated (Figure 2). The goal of the first-line therapy is to optimize nonmedical and medical, conservative management [20].

Table 1: The therapeutic focus and importance of a multidisciplinary team and the number of experts consulted in the development of each care pathway.

Manuscript identification	Therapeutic focus	Emphasis on MDT	Number (N) and spectrum of experts consulted
Avellanal et al. [24]	Epiduroscopy as a diagnostic and therapeutic tool in FBSS Psychological and medical management excluded	Yes	$N = 4$ Wide
Chan and Peng [25]	All considered	Yes	$N = 2$ Narrow
Desai et al. [12]	Medical, rehabilitative, and behavioral treatment	Related to medical, rehabilitative, and behavioral treatment only	$N = 5$ Wide
Durand et al. [20]	Medical management	Discussed in relation to cognitive or behavioral disorders only	$N = 3$ Narrow
Ganty and Sharma [26]	Neuromodulation	Yes	$N = 2$ Narrow
Van Buyten and Linderoth [2]	Neuromodulation Conservative management was not discussed Authors' comment concerning historical algorithms: "several algorithms for the treatment of FBSS that focus largely on diagnosis and possible orthopaedic and neurosurgical interventions have been published; however, the place of SCS in these algorithms has remained unclear"	None	$N = 5$ Wide

Consideration should at first hand be given to physiotherapy, rehabilitation, and management of psychological and social factors [33]. It is important to note that even though many clinical trials using these modalities to relieve pain have been conducted, their clinical effects on FBSS remain inconclusive [5, 34]. There is, however, growing evidence showing that a structured, mixed rehabilitative approach [35] combining pain education [36, 37], behavioral approach [38], and patient-centered exercise programs aiming to gradually expose the patient to fearful or painful movement to improve function [39] seems more effective than traditional rehabilitation programs [40].

At this stage in the care continuum, pharmacological therapy traditionally includes the World Health Organization (WHO) Step I and II analgesics only, preferentially utilizing nonnarcotic medication, such as nonsteroid anti-inflammatory drugs (NSAIDs) and paracetamol for treatment of pain of nociceptive origin [28]. Adjuvant short-term therapy with weak Step II opioids, e.g., tramadol or combinations of paracetamol and codeine, can be added to enhance the effects of nonopioid analgesics [33]. Given the lack of evidence of long-term effectiveness and clear evidence of harm associated with long-term use, WHO Step III analgesics with strong opioids should be avoided [41].

The pharmacological treatment of FBSS with a predominant neuropathic radicular component is based on the use of gabapentinoids (gabapentin and pregabalin) and antidepressants (amitriptyline and duloxetine) [20]. Two-drug combinations for the treatment of neuropathic pain in adults have been shown to improve analgesic efficacy [42]. Attention should, however, be payed to the potential risk of gabapentinoid dependency and abuse [43]. New data indicate that combinations of gabapentinoids and opioids are associated with an increased risk of opioid-related death [44]. The UK regulator recently reclassified gabapentinoids as Class C controlled drugs [45]. Furthermore, the effect of pregabalin and gabapentin in reducing the neuropathic leg pain in patients, including those with FBSS, has also been questioned [46, 47]. Hence, the use of gabapentinoid medication in the long term should be carefully reviewed [48].

The patient should be prescribed at least two different drugs consecutively for six weeks or more to determine treatment effects. If therapy is effective (at least a 30% improvement) [49], the first-line option is continued until deterioration is reported. If deterioration occurs or pain is refractory to treatment, second-line therapy options should be considered.

Transcutaneous electrical nerve stimulation may provide an alternative/complement to medication in patients with FBSS. Its effectiveness in chronic low back pain is, however, still controversial [50, 51]. Other nonpharmacological complementary therapies, such as acupuncture, manual therapy, functional restoration, and cognitive behavioral therapy, may also be utilized, although the level of evidence supporting most of these therapies in the management of chronic back pain is moderate at best [52, 53].

3.3. Level Two Treatment. Level Two treatment includes minimally invasive interventional therapies/diagnostic procedures. Several reviews and evidence-based clinical

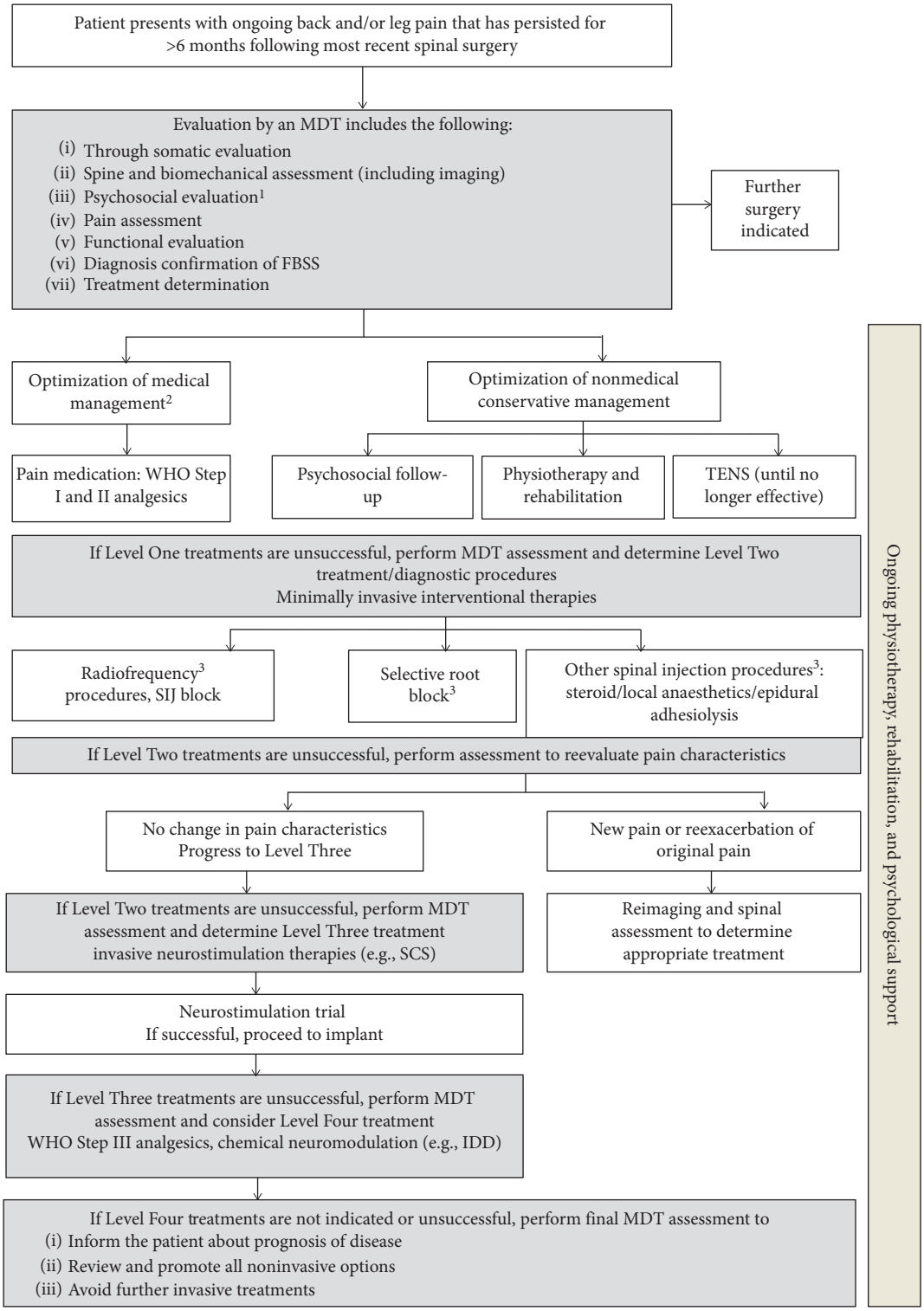

Figure 2: The proposed standardized multidisciplinary team's failed back surgery syndrome care pathway, as recommended by the Chronic Back and Leg Pain Network. FBSS, failed back surgery syndrome; IDD, intrathecal drug delivery; MDT, multidisciplinary team; SCS, spinal cord stimulation; SIJ, sacroiliac joint; TENS, transcutaneous electrical nerve stimulation; WHO, World Health Organization. *Note.* In cases of new pain and/or exacerbation of original pain at any stage of this flow, reimaging and spine expertise is required. [1]Best practice is for the psychosocial evaluation to be performed by a psychologist or psychiatrist with specific experience in the field of pain. Assessments may include the relevant tests and questionnaires aiming to identify patients with major psychological or psychiatric contraindications [23]. [2]Best practice is to avoid long-term use of WHO Step III analgesics and review ineffective long-term use of antineuropathic pain medication [28–30]. [3]There is limited evidence supporting a prolonged effect of epidural injections, selective nerve root blocks, and radiofrequency denervation in an FBSS population [20, 25, 31, 32]. Despite this lack of clinical evidence, these therapies may be tried/reserved for the management of acute exacerbation in pain.

practice guidelines and recommendations for interventional techniques in the diagnosis and treatment of chronic spinal pain, including FBSS, have been published and may be consulted for guidance [54–56]. Before second-line treatment is initiated, the patient should be reassessed. If a nociceptive pain component remains clinically significant, either in the back or in the leg or in both, a differential interventional strategy to clearly identify the potential pain generator will be a prerequisite to choose the best interventional option [57]. For example, if the sacroiliac joint (SIJ) is suspected to be a significant potential nociceptive pain generator, but a combination of clinical tests is negative (negative likelihood ratio (LR) −0.11), the posttest probability for SIJ pain is low. When this combination is positive (LR +7.0), SIJ could be the source of nociception [57]. These clinical findings need to be confirmed by a reference standard procedure, which in this case is an SIJ double anaesthetic block [58]. If a double-block procedure confirms the SIJ as a source of nociception, treatments such as steroid injections or radiofrequency ablation can be administered [59, 60]. The same approach can be used for other potential spine pain generators, such as lumbar facet pain [57, 61–64].

Second-line procedures also include selective nerve root block injections for neuropathic pain. If successful, pulsed radiofrequency or spinal cord stimulation (SCS) (see Level Three Treatment) may be considered to achieve a more sustained effect [19, 65]. Practitioners should be mindful of the paucity of evidence for the long-term effects of pulsed radiofrequency procedures and spinal injections on the FBSS population [20, 25, 31, 32, 34]. Despite the lack of robust clinical evidence, it is the view of the authors that these therapies may be useful for the management of acute exacerbation of pain, with the awareness of disappointing results in the long term.

Several systematic reviews have demonstrated sustained pain relief (up to 24 months) with percutaneous epidural adhesiolysis in the management of FBSS due to epidural/perineural fibrosis or scarring as the anticipated pain generator [34, 66–68]. Epidural adhesiolysis may be used when other less invasive Level Two treatment modalities have been ineffective. The procedure requires special technical skills and is considered to be of low risk for serious adverse events when performed by well-trained physicians.

3.4. Level Three Treatment. Level Three treatment includes interventional electrical neurostimulation therapies which mainly target the neuropathic pain component in FBSS. Before third-line treatment with neurostimulation is initiated, the patient should be assessed by an MDT to determine eligibility. Spinal cord stimulation (SCS) is the most commonly used interventional neurostimulation treatment for refractory chronic pain, the beneficial effects of which may persist for many years [5, 19, 34, 69, 70]. Spinal cord stimulation is a safe therapy because it is a minimally invasive and reversible procedure with exceedingly few serious complications [71–73]. Randomized controlled trials have demonstrated favourable long-term outcomes of SCS compared with conventional medical management [74, 75] and reoperation [76] in treating the radicular, neuropathic leg pain component in FBSS. Spinal cord stimulation is effective in reducing pain and medication use and improving HRQoL, function, and sleep in this subset of FBSS patients [74, 76–78]. The back pain component, on the contrary, has posed a major treatment challenge. Several new treatment options, involving refinement of traditional paraesthesia-based SCS, have evolved in order to find a solution to this problem. Recent reports on the use of multicolumn leads utilizing an algorithmic programming approach [79–81], peripheral nerve field stimulation, either alone or in combination with SCS [82–86], 1–10 kHz high-frequency stimulation [87–89], so-called burst stimulation [90], and closed-loop stimulation [91] have presented with varying success in treating the axial low back pain component in FBSS patients.

3.5. Level Four Treatment. For a patient whose pain is not sufficiently controlled by or who is ineligible for minimally invasive interventional pain management techniques, WHO Step III analgesic pain medication with strong oral opioids may be prescribed and monitored until the patient experiences intolerable drug-related adverse events or fails to achieve the primary aim of improvement in function because of development of tolerance or hyperalgesia. This approach is controversial and has been subject to intense debate during the last years since high-dose medication with potent opioids is often associated with severe side effects, such as hormonal dysfunction, weight gain, constipation, hyperalgesia, development of tolerance with time and the potential for dependence, abuse and addiction, and death by overdose [92–95]. In addition to the side effects, outcome data examining the long-term efficacy of opioids in treatment of FBSS-related chronic pain are lacking [29]. In a recent RCT with masked outcome assessment, it was shown that treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related functions over 12 months in patients with chronic back pain [96]. Returning to work has also been shown to be negatively associated with chronic opioid therapy in patients with persistent pain after lumbar fusion surgery for degenerative disc disease [97]. It is widely accepted that the use of high-potency opioids should be limited in the treatment of chronic pain.

Before initiating Level Four treatment, predictors of risk of long-term opioid use, such as duration of opioid intake in the year before lumbar surgery, refusion surgery, and any diagnosis of depression, have to be identified [30]. Patients prescribed WHO Step III analgesics should be followed up by the MDT at least three times per year to avoid uncontrolled increase in daily dose.

Chemical neuromodulation by continuous intrathecal drug delivery (IDD) based on morphine or ziconotide administration may be considered for patients preferentially with neuropathic pain who have responded to strong oral opioids in the presence of severe adverse events [98–100]. No protocols have specifically been developed for FBSS in this context. Long-term intrathecal opioid administration is

associated with an increased risk of late respiratory distress and pronounced side effects on hormone levels [100]. In addition, there is lack of prospective randomized, placebo-controlled studies to ratify the effect of IDD on treatment of FBSS in the long term.

If Level Four treatments are unsuccessful, a final MDT assessment is performed to inform the patient about the prognosis of the disease, to motivate the need of avoiding further invasive treatments, and to review and promote all available noninvasive options.

The CBLP Network recommends that structured physical and rehabilitation therapy and psychological support are provided on an ongoing basis and that a patient's disability/function and HRQoL are reevaluated before each new line of therapy using the same instruments as those administered before treatment for FBSS was initiated [101]. In cases of new pain and/or exacerbation of original pain at any stage, reevaluation as well as reimaging and new spine expertise is required in order to exclude indication for further surgery.

4. Discussion

Clinical guidelines and treatment algorithms have increased in popularity in disease management in an era of rising healthcare costs. Because of higher demands for efficient care, the availability of costly technologies, variations in service delivery among and between providers, and the overuse of inappropriate services and therapies, clinicians, payers, and policy-makers view such decision tools as instruments that can make healthcare delivery more efficient and consistent [102, 103].

Failed back surgery syndrome remains difficult to treat successfully not only because of the lack of a precise pathophysiology and complexity of its clinical presentation [4, 6–10] but also because of the lack of a gold standard therapy or one-size-fits-all solution [11] and the limited availability of clinical guidance [12]. There is a consensus in the literature, as well as among members of the CBLP Network, that patients with FBSS are at risk of being confined to the care of a single discipline and that differences in treatment recommendations are often determined by the managing healthcare provider's experience and discipline [3, 13, 23].

The development of the care pathway presented by the CBLP Network has been driven by an interest in and understanding the role and application of the available treatment options for FBSS in real-life practice, particularly in view of the recent reports of higher harm rates and inefficacy of opioids and gabapentinoids in treatment of chronic nonmalignant pain. Compared to previously published FBSS care pathways and algorithms, the CBLP Network's pathway puts an emphasis on amalgamation of three main criteria to further improve the quality and reliability of the pathway and to facilitate its adoption into clinical practice. The three cornerstones are (i) focus on all available aspects and means for patient evaluation and optimal utilization of therapeutic options, (ii) emphasis on the involvement of an MDT to improve decision-making, and (iii) involvement of a wide variety of experts who provide consensus in the development of the pathway. A quick reference care pathway for the assessment, treatment, and evaluation of outcomes with an integrated multidisciplinary approach is an important resource for specialist and nonspecialist clinicians who manage patients with FBSS [19–22].

One major challenge in the development of the presented care pathway was that the evidence of the clinical outcomes in the FBSS population has not been clearly determined in the available literature, even though a multitude of clinical trials using different therapeutic approaches with the intention of relieving pain and improving function have been conducted. Only a few studies have systematically analyzed and evaluated the overall clinical trial data using an evidence-based approach. Because of the paucity of evidence-based guidelines in the management of FBSS, the CBLP Network chose to adhere to a consensus-based approach to achieve the set goals to define FBSS and design outlines for appropriate patient evaluation and to propose a concise treatment pathway. Limitations of the used approach are discussed in the first of the two papers in this series on how to optimize outcomes of FBSS [23].

In a recent systematic review, the literature on various modalities for treating the back pain and/or radiating leg pain component in FBSS was critically analyzed by means of quality assessment and level of evidence for each modality [34]. The review established that, among the many treatment options that have been outlined in the care pathway developed by the CBLP Network, epidural adhesiolysis and SCS can be effective in the long term for controlling chronic back or leg pain due to FBSS, with recommendation grades A and B, respectively. Epidural injections showed a short-term effect (grade C). The evidence regarding the success of other therapies, including revision surgery, medication, exercise, psychotherapy, intrathecal infusion of opioids, and other types of interventions, was poor or inconclusive.

In a second review which also specifically investigated treatment options for FBSS patients with refractory chronic pain, it was concluded that evidence is weak for medications and reoperation, but strong (Level I-II) for active exercise, and some interventional procedures, such as epidural adhesiolysis and SCS [5]. In summary, in both reviews, the strongest evidence for a prolonged effect was obtained for epidural adhesiolysis and SCS, even though the evidence on the efficacy, effectiveness, safety, and cost-effectiveness was found to be insufficient of epidural adhesiolysis for treating FBSS in a recently published systematic review specifically investigating this treatment option [104]. All reviews underscore the need for further research and development of better and longer-term therapeutic options for FBSS patients.

Among the interventional techniques, SCS has been proven to be a very safe and effective therapy in the long term for a variety of chronic pain conditions, and therefore, its use earlier in the treatment algorithm for several of these conditions, including FBSS, has been advocated [69, 105–107]. With further strengthening of the evidence-based support for a sustained long-term efficacy of SCS, this minimally invasive treatment modality may deserve to be put among Level Two treatment options in the FBSS care pathway that has been outlined by the CBLP Network [5, 34, 69, 108].

5. Conclusions

Failed back surgery syndrome results from a cascade of medical and surgical events that have led to and left the patient with chronic back and radicular pain. This pain often remains refractory to sporadic (and usually not well-planned) management strategies for a considerable proportion of these patients, highlighting the need for a global, multidisciplinary-based approach. A clear and concise, standardized care pathway comprising recommendations for assessment, treatment, and outcome evaluation using an MDT approach would be an important resource for specialists and nonspecialists who manage patients with FBSS. A comprehensive reference FBSS care pathway has the potential to improve decision-making, reduce variation in practice, and optimize treatment outcomes for this often hard-to-treat condition.

Conflicts of Interest

Philippe Rigoard, Kliment Gatzinsky, Jean-Philippe Deneuville, Wim Duyvendak, Nicolas Naiditch, Jean-Pierre Van Buyten, and Sam Eldabe treat patients with failed back surgery syndrome in the private and/or the public healthcare sectors and may therefore gain from the implementation of the pathway. Philippe Rigoard, Kliment Gatzinsky, Wim Duyvendak, Jean-Pierre Van Buyten, and Sam Eldabe were reimbursed for travel to Chronic Back and Leg Pain Network meetings and received honoraria for Chronic Back and Leg Pain Network meeting participation from Medtronic Inc. and may therefore have a preexisting relationship with Medtronic, the funder, and be influenced by beliefs associated with treatments recommended in the pathway. Philippe Rigoard, Kliment Gatzinsky, Sam Eldabe, and Wim Duyvendak have served as consultants to Medtronic Inc. and Boston Scientific and may therefore have a preexisting relationship with them and be influenced by beliefs associated with treatments recommended in the pathway. Kliment Gatzinsky and Sam Eldabe have served as consultants to Abbott and may therefore have a preexisting relationship with them and be influenced by beliefs associated with treatments recommended in the pathway. Sam Eldabe has served as a consultant to Mainstay Medical and may have a preexisting relationship with them and be influenced by beliefs associated with treatments recommended in the pathway. Philippe Rigoard, Wim Duyvendak, and Sam Eldabe have received research funding from Medtronic Inc. and may be influenced by beliefs associated with treatments recommended in the pathway. Philippe Rigoard and Wim Duyvendak have received research funding from Boston Scientific and Abbott and may be influenced by beliefs associated with treatments recommended in the pathway. Sam Eldabe has received research funding from Nevro and may be influenced by beliefs associated with treatments recommended in the pathway. Nicolas Naiditch and Jean-Philippe Deneuville declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The authors thank Gillian Barnett of Gillian Barnett and Associates Limited for support in manuscript preparation and literature review. Medtronic provided sponsorship and logistical support in the form of meeting services and project coordination. The funder did not provide input to the discussions or the consensus. Medtronic manufactures devices indicated for failed back surgery syndrome and may therefore gain from the implementation of the pathway described in this article.

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Hindawi
Pain Research and Management
Volume 2019, Article ID 5948686, 15 pages
https://doi.org/10.1155/2019/5948686

Research Article

Microglial BDNF, PI3K, and p-ERK in the Spinal Cord Are Suppressed by Pulsed Radiofrequency on Dorsal Root Ganglion to Ease SNI-Induced Neuropathic Pain in Rats

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Received 30 November 2018; Revised 7 February 2019; Accepted 28 March 2019; Published 28 April 2019

Guest Editor: Ke Ma

Background. Pulsed radiofrequency (PRF) on the dorsal root ganglion (DRG) has been applied to alleviate neuropathic pain effectively, yet the mechanisms underlying pain reduction owing to this treatment are not clarified completely. The activated microglia, brain-derived neurotrophic factor (BDNF), phosphatidylinositol 3-kinase (PI3K), and phosphorylated extracellular signal-regulated kinase (p-ERK) in the spinal cord were demonstrated to be involved in developing neuropathic pain. Also, it has been just known that PRF on DRG inhibits the microglial activation in nerve injury rats. Here, we aim to investigate whether PRF treatment could regulate the levels of BDNF, PI3K, and p-ERK in the spinal cord of rats with spared nerve injury (SNI) via suppressing the spinal microglia activation to ease neuropathic pain. *Methods*. The rats with SNI were intrathecally treated with minocycline (specific microglia inhibitor) or same volume of dimethyl sulfoxide once daily, beginning from 1 h before nerve transection to 7 days. PRF was applied adjacent to the L_4-L_5 DRG of rats with SNI at 45 V for 6 min on the seventh postoperative day, whereas the free-PRF rats were treated without PRF. The withdrawal thresholds were studied, and the spinal levels of ionized calcium-binding adapter molecule 1 (Iba1), BDNF, PI3K, and p-ERK were calculated by western blot analysis, reverse transcription-polymerase chain reaction, and immunofluorescence. *Results*. The paw withdrawal mechanical threshold and paw withdrawal thermal latency decreased in the ipsilateral hind paws after SNI, and the spinal levels of Iba1, BDNF, PI3K, and p-ERK increased on day 21 after SNI compared with baseline ($P < 0.01$). An intrathecal injection of minocycline led to the reversal of SNI-induced allodynia and increase in levels of Iba1, BDNF, PI3K, and p-ERK. Withdrawal thresholds recovered partially after a single PRF treatment for 14 days, and SNI-induced microglia hyperactivity, BDNF upregulation, and PI3K and ERK phosphorylation in the spinal cord reduced on D14 due to the PRF procedure. *Conclusion*. Microglial BDNF, PI3K, and p-ERK in the spinal cord are suppressed by the therapy of PRF on DRG to ease SNI-induced neuropathic pain in rats.

1. Introduction

Neuropathic pain is a kind of refractory pain that arises as a direct consequence of a lesion or disease affecting the somatosensory system [1, 2]. A variety of damages to the peripheral nerves, including diabetes, zoster virus, human immunodeficiency virus-acquired immunodeficiency syndrome, and compression injury, can result in neuropathic pain [3]. Neuropathic pain, characterized by hyperalgesia or allodynia, is associated with central and peripheral sensitization of neurons in the nociceptors [4, 5]. It is hard to treat due to the complicated etiology and mechanisms, including several neurotransmitter systems, receptors, ionic channels, and cell types [6, 7]. Thus, current pharmacotherapy rarely resolves intractable pain in patients. Pulsed radiofrequency (PRF), a type of electromagnetic stimulation, has been successfully used to treat patients suffering from neuropathic pain [8, 9]. PRF on dorsal root ganglion (DRG) is considered to be superior to continuous radiofrequency because the electrode tip temperature of PRF does not exceed 42°C during the whole process to avoid massive tissue destruction. Nowadays, the application of PRF on DRG to treat

neuropathic pain has greatly helped clinicians. However, the analgesic mechanism of this therapy is not well clarified so far.

Recently, PRF was administered on DRG in rats with peripheral nerve injury (PNI) to downregulate microglial activation in the spinal cord and improve pain behaviors [10, 11]. Microglia are the resident macrophages in the central nervous system (CNS), and they react to the stimuli that may affect homeostasis and induce pathological alterations [12]. As a consequence of multiple types of damages in the nervous system, microglia can transform to reactive states through a progressive series of cellular and molecular changes, including morphological hypertrophy, proliferation, and expression of various genes [13]. The activated microglial cells play a key role in the peripheral and central sensitization to develop neuropathic pain conditions [14]. They secrete brain-derived neurotrophic factor (BDNF), which is a critical microglia-neuron signaling molecule that gates aberrant nociceptive processing in the spinal cord [15]. Many studies support the pronociceptive role of BDNF in pain processes in the peripheral and CNS. Nociceptor-derived BDNF has been shown to be involved in inflammatory pain and microglial-derived BDNF in neuropathic pain [16]. Recently, Liu et al. [17] reported that BDNF participated in colitis-induced spinal central sensitization, and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B pathway mediated BDNF action in the spinal cord. Moreover, the second messengers that PI3K generated could activate phosphorylated extracellular signal-regulated kinase (p-ERK) [18, 19]. In microglia, ERK activation occurred after nerve injury, and the inhibition of the activated ERK could suppress neuropathic pain development [20]. The spinal cord, which is the primary integration center of information and plays a crucial role in central sensitization, was preferred by pain physicians for exerting neuromodulation to relieve neuropathic pain, such as spinal cord stimulation. In precedent different animal models, the microglia, BDNF, PI3K, and p-ERK were involved in the development of neuropathic pain. However, it remains uncertain that whether the release of BDNF, PI3K and p-ERK in the spinal cord regulates chronic pain processing through microglia-dependent mechanism. In addition, whether the application of PRF on DRG for treating neuropathic pain is associated with the downregulated levels of microglia, BDNF, PI3K, and p-ERK in the spinal cord needs exploration further.

In this study, a microglial inhibitor was intrathecally administered to the rats with spared nerve injury (SNI) to affirm the release of BDNF, PI3K, and p-ERK in the spinal cord via the microglial-dependent mechanism. We also investigated whether PRF treatment could regulate the levels of BDNF, PI3K, and p-ERK in the spinal cord of SNI rats via suppressing the spinal microglia activation to alleviate the neuropathic pain.

2. Materials and Methods

2.1. Animals. Male Sprague–Dawley (SD) rats (4-month-old, 250–280 g) were obtained from the Experimental Animal Center of Fujian Medical University, Fuzhou. The animals were housed under a 12 h light-dark cycle at 22°C–24°C with ad libitum access to food and water in the Pharmacy College of Fujian Medical University (SPF class). All procedures in this study were approved by the Fujian Medical University Experimental Animal Welfare Ethics Committee (SYXK 2016-0007).

2.2. Treatment Group and Design. Ninety male SD rats were randomly (according to the method of random number table) divided into six groups ($n = 15$, each): Sham group, SNI group, SNI + PRF group, SNI + free-PRF group, SNI with minocycline (SNI + M) group, and SNI with dimethyl sulfoxide (SNI + DMSO) group.

2.2.1. Effect of Minocycline on Levels of Microglia, BDNF, PI3K, and ERK in the Spinal Cord. The rats in the following four groups (Sham, SNI, SNI + M, and SNI + DMSO) were studied. All rats (except the Sham group) were subjected to SNI of the right sciatic nerve. The rats in the SNI + M and SNI + DMSO groups were intrathecally treated with minocycline (specific microglia inhibitor) and an equal volume of DMSO, respectively. Pain behaviors and the levels of ionized calcium-binding adapter molecule 1 (Iba1), BDNF, PI3K, and p-ERK in the spinal cord were assayed and compared among the four groups.

2.2.2. Effect of PRF on DRG on the Neuropathic Pain and Levels of Microglia, BDNF, PI3K, and ERK in the Spinal Cord. Four groups were observed, including Sham, SNI, SNI + PRF, and SNI + free-PRF. All rats (except those in the Sham group) were subjected to SNI of the right sciatic nerve. On postoperative day 7, PRF was applied to the ipsilateral L_4-L_5 DRG in the SNI + PRF group, and SNI + free-PRF group was kept as a control. Pain behaviors and levels of Iba1, BDNF, PI3K, and p-ERK were measured.

The von Frey behavioral testing for paw withdrawal mechanical threshold (PWMT) and sting thermal imaging for paw withdrawal thermal latency (PWTL) were performed before the operation (D0), on 1st (D01), 3rd (D03), 5th (D05), and 7th (D07) postoperative days, and 1st (D1), 3rd (D3), 5th (D5), 7th (D7), 9th (D9), 11th (D11), and 14th (D14) days after PRF treatment or completion of intrathecal injection. The expression levels of Iba1, BDNF, PI3K, and p-ERK in the spinal cord were measured by western blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), and immunofluorescence on D14. Western blot, RT-PCR, and immunofluorescence were applied to five rats each.

2.3. Neuropathic Pain Model. PNI was performed according to the SNI model as described by Decosterd and Woolf [21]. Briefly, the rat's right common sciatic nerve at the trifurcation into the tibial, common peroneal, and sural nerves of the rats was exposed under anesthesia. The tibial and common peroneal nerves were transected, leaving the sural nerve intact. The procedures were performed in the same way without transecting the nerves in the Sham group. Then,

the muscles were massaged back into place, and the incision was closed. All operations were performed by the same researcher.

2.4. Intrathecal Catheters and Drug Administration. The rats received intrathecal catheter implantation before SNI. They were anesthetized with an intraperitoneal injection of 10% chloral hydrate (300 mg/kg). A PE-10 polyethylene catheter was implanted between the L_5 and L_6 vertebrae to reach the subarachnoid space of the spinal cord as described in a previous study [22]. The outer part of the catheter was plugged and fixed onto the skin upon wound closure. The rats showing neurological deficits after the catheter implantation were euthanized. Minocycline was dissolved in sterile 5% DMSO with 95% saline solution. The rats were intrathecally treated with minocycline (40 mg/kg, Sigma-Aldrich, St. Louis, MO, USA) or an equivalent volume of DMSO once daily for 7 days, 1 h before nerve transection. Drugs or vehicles were intrathecally injected through the implanted catheter in a 10 μl volume of solution followed by 10 μl of vehicle for flushing. Each injection lasted for at least 5 minutes. After injection, the needle was retained *in situ* for 2 minutes before being withdrawn.

2.5. PRF on DRG. The rats received PRF treatment on day 7 after SNI. They were anesthetized using an injection of 10% chloral hydrate (300 mg/kg). The right L_4-L_5 DRG was exposed in the SNI + free-PRF and SNI + PRF groups through laminectomy and facetectomy, without injury to the dura mater. An RF electrode (type 20 G, 5 cm long, 4 mm active tip) was placed adjacent to the corresponding DRG via direct visualization by using a radiofrequency device (Cosman Medical, Inc., Burlington, MA, USA) The motor stimulation test was used instead of the sensory stimulation test. PRF waves were applied after carrying out the motor stimulation test through muscle contraction of the lower extremities. Stimulation parameters of the PRF waves were set as follows: 2 bursts/s; duration = 20 ms; output voltage = 45 V; maximum temperature = 42°C; and the stimulated time = 6 min. After the PRF treatment, the RF probe was removed, and the muscles were closed. In the SNI + free-PRF group, the electrode was put in the same way without any stimuli.

2.6. Behavioral Testing. The rats were placed in a plastic chamber ($20 \times 25 \times 15\ cm^3$) and habituated for 15 min before the experiment. PWMT was evaluated using von Frey filaments (Stoelting, IL, USA) by the up-down method described in a previous study [23]. Each filament was applied perpendicularly to the ipsilateral territory, near the center of the vibrissal pad. Avoiding further contact with the filament, quickly turning head away, scratching the stimulated area, or attacking the filament was considered a positive response. An allodynic rat was defined as the one with 50% PWT <4.0 g (withdrawal in response to nonnoxious tactile stimulus).

PWTL was tested by measuring the withdrawal response of the hind paw to heat stimulation using the Plantar Test Apparatus (TaiMeng Science and Technology, Chengdu, China) as described by Hargreaves et al. [24]. The cutoff latency was 30 s to avoid thermal injury. The withdrawal latency at each time point was an average of three latencies separated by an interval of 5 min. The tests were conducted on the same days as the von Frey test, and both tests were conducted by the same researcher who was blind to the group allocation of the rats.

2.7. Western Blot Analysis. The spinal cord of the lumbar (L_4-L_5) ipsilateral quadrant to the lesion was collected, dissected, and homogenized in protein lysis buffer in the presence of protease inhibitors and incubated on ice for 10 min. The samples were centrifuged at 12,000 rpm for 15 min at 4°C. The total protein content was determined in the supernatants using the Bio-Rad DC Protein Assay Kit. Equal amounts of protein were resolved by 10% SDS-PAGE and transferred to PVDF membranes (Millipore, MA, USA). The membranes were blocked with 5% nonfat milk at room temperature and incubated overnight at 4°C with primary antibodies (rabbit anti-Iba1, ab178680, 1 : 1000, Abcam, USA; rabbit anti-BDNF, ab108319, 1 : 1000, Abcam, USA; rabbit anti-p-ERK, #4370, 1 : 1000, Cell Signaling Technology, USA; rabbit anti-PI3K, ab40776, 1 : 2000, Abcam, USA). Then, the membranes were incubated with a horse-radish peroxidase-conjugated secondary antibody (1 : 5000, Thermo Scientific, USA) at room temperature for 2 h. Finally, peroxidase activity was visualized using the ECL Western Blot Detection Kit (Beyotime, China). Western blots were quantitated using an image analysis system (Bio-Rad, USA). After normalization with β-actin, the data were presented as mean percentages of the ratio of total protein to their respective signal intensity levels found in the Sham group animals, indicated as 100%.

2.8. Real-Time RT-PCR. The total RNAs were extracted from the L_4-L_5 ipsilateral quadrant spinal cord using TRIzol and reverse transcribed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, CA, USA). The real-time PCR was performed using the Power SYBR Green Master Mix (Applied Biosystems) according to the manufacturer's protocols and analyzed by RT-PCR in a detection system (Applied Biosystems). The real-time PCR protocol was as follows: reverse transcriptase was activated and cDNA was synthesized (50°C for 5 min), PCR was activated (95°C for 3 min), 40 cycles of denaturation were performed (95°C for 30 s), and annealing and extension were done for 1 min at 60°C. At the end of PCR, a melting curve analysis was performed by slowly increasing the temperature from 60°C to 95°C. The data were analyzed using Software 2.2 using a cycle threshold (Ct) value as the readout and relatively normal levels of β-actin.

The primers used were as follows:

Iba1: 5′-GCAAGGATTTGCAGGGAGGA-3′ (forward), 5′-TGGGATCATCGAGGAAGTGC-3′ (reverse)

BDNF: 5′-AATAATGTCTGACCCCAGTGCC-3′ (forward), 5′-CTGAGGGAACCCGGTCTCAT-3′ (reverse)

PI3K: 5′-ATTTCCAGTGGGTGAGGCAG-3′ (forward), 5′-CTCATGGTAGCCGGTGACTC-3′ (reverse)

p-ERK: 5′-ATTATGTGCACCGGGACCTG-3′ (forward), 5′-TGTCATCCTGGAGGTAGCGA-3′ (reverse)

β-Actin: 5′-ACTCTGTGTGGATTGGTGGC-3′(forward), 5′-AGAAAGGGTGTAAAACGCAGC-3′(reverse)

2.9. Immunofluorescence Histochemistry. The rats were perfused with 200 mL of saline followed by 200 mL of 0.1 M phosphate buffer (pH 7.3) containing 4% paraformaldehyde. The L_4-L_5 spinal cord was removed, post-fixed in 4% paraformaldehyde for 24 h, and allowed to equilibrate in 30% sucrose in phosphate-buffered saline (PBS) overnight at 4°C. Transverse spinal sections (4–6 μm) were cut using a cryostat and collected in 0.01 M PBS, pH 7.3. After washing with PBS, the tissue was penetrated with 0.3% Triton X-100 and primary antibodies for rabbit anti-rat Iba1, BDNF, p-ERK, and PI3K (rabbit anti-Iba1, ab178680, 1 : 100, Abcam, USA; rabbit anti-BDNF, ab108319, 1 : 500, Abcam, USA; rabbit anti-p-ERK, #4370, 1 : 200, Cell Signaling Technology, USA; rabbit anti-PI3K, ab40776, 1 : 200, Abcam, USA). Next, the slides were covered with secondary antibodies containing 1 μM 4′-6-diamidino-2-phenylinedole (Sigma, USA). Some sections stained for BDNF, p-ERK, and PI3K were double labeled using cell-type-specific Abs for microglia (Iba1). The nuclei were stained with DAPI (5 μg/mL; Beyotime, USA). Fluorescence signal was detected using a fluorescence microscope (Olympus, Japan), images were captured, and signal co-localization was measured using MetaMorph (Molecular Devices, USA). The area fraction was quantified using Image J software (Rawak Software, Inc., Germany).

3. Statistical Analysis

All data were analyzed using SPSS 20.0 statistical software package (SPSS Inc., IL, USA) and presented as mean ± standard error of mean (SEM). All data were graphed using Prism 5.0 (GraphPad, CA, USA). After the data distribution was tested to be normal, behavioral data, western blot data, and enzyme-linked immunosorbent assay data were analyzed using a repeated-measures (multiple groups × time) analysis of variance (ANOVA). Multiple comparisons were performed using the Bonferroni post hoc test to determine the overall significance. When ANOVA showed a significant difference, pairwise comparisons between the means were tested using the post hoc Tukey method or Fisher's protected least significant difference (LSD) post hoc test. An alpha value of 0.05 was considered statistically significant.

4. Results

4.1. Inhibiting the Spinal Microglia Activation Produced a Significantly Neuropathic Pain Reduction in SNI Rats. Compared with baseline, the SNI group displayed long-lasting mechanical allodynia ($P < 0.01$; Figure 1(a)) and thermal hyperalgesia ($P < 0.01$; Figure 1(b)) in their ipsilateral paws, which reached a peak on the fifth day and maintained stable withdrawal thresholds until the end of observation. No significant changes were found in the contralateral hind paw in all the groups ($P > 0.05$; Figures 1(c) and 1(d)), similar to the ipsilateral paw in the Sham group ($P > 0.05$; Figures 1(a) and 1(b)). The mechanical allodynia and thermal hyperalgesia were not induced during intrathecal injection of minocycline. Although the withdrawal thresholds significantly decreased after completing injections in the SNI + M group compared with those in the Sham group ($P < 0.01$; Figures 1(a) and 1(b)), they were still higher than the values in the SNI and SNI + DMSO groups ($P < 0.01$; Figures 1(a) and 1(b)). No significant differences were found between the SNI and SNI + DMSO groups ($P > 0.05$; Figures 1(a) and 1(b)).

4.2. Suppression of Microglia Activation Contributes to a Remarkable Reduction of the Expression of Iba1, BDNF, PI3K, and p-ERK in the Spinal Cord. At a higher magnification, almost all BDNF, PI3K, and p-ERK immunofluorescence co-localized with the nuclear marker DAPI (Figures 2(a)–2(c)). The localization of BDNF, PI3K, and p-ERK in microglia was confirmed by triple labeling with BDNF/Iba1/DAPI, PI3K/Iba1/DAPI, and p-ERK/Iba1/DAPI (Figures 2(a)–2(c)). Western blot analysis (Figures 3(a)–3(d)), RT-PCR analysis (Figure 4), and immunofluorescence and histochemical analysis (Figures 5(a)–5(e)) in the spinal cord demonstrated that the levels of Iba1, BDNF, PI3K, and p-ERK were low in the Sham group and increased in the ipsilateral spinal cord in the SNI and SNI + DMSO groups ($P < 0.01$). They decreased in the SNI + M group compared with the SNI group but were still higher than those in the Sham group on D14 ($P < 0.01$).

4.3. PRF Treatment Results in a Significant Neuropathic Pain Reduction. Indeed, PNI induced long-lasting mechanical allodynia ($P < 0.01$; Figure 6(a)) and thermal hyperalgesia ($P < 0.01$; Figure 6(b)) since the first day after SNI, reached a peak on the fifth day, and maintained stable withdrawal thresholds until the end of observation compared with those in the Sham-operated rats. No significant changes were observed in the contralateral hind paw ($P > 0.05$; Figures 6(c) and 6(d)) throughout the duration of the study. Similar results were obtained on the ipsilateral side in the Sham group ($P > 0.05$; Figures 6(a) and 6(b)). In this study, PRF was applied on the L_4-L_5 DRG in rats with SNI for 6 min on the seventh day after nerve ligation; mechanical allodynia ($P < 0.01$; Figure 6(a)) and thermal hyperalgesia ($P < 0.01$; Figure 6(b)) were partially recovered in the SNI + PRF group from the first day after a single application of PRF and maintained throughout a period of 14 days, compared with those in the SNI and SNI + free-PRF groups, but could not return to pre-SNI baseline. In the SNI and SNI + free-PRF groups, the paw withdrawal threshold and paw withdrawal latency were maintained at a low level from postlesion 7–21 days.

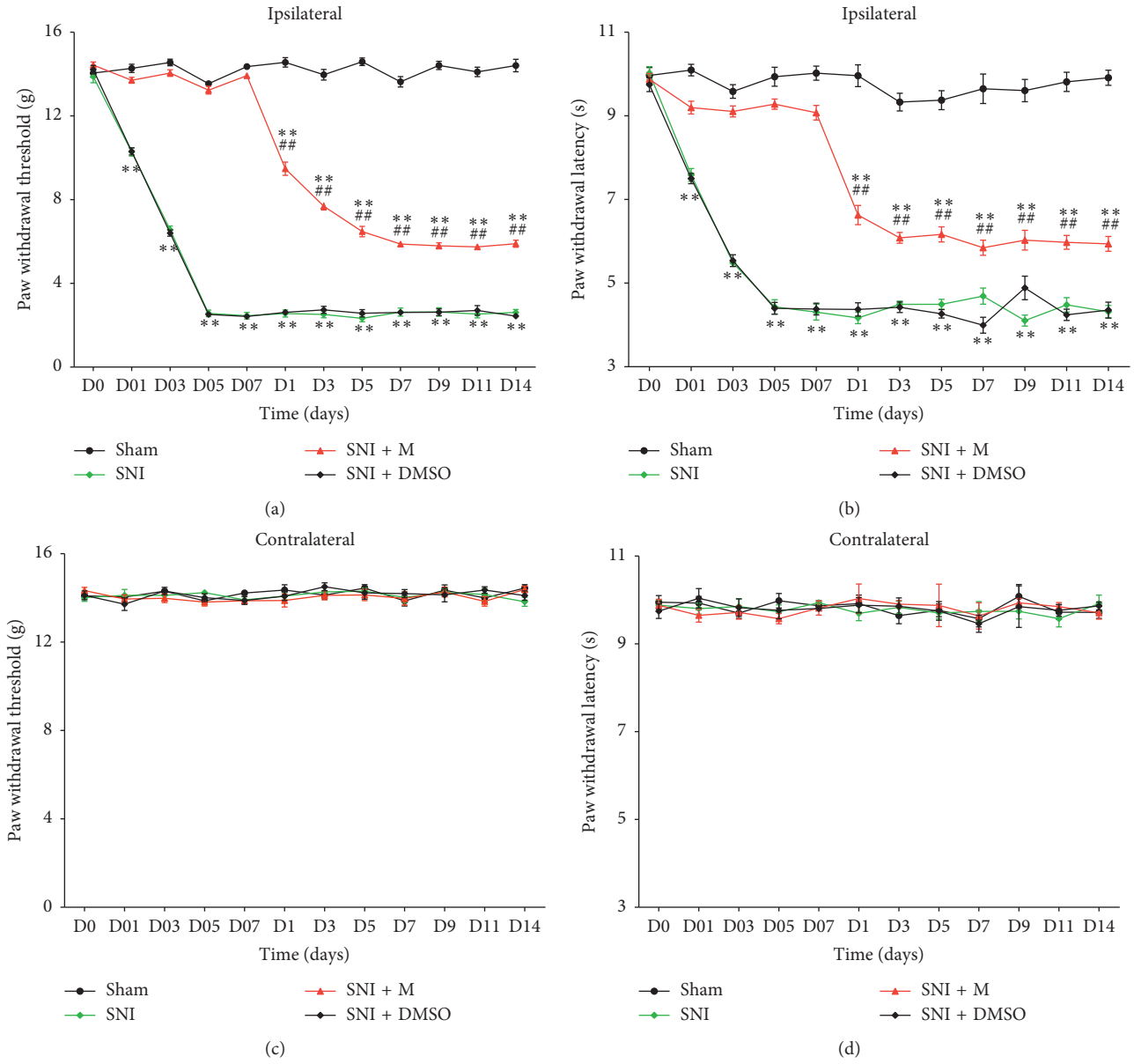


Figure 1: Therapeutic effects of minocycline on neuropathic pain in SNI rats. (a, b) Effects of minocycline (a specific inhibitor of microglial activation) on mechanical allodynia and thermal hyperalgesia. Reversal of SNI-induced allodynia by intrathecal administration of minocycline once a day for 7 days (1 h before nerve ligation) in the rats. All rats (except those in the Sham group) were subjected to SNI of the right sciatic nerve. The rats in the SNI + M and SNI + DMSO groups were intrathecally treated with minocycline and an equal volume of DMSO, respectively. Each symbol represents mean ± SEM; $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. Repeated-measures (multiple groups × time) ANOVA, $n = 15$ per group. (c, d) Changes in paw withdrawal threshold and paw withdrawal latency in contralateral hind paw of all groups.

4.4. PRF Treatment Reduced the Levels of Spinal Iba1, BDNF, PI3K, and p-ERK in SNI Rats. Western blot analysis (Figures 7(a)–7(d)), RT-PCR analysis (Figure 8), and immunofluorescent and histochemical analysis (Figures 5(a)–5(d), and 9) in the spinal cord showed that the expression levels of Iba1, BDNF, PI3K, and p-ERK in the SNI and SNI + free-PRF groups significantly increased compared with those in the Sham group after nerve injury ($P < 0.05$). The levels of Iba1, BDNF, PI3K, and p-ERK in the SNI + PRF group were downregulated significantly than those in the SNI and SNI + free-PRF groups ($P < 0.05$) but were still higher than those in the Sham group after a single application of PRF on D14 ($P < 0.05$).

5. Discussion

In the present study, SNI induced a long-lasting increase in microglia hyperactivity and BDNF, PI3K, and p-ERK upregulation in the spinal cord and resulted in pain sensitization. Minocycline, which was intrathecally injected in the early phase of pain generation, relieved mechanical allodynia and thermal hyperalgesia and reversed the

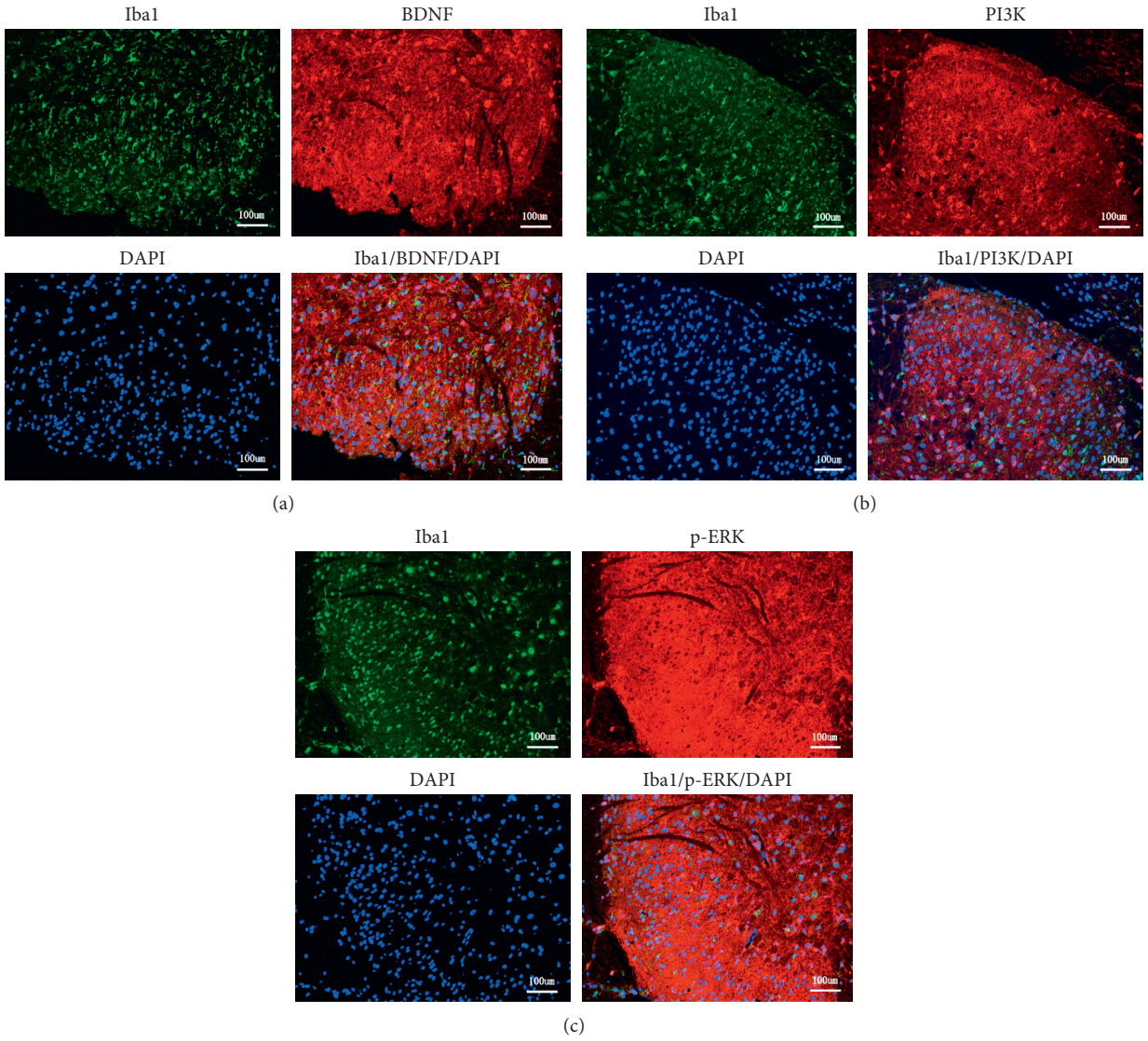


Figure 2: Three immunolabeling of Iba1/DAPI with BDNF (a), PI3K (b), and p-ERK (c). At a higher magnification, almost all BDNF, PI3K, and p-ERK immunofluorescence colocalized with the nuclear marker DAPI. The localization of BDNF, PI3K, and p-ERK in microglia was confirmed by triple labeling with BDNF/Iba1/DAPI, PI3K/Iba1/DAPI, and p-ERK/Iba1/DAPI. Scale bar: 100 μm.

upregulated levels of Iba1, BDNF, PI3K, and p-ERK in the spinal cord after injecting interruption. PRF was applied on the ipsilateral DRG of the rats on the seventh day after SNI, which also reversed mechanical allodynia and thermal hyperalgesia. The benefits of a single PRF application persisted for at least 2 weeks after treating interruption. Just like a specific microglia inhibitor, PRF reversed the microglial activation and expression of BDNF, PI3K, and p-ERK in the spinal cord as well.

5.1. Behavioral Changes Induced by the Therapy of PRF on DRG. Neuropathic pain is a kind of refractory pain. The conventional painkillers, such as opioids and nonsteroidal anti-inflammatory drugs afford poor efficacy and produce many side effects. Therefore, a good effective therapy for neuropathic pain is urgently required. PRF has been used to treat neuropathic pain and has shown satisfactory efficacy with minimal side effects. PRF electromagnetic pulse conveyed a signal to the target tissue with radiofrequency electrodes of 20 ms, 500 kHz radiofrequency electromagnetic energy, followed by 480 ms interval. The temperature of the tissue around the tip of the PRF does not exceed 42°C to avoid target tissue and nerve damage. DRG is the oval inflation of the dorsal root in the upper region of the intervertebral foramen, which contains the first-class neurons of sensory afferents. DRG has an important role in the process of peripheral sensitization. Nociceptive sensory neurons of DRG are activated by noxious stimuli in the periphery and transmit information to the CNS. The activation of immune and immune-like glial cells in the DRG and spinal cord leads to the release of both pro- and anti-inflammatory cytokines, which are involved in the spinal nociceptive transmission and central sensitization [25, 26].

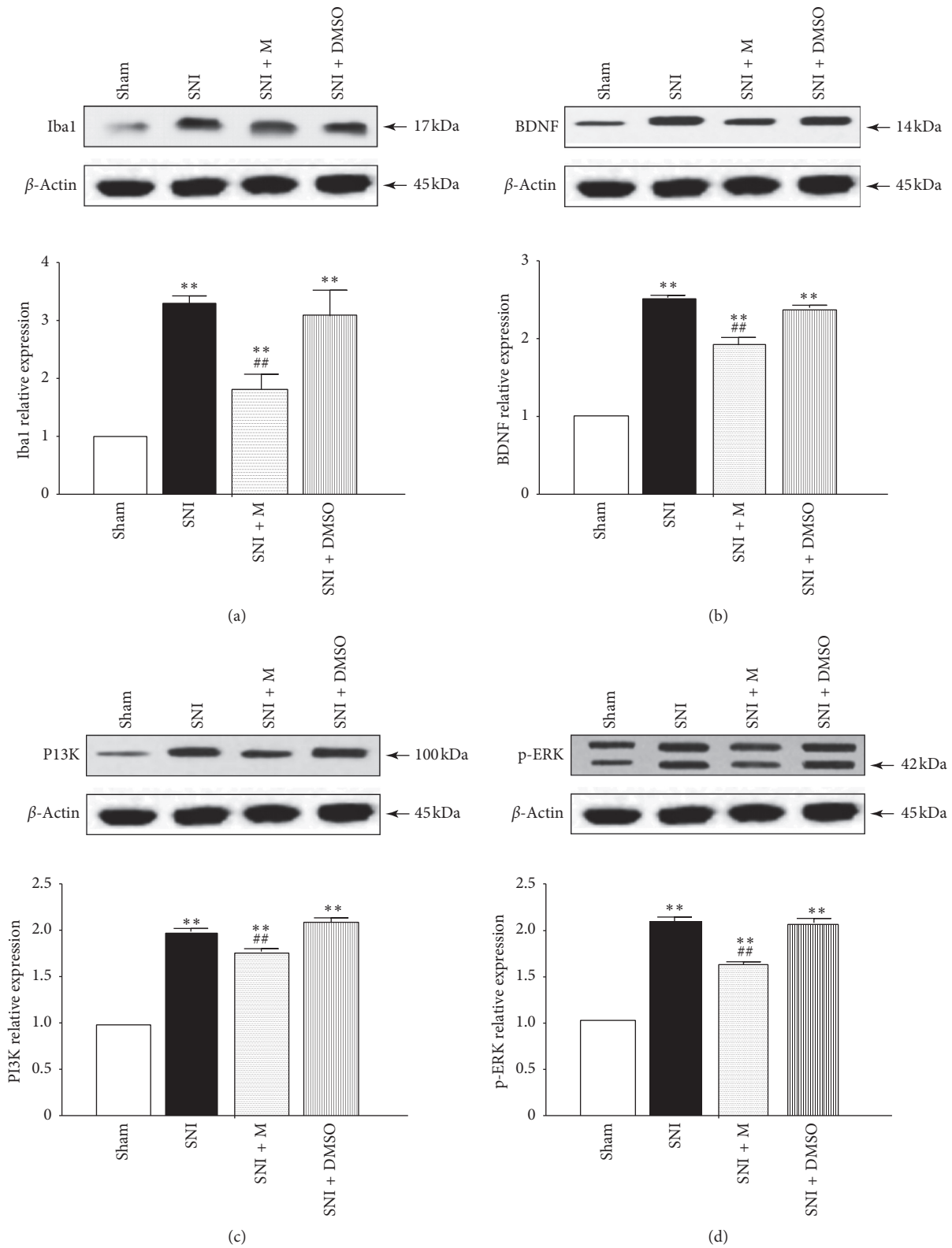


FIGURE 3: The western blot analysis of Iba1 (a), BDNF (b), PI3K (c), and p-ERK (d) proteins in the spinal cord of rats in different groups on D14. Values represented the relative ratio of Iba1, BDNF, PI3K, or p-ERK levels (normalized to β-actin) to that in the Sham rats. Each symbol represents mean ± SEM. In the Iba1 assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the BDNF assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the PI3K assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the p-ERK assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. LSD t test, $n = 5$ rats per assay.

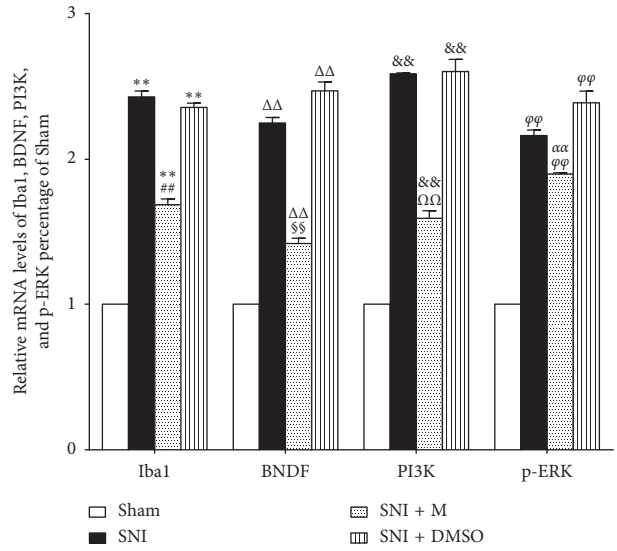


Figure 4: Real-time PCR analysis of Iba1, BDNF, PI3K, and p-ERK mRNA expression in the spinal cord in different groups on D14. Values represent the relative ratio of Iba1, BDNF, PI3K, and p-ERK mRNA (normalized to GAPDH mRNA) expression to that in the Sham rats. Each symbol represents mean ± SEM. In the Iba1 assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the BDNF assay, $^{\Delta\Delta}P < 0.01$ against the Sham group and $^{\S\S}P < 0.01$ against the SNI group. In the PI3K assay, $^{\&\&}P < 0.01$ against the Sham group and $^{\Omega\Omega}P < 0.01$ against the SNI group. In the p-ERK assay, $^{\varphi\varphi}P < 0.01$ against the Sham group and $^{\alpha\alpha}P < 0.01$ against the SNI group. LSD t test, $n = 5$ rats per assay.

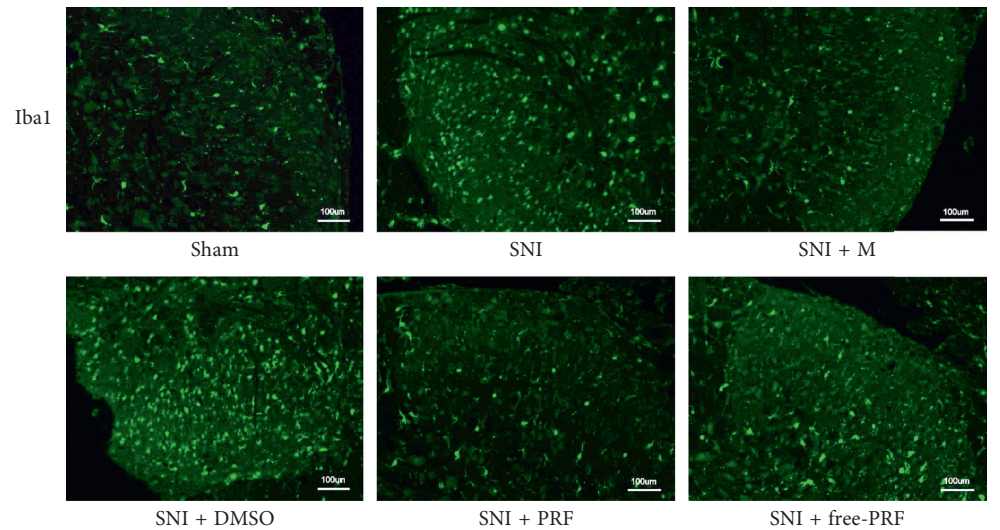
Because of its active role in the modulation of sensory processing and its anatomic accessibility to clinical intervention, DRG has become an excellent clinical target for pain treatment.

The therapy of PRF on DRG has been demonstrated to improve pain effectively. For example, Arai reported that the PRF on DRG provided pain relief for patients with intractable vertebral metastatic pain [27]. Van Boxem et al. achieved a similar efficacy in chronic intractable lumbosacral radicular pain with PRF therapy on DRG [28]. Here, PRF was applied on DRG to treat neuropathic pain induced by SNI. As neuropathic pain developed significantly and reached the peak point on day 7 after SNI [29], day 7 was appointed as the PRF treatment time in the present study.

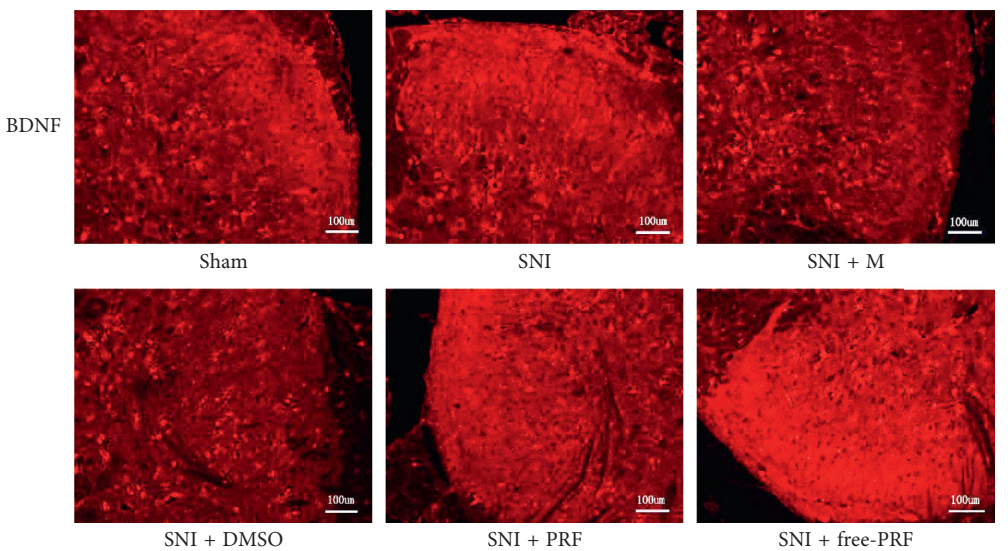
Various experimental neuropathic pain models have also been shown a pain-relieving effect of PRF on mechanical hypersensitivity and sometimes on thermal allodynia. The effect of PRF on chronic pain was still very discrepant, likely because of differences in therapy protocols, various exposure time, duration of pain, stimulation site of PRF, pain model, and species used. Treatment with 5 min PRF stimulation on L_5 DRG in the unilateral L_5 spinal nerve ligation (SNL) model of rats significantly reduced mechanical hypersensitivity and heat analgesia [30]. In the CFA-induced peripheral inflammatory pain, PRF to the L_4 anterior primary ramus just close to DRG significantly increased PWMT and PWTL, but PRF to the sciatic nerve in the midthigh just increased PWTL [31, 32]. However, these studies focused on the prophylactic effect of PRF rather than on its therapeutic application for an established chronic pain syndrome. They showed that PRF relieved, even reversed, mechanical hypersensitivity and some thermal allodynia. However, the pain-relief effect was seen on mechanical hypersensitivity only when PRF was applied to established chronic pain [10, 33]. An important finding in the study by Tanaka et al. [34] was that increased exposure time of 2–6 min to PRF current showed a significant antiallodynic effect without motor impairment. Therefore, this study applied PRF current for 6 min to the L_4-L_5 DRG in rats with SNI on the seventh day after nerve ligation. PWMT and PWTL were significantly increased following PRF on DRG therapy on day 7 after SNI until day 21. These results were consistent with clinical observations and the findings of Liu et al. [35], further indicating that PRF on DRG was a beneficial treatment for neuropathic pain. A significant finding in this study was that thermal hyperalgesia was also restrained when PRF was applied for established chronic pain. We also observed that nerve injury-induced mechanical allodynia and thermal hyperalgesia could be reversed for long-lasting relief by a single PRF on DRG even after PRF cessation, and they could not return to pre-SNI baseline. The exact mechanisms underlying the analgesic effect of PRF on neuropathic pain deserve further study.

5.2. Mechanisms Underlying the Analgesic Effect of PRF

5.2.1. Decreased Microglia Activation. Increasing evidence demonstrates the pivotal role of spinal microglia in neuropathic pain [36, 37]. Following varied types of insults in the nervous system, including PNI, microglial cells were the first to become activated and remained so for several weeks. Microglia transformed to reactive phenotype via displaying a progressive series of cellular and molecular changes, including morphological hypertrophy, rapid proliferation, upregulated expression of various genes, and increased



(a)



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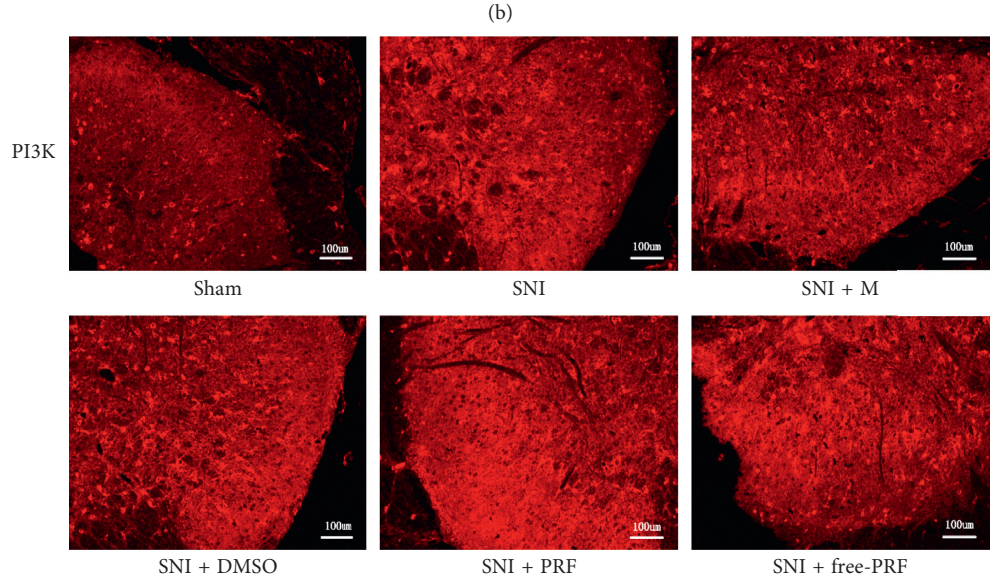

(c)

Figure 5: Continued.

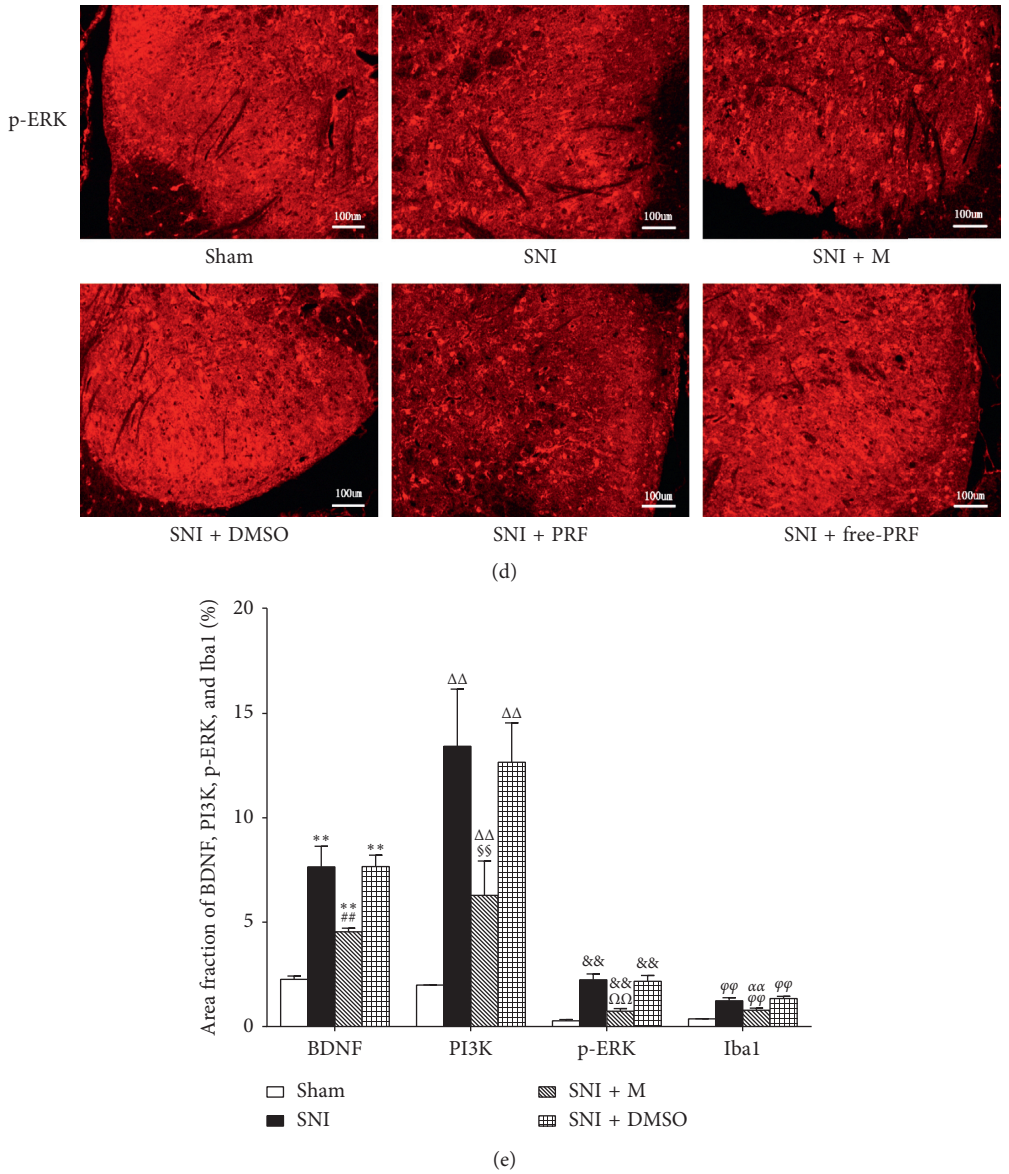

Figure 5: Expression of Iba1 (a), BDNF (b), PI3K (c), and p-ERK (d) in the spinal cord of rats in different groups (immunofluorescence, ×100), scale bar = 100 μm. (e) The intensity of Iba1, BDNF, PI3K, and p-ERK immunofluorescence in the spinal cord in different groups on D14. Each symbol represents mean ± SEM. In the BDNF assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the PI3K assay, $^{\Delta\Delta}P < 0.01$ against the Sham group and $^{\S\S}P < 0.01$ against the SNI group. In the p-ERK assay, $^{\&\&}P < 0.01$ against the Sham group and $^{\Omega\Omega}P < 0.01$ against the SNI group. In the Iba1 assay, $^{\varphi\varphi}P < 0.01$ against the Sham group and $^{\alpha\alpha}P < 0.01$ against the SNI group. LSD t test, $n = 5$ rats per assay.

expression of microglia characteristic markers, such as ionized calcium-binding adapter molecule 1 (Iba1). Then, inflammatory cytokines were released by microglia and contributed to the development of pain hypersensitization and long-persisting pain [38]. Inhibitors of microglia by intrathecal administration have shown great analgesic efficacy in pain models [39, 40], but it was limited to reduce the established late-phase pain [41]. In this study, minocycline was intrathecally injected to rats with SNI at early stages. The pain was completely inhibited by minocycline during the period of drug administration. However, the withdrawal thresholds decreased slightly after treatment interruption, and the analgesic effect persisted for 21 days. Moreover, the spinal microglia level was restrained. Our finding also indicated that microglia inhibition as early as possible could gain more long-lasting pain relief.

The therapy of PRF on DRG could induce the changes in the cell morphology. Ultrastructural changes in the axons, including abnormal membranes and morphology of mitochondria, and the disruption and disorganization of microfilaments and microtubules were observed in C- and Aδ-fibers on electron microscopy [42]. Recently, it was reported that the analgesic effect of PRF might derive from long-term modulation of cell functions by changing gene expression.

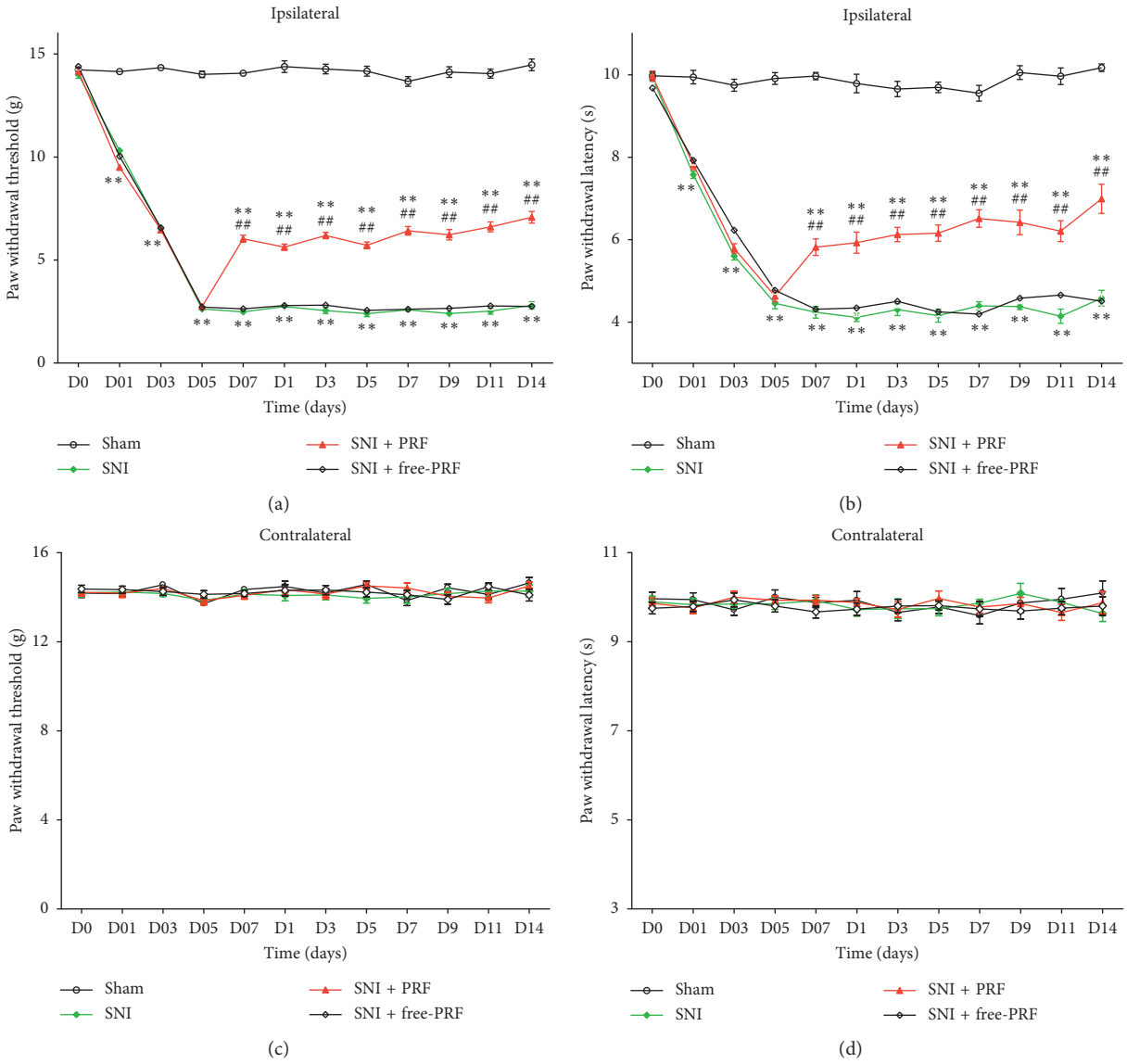

FIGURE 6: Therapeutic effects of PRF on DRG on neuropathic pain. (a, b) Effects of PRF on mechanical allodynia and thermal hyperalgesia applied to L_4-L_5 DRG. The paw withdrawal threshold in response to mechanical hypersensitivity (a) and paw withdrawal latency in response to thermal hyperalgesia (b) partially recovered from the first day after a single application of PRF and maintained throughout a period of 14 days. On postoperative day 7, PRF was applied to the ipsilateral L_4-L_5 DRG in the SNI + PRF group, and SNI + free-PRF group was kept as control. Each symbol represents mean ± SEM; $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. Repeated-measures (multiple groups × time) ANOVA, $n = 15$ per group. (c, d) Changes in paw withdrawal threshold and paw withdrawal latency in contralateral hind paw of all groups.

The expression of pain regulatory genes such as a proinflammatory gene returned to baseline values. Numerous reports suggested that microglia in the spinal dorsal horn were vital in pain facilitation. PRF applied on DRG in a rat model of neuropathic pain revealed that the established mechanical hypersensitivity reduced, and the activation of microglia in spinal dorsal horn was significantly attenuated [10, 11]. The findings of this study were consistent with those of previous studies. Mechanical allodynia and thermal hyperalgesia were reversed, accompanied by a significantly downregulated the expression of Iba1 which was maintained for 14 days after a single application of PRF. This demonstrated that PRF might have suppressed the activation of microglia and contributed to the nociceptive relief.

5.2.2. Reversing the Increase of Microglial BDNF, PI3K, and p-ERK in the Spinal Cord of Rats with SNI. Some studies have shown that neurotrophins, especially BDNF, play an important role as pain mediators/modulators [43, 44]. BDNF is a secreted protein and part of the family of neurotrophin family. Neutrophins act on neurons to promote the survival, growth, and differentiation of new neurons and synapses. However, it has a deleterious effect on the spinal

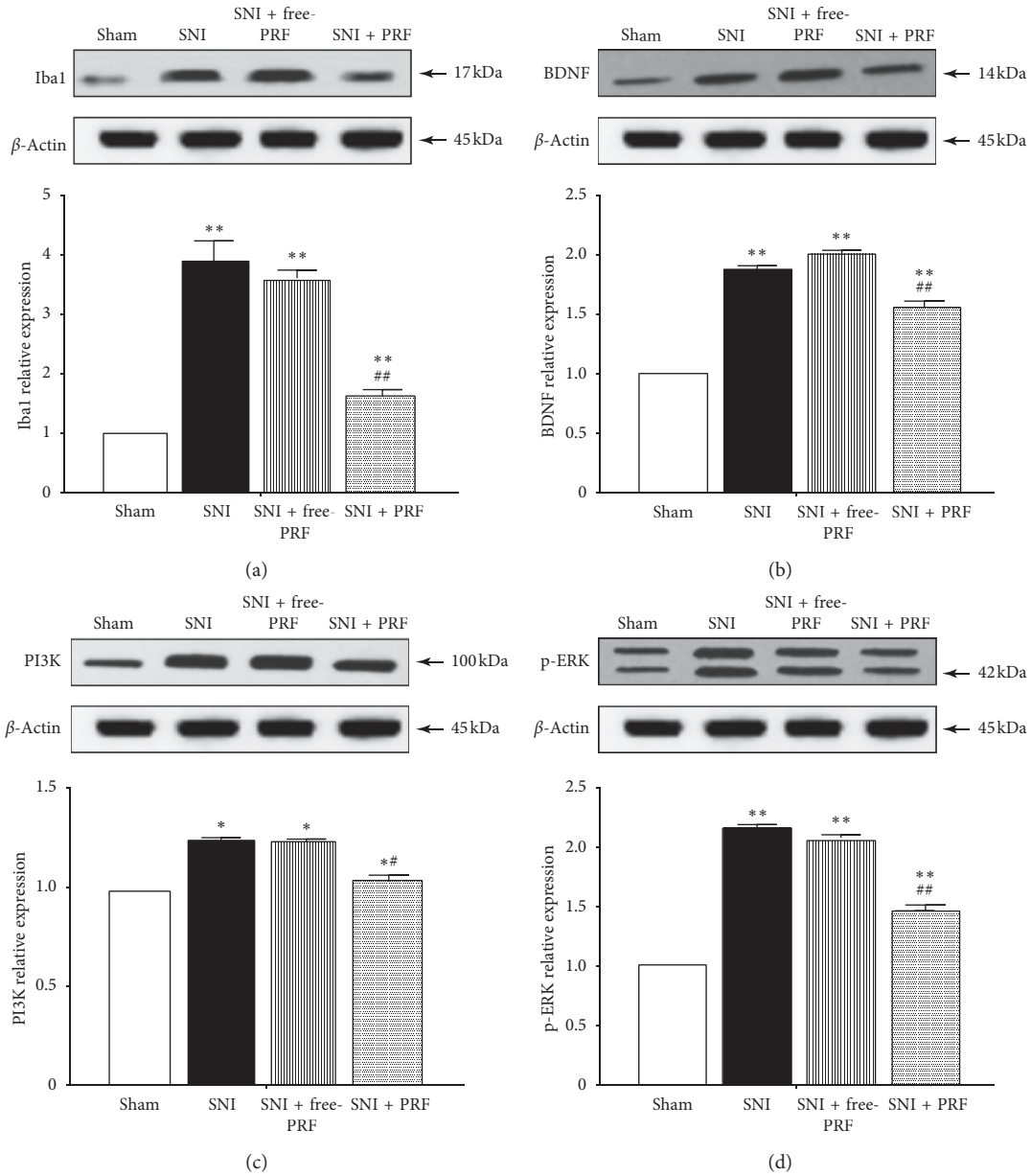

FIGURE 7: (a–d) The western blot analysis of Iba1, BDNF, PI3K, and p-ERK proteins in the spinal cord of rats in different groups on D14. Values represent the relative ratio of Iba1, BDNF, PI3K, and p-ERK levels (normalized to β-actin) to that in the Sham rats. Each symbol represents mean ± SEM. In the Iba1 assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the BDNF assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the PI3K assay, $^{*}P < 0.05$ against the Sham group and $^{\#}P < 0.05$ against the SNI group. In the p-ERK assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. LSD t test, $n = 5$ rats per assay.

cord following nerve injury. Trang found that P2X4 receptor on the activated microglial surface promoted the synthesis and release of BDNF, which in turn accelerated central sensitization and maintained neuropathic pain [45]. Microglia-derived BDNF is a critical microglia-neuron signaling molecule that gates aberrant nociceptive processing in the spinal cord. The enhanced BDNF, which elicited nociceptive hypersensitivity, also contributed to the activation of microglia in the spinal cord in a feedforward manner, and the functional inhibition of BDNF signal reversed allodynia in rats with SNI. The upregulated expression of BDNF was detected in the spinal cord on day 21 after SNI in the present study, consistent with the previous reports, and further indicated that BDNF was highly involved in neuropathic pain.

PI3K, a lipid kinase that phosphorylates the D_3 position of phosphatidylinositol lipids to produce PI(3,4,5)P_3, acts as a membrane-embedded second messenger. Some progress has been made about the role of PI3K in the refractory pain. Plantar incision induced a time-dependent activation of PI3K in the microglia, and the inhibition of PI3K prevented pain behaviors induced by plantar incision [46]. Specific inhibitors of PI3K applied before SNI reduced the neuropathic pain behaviors induced by L5 SNL [47]. The PI3K

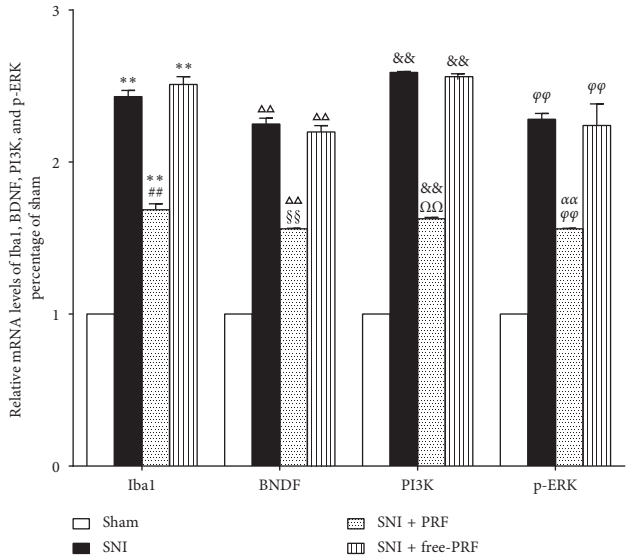

Figure 8: Real-time PCR analysis of Iba1, BDNF, PI3K, and p-ERK mRNA in the spinal cord in different groups on D14. Values represent the relative ratio of Iba1, BDNF, PI3K, and p-ERK mRNA (normalized to GAPDH mRNA) to that in the Sham rats. Each symbol represents mean ± SEM. In the Iba1 assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the BDNF assay, $^{\Delta\Delta}P < 0.01$ against the Sham group and $^{\S\S}P < 0.01$ against the SNI group. In the PI3K assay, $^{\&\&}P < 0.01$ against the Sham group and $^{\Omega\Omega}P < 0.01$ against the SNI group. In the p-ERK assay, $^{\varphi\varphi}P < 0.01$ against the Sham group and $^{\alpha\alpha}P < 0.01$ against the SNI group. LSD t test, $n = 5$ rats per assay.

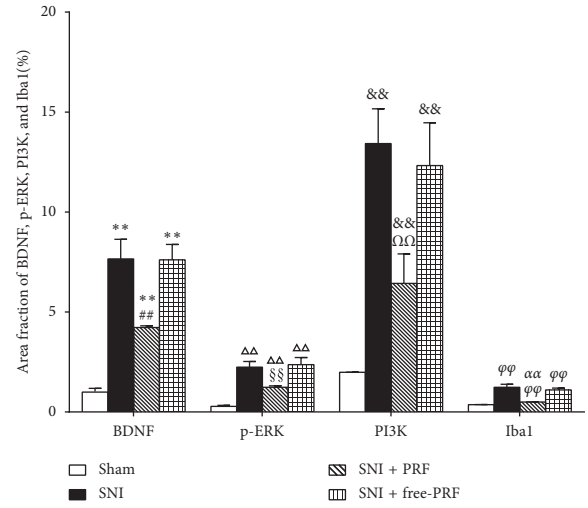

Figure 9: The intensity of Iba1, BDNF, PI3K, and p-ERK immunofluorescence in the spinal cord in different groups on D14. Each symbol represents mean ± SEM. In the BDNF assay, $^{**}P < 0.01$ against the Sham group and $^{\#\#}P < 0.01$ against the SNI group. In the p-ERK assay, $^{\Delta\Delta}P < 0.01$ against the Sham group and $^{\S\S}P < 0.01$ against the SNI group. In the PI3K assay, $^{\&\&}P < 0.01$ against the Sham group and $^{\Omega\Omega}P < 0.01$ against the SNI group. In the Iba1 assay, $^{\varphi\varphi}P < 0.01$ against the Sham group and $^{\alpha\alpha}P < 0.01$ against the SNI group. LSD t test, $n = 5$ rats per assay.

signaling pathway was expressed in microglia and participated in bone cancer pain [48]. The treatment of bone cancer pain model in rats with PI3Kcb-specific small-interfering RNA resulted in the inhibition of pain-related behavior [49]. The expression of PI3K was assayed in the spinal cord on day 21 after SNI in the present study. PI3K was found to be significantly increased on day 21 after SNI. Therefore, the present results implied that PI3K also played an important role in neuropathic pain.

ERK, a member of the mitogen-activated protein kinase family, could transmit a great quantity of extracellular information into intracellular responses. The ERK signaling pathway in the microglia has been reported to modulate various types of pain, and the inhibition of p-ERK could alleviate the associated pain [50, 51]. The level of p-ERK in the spinal cord was found to be significantly upregulated on day 21 after SNI in the present study. These results were consistent with other reports [52] and suggested that activated ERK contributed to the development of neuropathic pain.

The microglia, BDNF, PI3K, and p-ERK were confirmed to be involved in developing neuropathic pain in present study. However, whether the release of BDNF, PI3K, and p-ERK in the spinal cord in rats with SNI to regulate chronic pain processing is through microglia-dependent mechanism remains undetermined. In order to clarify this question, firstly, we adopted the method of triple labeling with BDNF/Iba1/DAPI, PI3K/Iba1/DAPI and p-ERK/Iba1/DAPI to prove that the localization of BDNF, PI3K, and p-ERK is in microglia. Secondly, minocycline (as microglia inhibitor) was intrathecally injected into rats with SNI at early stages; the increased levels of Iba1, BDNF, PI3K, and p-ERK in the spinal cord were all restrained. Hence, these findings indicated that BDNF, PI3K, and p-ERK might have been released in the spinal cord in a microglia-dependent manner.

Although the analgesic efficacy of PRF on DRG for neuropathic pain was exact, the mechanisms were not fully understood. The effects of PRF might, via electromagnetic fields, disrupt or somehow modulate pain signal transmission and gene expression in the treated sites and CNS. The suppression of Iba1, BDNF, PI3K, and p-ERK in the spinal cord was important in alleviating neuropathic pain in rats with SNI in the present study, and the release of BDNF, PI3K, and p-ERK in the spinal cord might have occurred in a microglia-dependent manner. Since the therapy of PRF on DRG in rats with neuropathic pain could induce pain relief by reducing microglial activation, we deduced that PRF might regulate the release of BDNF, PI3K, and p-ERK in the spinal cord to relieve neuropathic pain. Just as we assumed, the increased expression of BDNF, PI3K, and p-ERK on day 21 was simultaneously downregulated for 6 min PRF therapy after SNI. So, these results revealed that PRF therapy on DRG might attenuate neuropathic pain by reducing the release of BDNF, PI3K, and p-ERK in the spinal cord in microglia-dependent way.

6. Limitations

This study had some limitations. Firstly, only the short-term effectiveness of PRF on DRG was explored. Secondly, *in vivo* field potential recording in PRF-treated rats was absent.

Thirdly, only one time point was selected to assay the levels of Iba1, BDNF, PI3K, and p-ERK. Fourthly, the relationship among BDNF, PI3K, and p-ERK was not investigated. More detailed research about PRF on the DRG to ease the neuropathic pain is needed.

7. Conclusions

The application of PRF on DRG could reverse SNI-induced neuropathic pain after the treatment period. The mechanisms underlying this treatment might be suppressed microglia and downregulated levels of BDNF, PI3K, and p-ERK in the spinal cord in microglia-dependent way. It supported PRF treatment as a valuable intervention for chronic neuropathic pain.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors would like to acknowledge the financial support from the provincial health system. This study was supported by the Project of Medical Innovation of Fujian Province (2016-CX-3 and 2018-CX-6).

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Hindawi
Pain Research and Management
Volume 2019, Article ID 9617280, 6 pages
https://doi.org/10.1155/2019/9617280

Review Article

The Chinese Association for the Study of Pain (CASP): Expert Consensus on the Cervicogenic Headache

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Received 18 September 2018; Revised 15 January 2019; Accepted 24 February 2019; Published 1 April 2019

Academic Editor: Fabio Antonaci

Cervicogenic headache is a relatively common but unique form of headache, and in China, as well as in several other countries, both diagnosis and a clear evidence-based treatment plan remain controversial. Therefore, the Chinese Association for the Study of Pain organized a meeting of pain management experts and created an expert consensus on the diagnosis and treatment of cervicogenic headache in China. This article summarizes the conclusions of the consensus group regarding the epidemiology, etiology, clinical features, diagnosis, differential diagnosis, treatment, and rehabilitation of cervicogenic headache in China.

1. Introduction

Although cervicogenic headache (CEH) is a common clinical challenge [1–3], controversies still exist regarding its diagnosis and treatment. Therefore, the Chinese Association for the Study of Pain organized a meeting of pain management experts from China to reach consensus on issues surrounding its diagnosis, treatment, and rehabilitation. The group comprised neurologists, orthopedists, and headache specialists. This article reflects the resulting expert consensus on the diagnosis and treatment of CEH in China. Suggestions are also proposed for consideration by headache specialists from other countries.

2. Definition

In 2013, the International Headache Society proposed the most recent definition for CEH [2]. According to this, CEH is defined as any headache caused by a disorder of the cervical spine or its components, such as bone, disc, and/or soft tissue elements, usually, but not invariably, accompanied by neck pain.

3. Diagnostic Criteria

CEH is typically diagnosed based on a detailed history, physical examination, and comprehensive evaluation of the nervous system. Disappearance of headache following a diagnostic block test supports a cervical source of the pain. The diagnostic criteria recommended by the International Classification of Headache Disorders (ICHD) 3rd edition [3] are as follows:

(a) Any headache fulfilling criterion (c)

(b) Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck that can cause headache

(c) Evidence of causation demonstrated by at least two of the following findings:

(1) Headache has developed in temporal relation to the onset of cervical disorder or appearance of the lesion

(2) Headache has significantly improved or resolved along with improvement in or resolution of cervical disorder or lesion

(3) Cervical range of motion is reduced, and headache is significantly aggravated by provocative maneuvers

(4) Headache disappears after diagnostic block to the suspected cervical spine structure or its supply nerve

(d) Not better accounted for by another ICHD-3 diagnosis

4. Epidemiology

The prevalence of CEH varies in the general population depending on the diagnostic criteria used. However, it has been estimated that 1.0%–4.1% of the population experience CEH [4–6]. Data have revealed that it even ranged to 17.5% in patients with severe headache [7]. Better-controlled and larger-scale epidemiological studies are needed to clarify the true prevalence of CEH.

5. Etiology

5.1. Anatomy. Recent studies have indicated that head and face pain in CEH originate from disorders of the upper cervical nerves (C1–C3) [8]. Indeed, lesions in the atlantooccipital joint, atlantoaxial joint, C2-C3 zygapophyseal joint, and intervertebral disk can all cause occipital pain [9–11]. In contrast, there is no evidence that regions innervated by the lower cervical nerves directly induce headache. Thus, the spinal nerves and branches from C1–C3 are thought to be the main anatomical bases of CEH.

The C1 spinal nerve (suboccipital nerve) innervates the atlantooccipital joint. Pathological change in or damage to this joint may cause pain to be referred in the occipital region. The C2 spinal nerve innervates the atlantoaxial and C2-C3 zygapophyseal joints and is adjacent to the lateral portion of the articular capsule of the C1-C2 zygapophyseal joint (atlantoaxial joint). Pathological changes or injures in these joints or the surrounding tissues can lead to referred pain in the head. The third occipital nerve (C3 medial branch) approaches and dominates the C2-C3 zygapophyseal joint, from where pain can radiate to the occipital, frontal, temporal, and periorbital regions (third occipital neuropathic headache) of the head.

Although the pain resulting from each pathology is not always consistent among patients, the distribution range of pain is typically similar. Neck pain originating near the cranium can radiate to the head, including the frontal and periorbital regions. Conversely, neck pain originating from the pars caudalis of the upper three cervical spines always causes pain in the occipital region. Moreover, a study showed that impairment of the C2-C3 zygapophyseal joint causes CEH in 70% of patients [12], of whom 27% can be diagnosed with third occipital neuropathic headache. Deterioration of the C3-C4 zygapophyseal joints, upper cervical intervertebral discs, and lower cervical zygapophyseal joints are less common causes of CEH.

5.2. Pathophysiology. The pathophysiology of CEH is poorly understood, but it is thought to be a referred pain originating from pathological changes in the upper cervical zygapophyseal joints. As shown in Figure 1 [1], anatomical convergence of pain fibers from the trigeminal nerve (including the ophthalmic division) and the upper three cervical nerves forms the basis for pain to be referred from the upper cervical region to the head, including radiation to the frontal and periorbital regions [13, 14]. The trigeminocervical nucleus receives not only the C1–C3 afferents but also the first branch of the trigeminal sensory afferents, indicating that it receives second-order neuron afferents from the trigeminal and upper three cervical spinal nerves. Therefore, pathological changes in the cervical zygapophyseal joints can generate pain in the areas innervated by either the trigeminal nerve (e.g., frontal and periorbital regions) or the upper three cervical spinal nerves (e.g., occipital and ear regions). Convergence between the trigeminal sensory descending tracts and the upper cervical nerve roots can also cause referred pain in the neck, face, and head.

6. Clinical Features

6.1. Symptoms

(1) CEH is a chronic unilateral headache; it is also a side-locked headache [15].

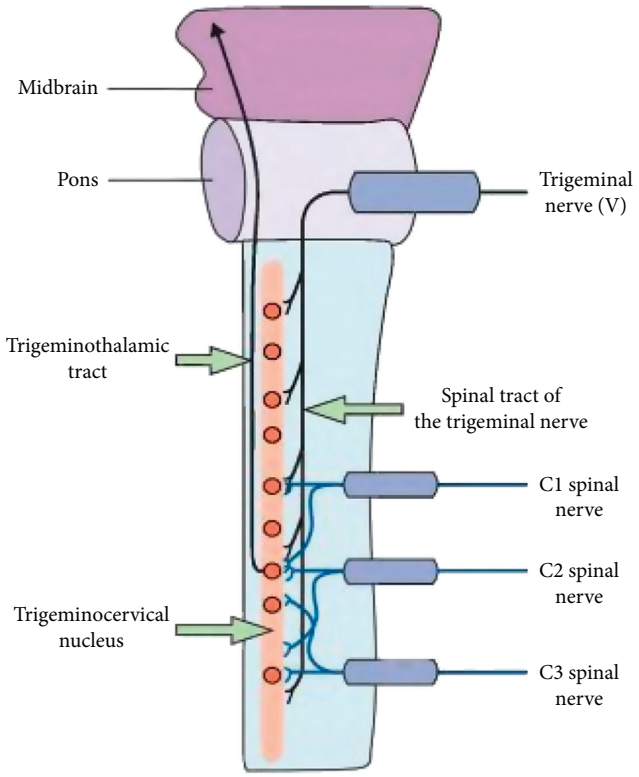

Figure 1: Mechanism of pain referral from the cervical spine to the head.

(2) Pain is first noted in the neck or occipital region before it radiates to the ipsilateral frontotemporal and orbital regions. Temporal regions are the most commonly affected.

(3) CEH is usually a deep, blunt, distending, and tense pain without pulsation. The frontotemporal region is the most painful, and the headache is aggravated by neck movements, fatigue, or an unhealthy neck position and relieved by rest.

(4) Headache may intermittently occur and last for hours or days, but during the late stages, it can cause persistent pain.

(5) Stiffness and a restricted range of motion in the neck may occur and be accompanied by ipsilateral shoulder or arm pain.

(6) Most patients also have concomitant symptoms of nausea, tinnitus, dizziness, phonophobia, photophobia, blurred vision, or disordered sleep.

6.2. Physical Examination. Patients with CEH are more likely to have myofascial trigger points on the transverse processes of the second cervical vertebra that can spread to the head and splenius capitis, trapezius, sternocleidomastoid, and suboccipital muscles [16]. Tenderness is observed in the occiput, paravertebral muscles, mastoid process, unilateral or bilateral outlets of the greater occipital nerve, and transverse process of the third cervical vertebra [17]. Patients often present with a limited range of motion of the cervical spine. There is no tenderness of the head and face.

6.3. Investigations. Magnetic resonance imaging (MRI) may show cervical disc degeneration, herniation, or bulging, mostly in the discs of C2–C5. Radiographs may show degenerative changes in the atlantoaxial, zygapophyseal, and uncovertebral joints [18]. However, radiography, MRI, and computed tomography (CT) are typically of limited value in the diagnosis of CEH.

7. Differential Diagnosis

7.1. Primary Headache. Primary headaches can be identified by their typical clinical manifestations [19].

(1) Tension-type headache has the following characteristics: (1) bilateral; (2) pressing or tightening (nonpulsating) pain; (3) paroxysmal pain; (4) not aggravated by routine physical activity; (6) no nausea or vomiting; (7) can be aggravated by compression of the frontal, temporal, masseter, pterygoid, sternocleidomastoid, splenius, and trapezius muscles.

(2) Migraine has the following characteristics: (1) unilateral, (2) pulsating pain, (3) headache lasting 4–72 h, (4) aggravation by routine physical activity (e.g., walking or climbing stairs), (5) accompanied by nausea/vomiting/photophobia/phonophobia, (6) ipsilateral premonitory visual symptoms (e.g., flashing, darkness, lines, or blindness), or sensory symptoms (e.g., numbness) lasting >5 min, (7) ergotamine or triptans can be effective, and (8) alleviated by pregnancy.

7.2. Secondary Headaches

(1) Posttraumatic headache can be diagnosed based on its clinical manifestation and MRI and CT findings.

(2) Vascular headache, including poststroke, hemangioma, and hypertensive headaches, can be diagnosed based on its clinical manifestation and MRI (including angiography) and CT (including CT or digital subtraction angiography) findings.

(3) Headache caused by high or low intracranial pressure. High intracranial pressure is usually caused by tumor or inflammation, which can result in a persistent, nonpulsatile, and severe headache with papilledema and emesis. Low intracranial pressure is usually caused by lumbar puncture, which can be relieved after lying down and aggravated by sitting in an upright posture.

(4) Referred headache from skull structures, such as eyes, ears, sinuses, and teeth (e.g., glaucoma, sinusitis, and periodontitis). Specialist examination can aid in the diagnosis, such as intraocular pressure determination, sinus CT, and dental examination.

(5) Somatoform disorders should also be considered. Physical and auxiliary examinations are normal in these patients. Repeated and changing physical symptoms are presented, and pain areas are not fixed. The patient may also have anxiety and depression.

8. Treatment

8.1. Pharmacotherapy. Despite a lack of convincing clinical studies on effective medications for CEH, pharmacotherapy remains among the best available treatments [20, 21]. Several types of medications are commonly used [22, 23]:

(1) Nonsteroidal anti-inflammatory drugs (NSAIDs) can be effective, including nonselective COX and selective COX-2 inhibitors.

(2) Muscle relaxants, particularly tizanidine, baclofen, and eperisone hydrochloride, that have central mechanisms of action can also provide analgesic effects in both the acute phase and for prevention. Tizanidine can be combined with NSAIDs because of its gastroprotective effect and good safety.

(3) Antiepileptic drugs and antidepressants can be used in patients with neuropathic pain. Common drugs for this purpose include gabapentin, pregabalin, amitriptyline, venlafaxine, and duloxetine.

8.2. Injection to the Atlantoaxial and C2-C3 Zygapophyseal Joints and Nerve Block. Individualized injection therapy can be selected according to the pain's location and characteristics. These procedures are associated with risks of structural damage from needle placement but can also result in the injection of local anesthetic into the vertebral artery, high-level epidural anesthesia, total spinal cord anesthesia, or injury of the spinal cord and nerve roots. Nonparticulate, water-soluble steroid hormones are recommended to prevent the embolism of steroid hormone particles.

8.2.1. Joint Injection

(1) Atlantoaxial Joint Injection. This can benefit patients with suboccipital or occipital pain aggravated by cervical rotation [24] or pain due to inflammatory stimuli [25]. Intraarticular injection can use a lateral or posterior approach and should be slow, with the volume not exceeding 1 ml. One study has shown that injection to the atlantoaxial joint was effective in 81.2% of cases. After 3 months' follow-up, 20% of patients had pain relief exceeding 50% [26].

(2) C2-C3 Zygapophyseal Joint Injection. This injection can be considered for patients with upper neck pain spreading to the occipital region or pain that increases when the neck is rotated or back is stretched. During the procedure, the head can be rotated for a better field of vision. Again, the injection should be slow and should not exceed a total volume of 1 ml. However, the therapeutic efficacy of C2-C3 intra-articular injection remains controversial [27–29].

8.2.2. Nerve Block

(1) Cervical Spinal Nerve Root Block. Selective nerve root injection could be used in patients with cervical spondylotic radiculopathy although the depth of the needle should be monitored to prevent complications. The effectiveness of this method is 70%, with 50% still reporting relief after 12 months [30].

(2) Third Occipital Nerve Block. This block can be used to diagnose CEH and predict the efficacy of radiofrequency treatment.

(3) Occipital Nerve Block. This block can be used to diagnose and treat occipital pain [21]. Clinically, occipital nerve injection can be repeatedly and intermittently used for symptomatic treatment. Dose for diagnostic injection should be limited to 2 ml; however, when it reaches 3–5 ml, the greater and small occipital nerves are completely blocked.

8.3. Minimally Invasive Interventional Management. Radiofrequency therapy, including radiofrequency thermocoagulation and pulse radiofrequency, is minimally invasive interventional techniques. Nerve properties can be distinguished by monitoring the stimulation frequency and impedance. Interventional radiofrequency therapy can be considered if a diagnostic nerve block is effective [31].

Radiofrequency intervention is recommended for patients with intractable cervical headache from the C2-C3 zygapophyseal joint for which conservative treatment has failed and complete relief has been obtained from a diagnostic nerve block [13]. The efficacy for CEH of other origins needs to be confirmed. Pulse radiofrequency is a type of neuromodulation therapy that has shown satisfactory short-term efficacy, albeit with recurrence during long-term follow-up that requires repeated treatments [32]. The reason for poor performance of C2 ganglion pulse radiofrequency treatment in some patients may be occipital pain from the C1 and C3 spinal nerve branches through the superior cervical plexus. Percutaneous laser disc decompression is another effective minimally invasive procedure for patients with cervical disc herniation, protrusion, or disc degeneration who have neck and shoulder pain with nerve root symptoms. Also, plasma radiofrequency can be considered when other methods fail to achieve satisfactory results by reducing the volume of the nucleus pulposus, potentially improving symptoms.

Finally, ozone has strong anti-inflammatory and analgesic effects that can benefit patients in whom glucocorticoid use is contraindicated. Its efficacy can be further improved through combination with a nerve block. Clinical effectiveness of percutaneous radiofrequency ablation combined with ozone is superior to that of percutaneous radiofrequency ablation alone in the treatment of cervical disc herniation, providing better medium- and long-term outcomes. Percutaneous laser disc decompression, ozone therapy, and other techniques have shown some clinical efficacy.

8.4. Surgical Procedures. Surgery is not usually recommended for CEH, except when CEH is refractory and does not respond to noninvasive treatment, and there is

convincing evidence that CEH is caused by pathological changes amenable to surgical treatment. Surgery may be beneficial for three specific causes of CEH as follows: (1) C2 spinal nerve compression by vascular/ligamentous structures, (2) osteoarthritis of the lateral atlantoaxial joint, and (3) upper cervical intervertebral disc pathology [33].

8.5. Physical Therapy. Physiotherapy is almost universally available and risk-free and has enormous benefits [34–36], such as reducing the frequency of CEH and improving headaches in the long-term. In view of the noninvasive nature of physiotherapy, it is recommended that it be the first choice for patients with CEH. Options include manipulation therapy (e.g., pulling, relaxation, and chiropractic), specific training therapy (e.g., static and dynamic stretching and training), and low-load endurance muscle exercise focusing on the neck and shoulder joints or the upper limbs (moderately strong evidence) [37–39]. In the initial stages, the muscles are gently stretched and artificial neck traction is performed to make physical therapy easier for the patient. Next, strength training and aerobic exercise are gradually introduced according to the patient's tolerance. High-velocity manipulation is not recommended because of the risk of interregional arterial dissection and stroke.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All the authors prepared and drafted part of Chinese version of the manuscript. Hong Xiao and Baogan Peng drafted the English version of the manuscript; Hui Liu and Yanqing Liu reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Hindawi
Pain Research and Management
Volume 2019, Article ID 8185316, 5 pages
https://doi.org/10.1155/2019/8185316

Research Article

Analyzing the Influence of Modic Changes on Patients with Lower Back Pain Undergoing Conservative Treatment

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Received 7 November 2018; Accepted 3 March 2019; Published 19 March 2019

Guest Editor: Baogan Peng

Objective. This study aimed to investigate if the presence of Modic changes (MCs) was correlated with lower back pain (LBP) and LBP-related disability in patients who underwent nonsurgical treatment. *Methods*. In this study, 129 patients who experienced consecutive LBP and underwent lumbar spine magnetic resonance imaging in our institute were divided into three groups according to the presence or type of MCs. The Oswestry Disability Index (ODI) and visual analog scale (VAS) were used to assess the outcomes of the treatment. *Results*. Based on the achieved results, there was no significant difference between three groups before treatment ($P > 0.05$). Three months after undergoing nonsurgical treatment, the rates of improved ODI and VAS scores were statistically significantly different ($P = 0.014,\ 0.023$). After an additional 3 months of treatment, in patients with Modic type I changes, the symptoms significantly improved in comparison with those 3 months prior ($P = 0.037,\ 0.026$), while that improvement did not occur in patients with Modic type II changes ($P > 0.05$). *Conclusions*. The existence of MCs affects the outcomes of nonsurgical treatment in patients with LBP. However, symptoms can be improved after an additional round of treatment for Modic type I changes, while this is not confirmed for Modic type II changes.

1. Introduction

Lower back pain (LBP) is a common health problem, and an estimated 80% of adults have experienced LBP at least once during their lifetime [1]. LBP nowadays seriously threatens Western societies in terms of the years lived with disability (YLDs) [2]. A nonsurgical treatment technique has shown significant efficacy in treating LBP. It is noteworthy that around 11% of patients with LBP require an additional surgery [3]. However, the main challenge for nonsurgical treatment is to identify the most appropriate intervention [4]. In addition, 85% of patients with isolated LBP cannot be precisely diagnosed with pathoanatomical methods [5]. The unknown etiologies may result in poor outcomes of nonsurgical treatment in some patients as well.

Modic changes (MCs) are a common phenomenon observed using magnetic resonance imaging (MRI) in spinal degenerative diseases and are greatly associated with LBP [6]. MCs are classified based on T1-weighted (T1W), T2-weighted (T2W), and T2W with fat suppression images in MRI [6, 7]. Modic type I changes are basically regarded as bone marrow edema and inflammation. In addition, Modic type II changes represent fatty degeneration of the bone marrow. MCs are associated with age, gender, body weight, smoking, previous spinal cord injuries, and physical workload [8]. Some researchers have previously reported a close relationship between MCs and LBP, particularly for type I changes [9–12]. According to our knowledge, the influence of MCs on patients with LBP has not been deeply studied yet. Hence, the present study retrospectively analyzed if the presence of MCs was correlated with LBP and LBP-related disability in patients who underwent nonsurgical treatment.

2. Materials and Methods

Herein, 129 patients who were admitted to the Department of Orthopaedic Surgery in the First Affiliated Hospital of Soochow University between January 2013 and December 2015 were enrolled. This study was approved by the Ethics

Committee of the first affiliated hospital of Soochow University and was in accordance with the Helsinki Declaration. Written informed consent was obtained from every participant. Several criteria were adopted, involving age with a range of 20–70 years, LBP experienced for 3 to 12 months, without radicular leg pain, and no history of formal treatment. The exclusion criteria were mixed MCs, a history of abdominal/pelvic surgery, as well as a specific spinal disease (e.g., scoliosis, spondylolisthesis, infection, and tumor).

Two experienced surgeons evaluated the images according to the criteria presented by Modic [6] for the presence of subchondral signal abnormalities. All patients used the same machine, and both T1W and T2W scanned 12 images from left to right and two consecutive images with abnormal signal changes are considered to have MCs. The overall interobserver agreement was excellent with a κ value of 0.85.

Patients were divided into three groups. Group A consisted of 50 patients without MCs, involving 22 men and 28 women with the age range of 25–62 years (a mean age of 40.5 years). Group B involved 31 patients with Modic type I changes, including 13 men and 18 women with the age range of 21–65 years (a mean age of 41.6 years). Group C consisted of 48 patients with Modic type II changes, involving 21 men and 27 women with the age range of 24–67 years (a mean age of 44.5 years), which are listed in Table 1.

2.1. Assessment of Images. Modic type I changes reflect hypointense and hyperintense signals on T1W and T2W images, respectively, while Modic type II changes represent hyperintense signals on T1W images and isointense or slightly hyperintense signals on T2W images, as illustrated in Figures 1 and 2.

2.2. Assessment of Symptoms. Two experienced nurses collected and completed the questionnaires according to patients' symptoms. For this purpose, the Oswestry Disability Index (ODI), derived from the Oswestry Low Back Pain Questionnaire, and visual analog scale (VAS) were utilized to assess the severity of symptoms, and rates of improved ODI and VAS scores were used to assess the efficacy of treatment. For this purpose, the rate of improved ODI scores was calculated as ((prior ODI − follow-up ODI)/prior ODI) × 100%, and the rate for improved VAS scores was calculated as ((prior VAS − follow-up VAS)/prior VAS) × 100%.

2.3. Nonsurgical Treatment. All patients underwent nonsurgical treatment for 6 months (two courses) involving the McKenzie method and pharmacological therapy. Regarding the McKenzie method, the treatment procedure occurs in only one position, consisting of a number of stages which are as follows: lie on a hard bed in the prone position, place head and leg at angles up to 20 degrees each, place hands on back, hold this position for 15 seconds, then release slowly, rest for 5 seconds, and repeat the action 30 times twice per day. Some small adjustments were undertaken according to each patient's characteristics. Using pharmacological therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) and muscle relaxants were administered once per day for two weeks. Patients were advised to continue consuming the drugs if pain was unrelieved, but not for more than four weeks. Next, patients were asked to select a hard bed, in lieu of a soft bed, and lie on it as much as possible for 3 months; then, the bending and sedentary time was decreased, as well as the workload to avoid increasing the waist load. A traditional Chinese medicine (TCM) therapeutic massage was performed, which relaxed whole muscles. Afterward, an experienced therapist repeatedly and gently massaged patients' back muscles for 30 minutes, once a week for 3 months.

2.4. Statistical Analysis. The data were presented as means and standard deviations. A one-way analysis of variance (ANOVA) was used to compare the basic characteristics of

Table 1: Fundamental characteristics of the three groups before treatment.

	Group A	Group B	Group C
Number	50	31	48
Male	22 (44%)	13 (42%)	21 (44%)
Female	28 (56%)	18 (58%)	27 (56%)
Average age (range)	40.5 (25–62)	41.6 (21–65)	44.5 (24–67)
BMI	20.4 ± 1.0	20.1 ± 0.9	20.5 ± 0.9
Smoking	13 (26.0%)	8 (25.8%)	14 (29.2%)
Heavy work	29 (58%)	18 (58.1%)	28 (58.3%)
Involved disc			
L3–4		3	3
L4–5		13	20
L5–S1		15	25

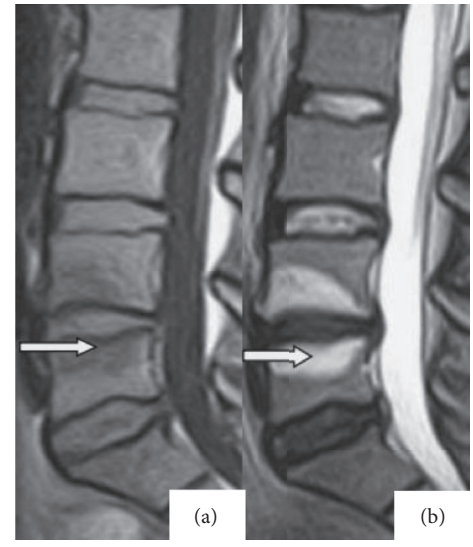

Figure 1: Illustration of Modic type I changes. (a) Hypointense changes on T1-weighted images at the L4 vertebral lower endplate and L5 vertebral body upper endplate. (b) Hyperintense changes on T2-weighted images at the L4 vertebral lower endplate and L5 vertebral upper endplate.

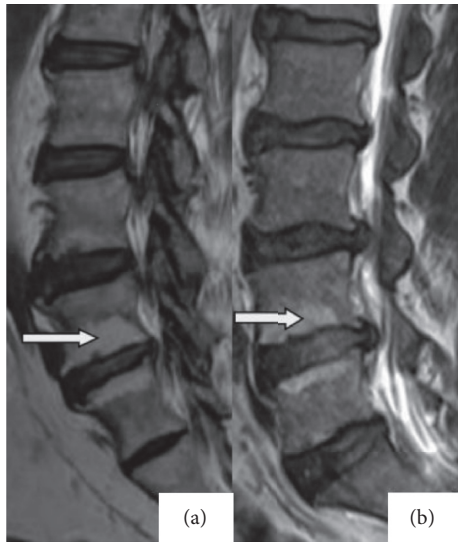

Figure 2: Illustration of Modic type II changes. (a) Hyperintense changes on T1-weighted images at the L4 vertebral lower endplate and L5 vertebral body upper endplate. (b) Hyperintense changes on T2-weighted images at the L4 vertebral lower endplate and L5 vertebral upper endplate.

VAS and ODI scores, as well as rates of improved ODI and VAS scores among the three presented groups. The chi-squared test was used to compare numbers of smokers and heavy workers or gender distribution between the groups. A paired sample t-test was used to compare the ODI and VAS scores at different time points in each group. P values less than 0.05 were considered statistically significant. All data were analyzed using SPSS software version 22.0 for Windows (SPSS Inc., IL, USA).

3. Results

There were no statistically significant differences in gender, body weight, workload, smoking, or involved discs between the three groups (Table 1). Before treatment, the ODI scores for no MC, MC1, and MC2 were 22.7 ± 4.6, 22.0 ± 5.2, and 22.7 ± 5.1, respectively, and those for VAS scores were 6.3 ± 1.6, 6.4 ± 1.8, and 6.3 ± 2.2, respectively. No significant difference was found between the three groups ($P > 0.05$), as mentioned in Table 2. Three months after undergoing nonsurgical treatment, the rates of improved ODI scores were 60.8%, 57.7%, and 48.0%, respectively, and those for improved VAS scores were 61.9%, 54.7%, and 46.0%, respectively. There was a significant difference between the three groups ($P < 0.05$). An additional 3 months after undergoing the treatment, in the MC1 group, again the rates of improved ODI and VAS scores were 16.1% and 13.8%, respectively, which were significantly higher than those 3 months priorly. However, no significant improvement was found in the MC1 group, as demonstrated in Tables 3 and 4.

4. Discussion

It has been reported that endplate changes are associated with LBP, and our previous research revealed that four types of endplate lesions (Schmorl's nodes, fracture, erosion, and calcification) were associated with disc degeneration as well as LBP [13, 14]. However, whether they have an influence on nonsurgical treatment remains unknown.

The presented nonsurgical treatment involves McKenzie exercises (extension in lying), pharmacological therapy, bed rest, change in lifestyle, and TCM therapeutic massage. McKenzie exercises can increase the strength of lumbar muscles, and several researchers have previously assessed the role and activation patterns of the trunk musculature as they correlate with the concept of spinal stability [15]. NSAIDs function through various degrees of reversible blockade of cyclooxygenase isoenzymes (COX-1 and COX-2), thus blocking the inflammatory cascade of arachidonic acid to prostaglandins, mediating inflammation as well as sensitizing peripheral nociceptors. Muscle relaxants generally act through inhibiting central polysynaptic neuronal events, indirectly acting on skeletal muscle [16]. Bed rest and massages could reduce waist load, which relaxes back muscles and relieves pain as well.

Some researchers have reported that cases of LBP with MCs are mainly related to inflammation [17–19].

Table 2: Scores of ODI and VAS for the three groups before treatment.

	Group A	Group B	Group C
Number	50	31	48
Male : female	22 : 28	13 : 18	21 : 27
ODI	22.7 ± 4.6	22.0 ± 5.2	22.7 ± 5.1
VAS	6.3 ± 1.6	6.4 ± 1.8	6.3 ± 2.2

Table 3: Scores of ODI and VAS, as well as corresponding improved rates for the three groups 3 months after treatment.

	Group A	Group B	Group C	P
Number	50	31	48	
ODI	8.9 ± 2.1	9.3 ± 2.4	11.8 ± 2.9	
ODI improvement rate (%)	60.8	57.7	48.0	0.014*
VAS	2.4 ± 0.8	2.9 ± 0.8	3.4 ± 1.2	
VAS improvement rate (%)	61.9	54.7	46.0	0.023*

*Statistically significant.

Table 4: Scores of ODI and VAS and corresponding improved rates for the three groups 6 months after treatment, as well as comparing with the results in Table 3.

	Group A	Group B	Group C
Number	50	31	48
ODI	8.5 ± 2.0	7.8 ± 2.8	11.3 ± 2.6
ODI improvement rate (%)	4.5	16.1	4.2
P	0.130	0.037*	0.178
VAS	2.3 ± 0.8	2.5 ± 1.2	3.2 ± 0.9
VAS improvement rate (%)	4.2	13.8	5.9
P	0.097	0.026*	0.082

*Statistically significant.

Inflammatory factors, e.g., interleukin 6, interleukin 8, prostaglandin E2, and tumor necrosis factor alpha, cause pain after stimulating nerve endings. Crock [17] suggested that upregulation of inflammatory mediators in the nucleus pulpous could be associated with a local inflammation response. Zhang et al. [18] found that nucleus pulposus could produce a series of inflammatory factors and transmit them to vertebrae through the fissures in endplates. Ohtori et al. [19] reported that the expression of inflammatory factors in endplates from patients with Modic type I changes was significantly higher than that in endplates from patients with Modic type II changes. Therefore, NSAIDs might have a sensitive efficacy to LBP because of the control of pain induced by inflammation. This can be justified by the finding that the improvement rate of pain 3 months after the treatment in group B (54.7%) was remarkably higher than that in group C (46.0%), reflecting that Modic type I changes demonstrated a superior outcome than Modic type II changes.

Toyone et al. [20] studied 74 patients with MCs and found that 70.3% (26/37) of patients with Modic type I changes had LBP, while only 16.2% (6/37) of patients with Modic type II changes had LBP. They reported that type I changes were correlated with segmental instability and LBP, while type II changes were more common in patients with stable degenerative disc disease. However, the relationship between MCs and segmental instability is mostly supported by indirect evidence of the efficacy of lumbar fusion surgery [21]. Kulig et al. [22] investigated 45 patients with LBP and 20 patients without LBP and determined that LBP has a strong correlation with segmental instability. In the present study, the rate of improved ODI enhanced to 16.1% after an additional round of treatment in group B, while that rate was only 4.2% in group C. It is apparent that a disability symptom can be improved after an additional round of treatment for Modic type I changes; however, that is not feasible for Modic type II changes. McKenzie extension exercises could increase muscle strength, resulting in an increase in lumbar segmental stability, as the exercise itself and the strength of muscle demonstrate a long process; as for patients with type I changes, an additional round of treatment could facilitate satisfactory results.

Modic type I and type II changes represent different stages of the same pathological process [9]. Mitra et al. [23] investigated 44 patients with type I changes with a follow-up that lasted for 12–72 months. They found that 37.5% (18/48) of patients fully converted to type II changes and 14.6% (7/48) of patients partially converted to type II changes. They demonstrated that type I changes are an acute phase and eventually can be transformed into other types, and a positive correlation was found in the evolution of type I changes to type II changes, as well as symptom improvement. Hutton et al. [24] reported a similar conclusion with a study of 36 endplate cases. In the current study, the rate of improved VAS enhanced to 13.8% after an additional round of treatment in group B; however, the rate was only 5.9% in group C, reflecting that pain symptoms can be relieved after an additional round for type I changes, while no significant intensity was found for type II changes. As a result, over time, Modic type I changes would have superior intensity of pain than Modic type II changes.

Modic type III changes were not included in this study, as the population of study samples was small, and this is a preliminary study with a short follow-up, requiring further investigation.

5. Conclusions

In summary, the existence of MCs affects the outcomes of nonsurgical treatment in patients with LBP. In addition, the outstanding role of a formal nonsurgical treatment and the importance of confidence were revealed. Moreover, symptoms can be improved after an additional round of treatment through type I changes.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jun Zou was responsible for designing the study, writing the protocol and report, and screening potentially eligible studies. Yufeng Chen was responsible for conducting the search and writing the protocol and report. Huilin Yang, Lianfang Zhang, and Yue Wang contributed to data extraction and provided feedback on the report.

Acknowledgments

This work was supported by the National High Technology Research and Development Program of China (2015AA020316), National Natural Science Foundation of China (81301646, 81601865 and 81672220), National Natural Science Foundation of Jiangsu Province (BK201502990) and Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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Hindawi
Pain Research and Management
Volume 2019, Article ID 9394715, 11 pages
https://doi.org/10.1155/2019/9394715

Research Article

Locating the Site of Neuropathic Pain *In Vivo* Using MMP-12-Targeted Magnetic Nanoparticles

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Received 16 November 2018; Revised 29 January 2019; Accepted 14 February 2019; Published 6 March 2019

Guest Editor: Ke Ma

Neuropathic pain remains underrecognised and ineffectively treated in chronic pain sufferers. Consequently, their quality of life is considerably reduced, and substantial healthcare costs are incurred. The anatomical location of pain must be identified for definitive diagnosis, but current neuropsychological tools cannot do so. Matrix metalloproteinases (MMP) are thought to maintain peripheral neuroinflammation, and MMP-12 is elevated particularly in such pathological conditions. Magnetic resonance imaging (MRI) of the peripheral nervous system has made headway, owing to its high-contrast resolution and multiplanar features. We sought to improve MRI specificity of neural lesions, by constructing an MMP-12-targeted magnetic iron oxide nanoparticle (IONP). Its *in vivo* efficiency was evaluated in a rodent model of neuropathic pain, where the left lumbar 5 (L5) spinal nerve was tightly ligated. Spinal nerve ligation (SNL) successfully induced mechanical allodynia, and thermal hyperalgesia, in the left hind paw throughout the study duration. These neuropathy characteristics were absent in animals that underwent sham surgery. MMP-12 upregulation with concomitant macrophage infiltration, demyelination, and elastin fibre loss was observed at the site of ligation. This was not observed in spinal nerves contralateral and ipsilateral to the ligated spinal nerve or uninjured left L5 spinal nerves. The synthesised MMP-12-targeted magnetic IONP was stable and nontoxic *in vitro*. It was administered onto the left L5 spinal nerve by intrathecal injection, and decreased magnetic resonance (MR) signal was observed at the site of ligation. Histology analysis confirmed the presence of iron in ligated spinal nerves, whereas iron was not detected in uninjured left L5 spinal nerves. Therefore, MMP-12 is a potential biomarker of neuropathic pain. Its detection *in vivo*, using IONP-enhanced MRI, may be further developed as a tool for neuropathic pain diagnosis and management.

1. Introduction

Back pain is the highest reported pain condition and progresses to chronic lower back pain in two-thirds of patients. These patients present nociceptive and/or neuropathic components, but the later component is usually underrecognised [1]. Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease, affecting the somatosensory system. Diagnosis requires identifying the anatomical location and pathology. However, the most

convenient methods of documenting patient history, and physical examination, rely on patient collaboration [2]. Since patients' experience of pain is influenced by cognitive, emotional, and educational factors, more objective measurements of neuropathic pain are called for. Current screening tools to assess nerve damage are neuropsychological in nature, which include questionnaires and various electrodiagnostic tests. However, they cannot provide conclusive evidence for neuropathic pain or locate the exact pain-generating site [3].

MRI techniques are increasingly applied to observe neural injuries and diseases noninvasively. In T2-weighted images (T2-WI), peripheral nerves are normally indistinguishable from surrounding tissues and may appear slightly hyperintense, or isointense, relative to muscle tissue. However, injured nerves appear bright on T2-WI, as the T2 relaxation time is prolonged [4]. Although MR signal changes in injured peripheral nerves are significant, it lacks specificity. Regenerating nerves cannot be distinguished from chronically degenerating ones [5], and the same signal changes may be observed for normal nerves [6]. MRI contrast agents, such as gadolinium [7, 8], manganese [9], perfluorocarbon [10], and IONP [11–13], were developed to address this gap. However, contrast agents used thus far in patients and animal models are nonspecific. Hence, in the present study, we sought to design an IONP-based MR contrast agent that would be selectively cleaved and taken up locally by injured nerve roots.

IONP markedly decreases T2 signals by enhancing the spin-spin relaxation times of surrounding water protons [14]. IONP has been used to observe macrophage migration into experimentally injured sciatic nerves *in vivo* [11, 13]. Bendszus and Stoll [13] reported IONP-induced signal loss up to 8 days after sciatic nerve injury. However, the signal increases by day 11 because iron-laden macrophage recruitment is transient, and infiltrated macrophages remain stationary within the injured nerve [13]. IONP can detect enzymatic activity, when conjugated to peptide sequences. When the peptide sequence is cleaved by the extracellular target enzyme, the released IONP would be taken up by surrounding tissues [15–18]. Unlike nontargeted IONPs, targeted IONPs may prevent damage to other tissues, as they would only be absorbed by those expressing the targeted enzyme [19]. Hence, macrophage factors, including MMPs, may instead present as potential targets for *in vivo* IONP-based MRI.

MMPs are a family of calcium dependent zinc endopeptidase, which are responsible for extracellular matrix (ECM) degradation. Their activity is tightly controlled under physiological conditions. Upon nerve damage, MMPs degrade blood-nerve barrier and myelin. In addition, they exacerbate leukocyte infiltration and cytokine release. Hence, MMPs are thought to maintain inflammatory pathologies such as peripheral neuropathy [20]. Certain MMPs, such as MMP-12, maintain low expression in undamaged sciatic nerves. However, upon nerve injury, there is increased expression, which remains elevated for up to 20 days after injury [21, 22]. We hypothesise that elevated MMP-12 activity at the site of nerve injury can be detected *in vivo*. An MMP-12-targeted magnetic IONP may be able to locate the pain-generating site by MRI. Thus, we sought to evaluate an MMP-12-targeted IOPN in a rat SNL model. This particular model better recapitulates partial nerve injury seen in most neuropathic pain patients [23]. The first aim was to determine the effect of SNL on mechanical withdrawal threshold (MWT), thermal withdrawal latency (TWL), macrophage infiltration, MMP-12 expression, myelination, and elastin fibre content. The second aim was to evaluate the cytotoxicity, cellular uptake, and specificity, of the synthesised MMP-12-targeted magnetic IONP, *in vitro*. The last aim was to examine *in vivo* MRI of animals receiving the MMP-12-targeted magnetic IONP and to verify IONP uptake by histology analysis of spinal nerves.

2. Materials and Methods

2.1. Animals. Procedures involving animals were approved by the Institutional Animal Care and Use Committee, of the National University of Singapore (R13-4649, R14-0009), and carried out in accordance with the National Advisory Committee for Laboratory Animal Research guidelines. 7-week-old male Sprague–Dawley rats (InVivos, Singapore), initially weighing 200 to 250 g, were housed under controlled temperature (20–26°C) and humidity (30–70%), with a 12-hour light-dark cycle (lights on 7:00 AM to 7:00 PM). Food and water were provided *ad libitum*. Animals underwent either SNL or sham surgery. They were assessed for mechanical allodynia and thermal hyperalgesia, by von Frey and Hargreaves' tests, respectively. These tests were done 3 days preoperatively, as well as 7 and 13 days postoperatively. Spinal nerves harvested from rats euthanized 1 or 2 weeks after SNL or sham surgery were studied by immunohistochemistry and histology staining or MMP-12 activity assay. Rats that underwent intrathecal injection of MMP-12-targeted IONP, 2 weeks after SNL or sham surgery, were euthanized after MRI.

2.2. Surgical Procedures. All surgical procedures were performed after subcutaneous administration of enrofloxacin (10 mg/kg). Rats were deeply anesthetised with isoflurane (5% induction and 2% maintenance in air) and placed in a prone position. The dorsal thoracic area was shaved of fur, and the skin was scrubbed thrice, alternating between iodine and 70% ethanol, before animals were draped.

SNL surgery began by making a dorsal midline incision. The left paraspinal muscles were separated from the spinous processes by sharp and blunt dissection, to expose the left L6 transverse process. The left L6 transverse process was carefully removed using a bone trimmer, to expose the left L5 spinal nerve. The nerve was tightly ligated with a 5-0 chromic gut suture, 3–5 mm distal to the dorsal root ganglion (DRG). Muscle and skin were closed with 3-0 absorbable suture. Lignocaine (10 mg/ml, Pfizer) was injected under the sutured skin, and Banocin powder was applied on the sutured skin. In sham surgery, the left L5 spinal nerves are exposed but not ligated [24]. To inject the MMP-12-targeted probe, the L5 vertebrae were exposed in a similar manner. The laminar bone

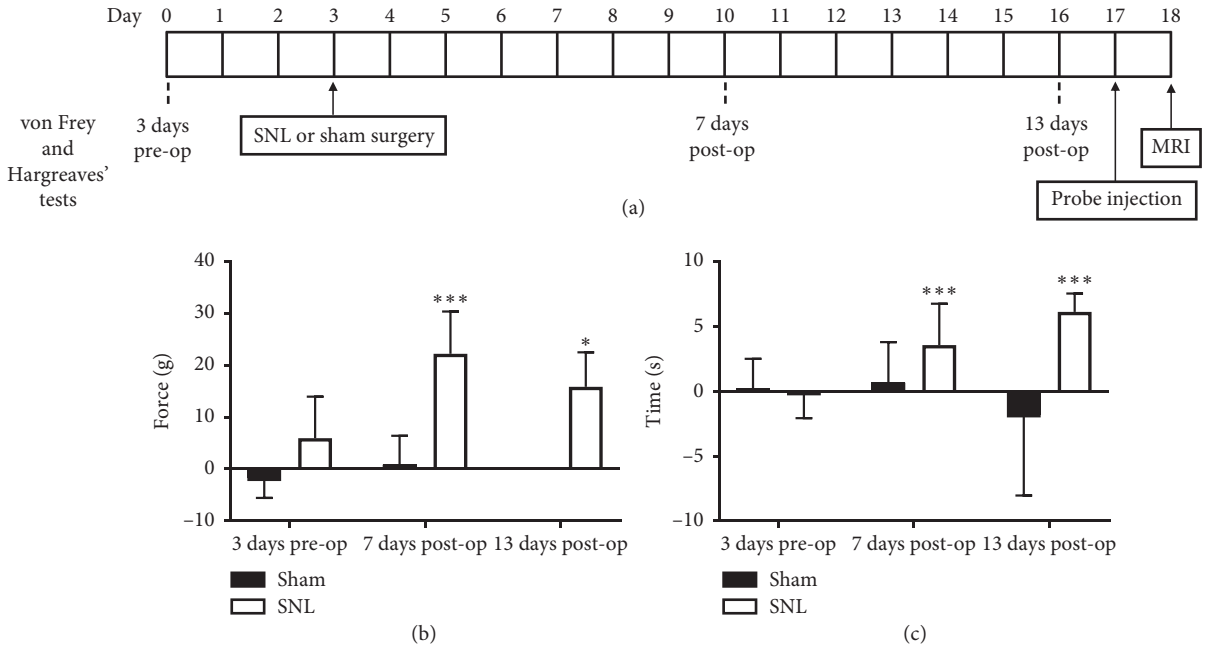


Figure 1: Left L5 SNL induces neuropathic pain in rats. Behavioural assessments were done (a) 3 days pre-op, 7 (sham $n = 12$; SNL $n = 16$) and 13 days post-op (sham $n = 2$; SNL $n = 6$). Marked increase in right and left hind paws (b) MTW and (c) TWL difference was observed after SNL, whereas sham surgery did not affect MTW or TWL difference. Statistically significant differences between pre-op and post-op MTW and TWL for each group were observed by Mann–Whitney U test ($^{*}p < 0.05$, $^{***}p < 0.001$).

was minimally removed using a rongeur, to allow intrathecal injection of 10 μl of the MMP-12-targeted IONP onto the left L5 DRG with a GC syringe [25].

After any surgery, animals were housed individually with clean bedding and treated with subcutaneous enrofloxacin twice daily for 3 days. Those injected with MMP-12-targeted probe were also given buprenorphine (0.06 mg/kg) twice daily for 3 days. Animals were monitored for signs of distress after any surgery. There were no instances of neurological deficit or paralysis due to SNL throughout the course of this study.

2.3. Behavioural Assessments. Mechanical allodynia was evaluated using von Frey filaments, in an automated Dynamic Plantar Aesthesiometer system (UgoBasile, Italy). The system is placed under an elevated wire mesh, and rats are placed singly in transparent boxes upon the mesh. For every trial, the filament is carefully positioned under the plantar surface of the hind paw and rises to press against the paw. The applied force ranged from 5 g to 40 g, for a maximum of 6 seconds or until the paw is withdrawn. MWT is reached at a force, when hind paws are withdrawn in under 6 seconds, for at least 5 out of 6 trials. Thermal hyperalgesia was evaluated by Hargreaves' method using the thermal plantar test apparatus (UgoBasile, Italy). This system is placed below an elevated plastic platform, and rats were placed singly in transparent boxes upon this platform. For every trial, the infrared source (40 mW) is positioned beneath the midplantar surface of the hind paw, for a maximum of 20 seconds or until the paw was withdrawn [26]. The average withdrawal time of five trials, where the paw is withdrawn in under 20 seconds, was calculated as the TWL. The MWT and TWL difference was calculated for each rat, by subtracting the MWT or TWL of the left hind paw from that of the right hind paw [24].

2.4. Histology and Immunohistochemistry. Specimens were obtained from animals euthanized by terminal cardiac perfusion. These rats were deeply anesthetised with 1 ml urethane and perfused with 400 ml 1% sodium nitrite, followed by 400 ml 4% paraformaldehyde (PFA). The proximal and distal lengths, between the DRG, and each end of the excised spinal nerves, were 5–7 mm. The harvested left L4, L5, and L6, and right L5 spinal nerves were placed in 4% PFA and processed for paraffin embedding. Before any staining, 5 μm thick sections were deparaffinised by xylene and hydrated using graded ethanol and distilled water.

Immunohistochemistry began with antigen retrieval using pepsin for 15 min at 37°C. Endogenous peroxidase activity was blocked with 1% hydrogen peroxide for 10 min, followed by avidin and biotin block (SP-2001, Vector Laboratories, CA, USA) for 15 min each. Sections were incubated with 1.5% normal goat serum (AK-5001, Vector Laboratories, CA, USA), before a 2 h incubation with either a mouse monoclonal antibody to CD68 (MAB1435, Merck Millipore, MA) or a rabbit polyclonal antibody to MMP-12 (bs-1854R, Bioss, MA, USA), at a dilution of 1 : 200. biotinylated goat anti-mouse (Ba-2900, Vector Laboratories, CA, USA) or anti-rabbit (AK-5001, Vector Laboratories, CA, USA) IgG antibodies diluted by 1 : 200 in 1.5% normal goat serum were applied for 30 min. Thereafter, an avidin-biotin complex reagent (AK-5001, Vector Laboratories, CA, USA) was applied for 30 min, followed by visualisation using ImmPACT Vector Red Alkaline Phosphatase (SK-5105,

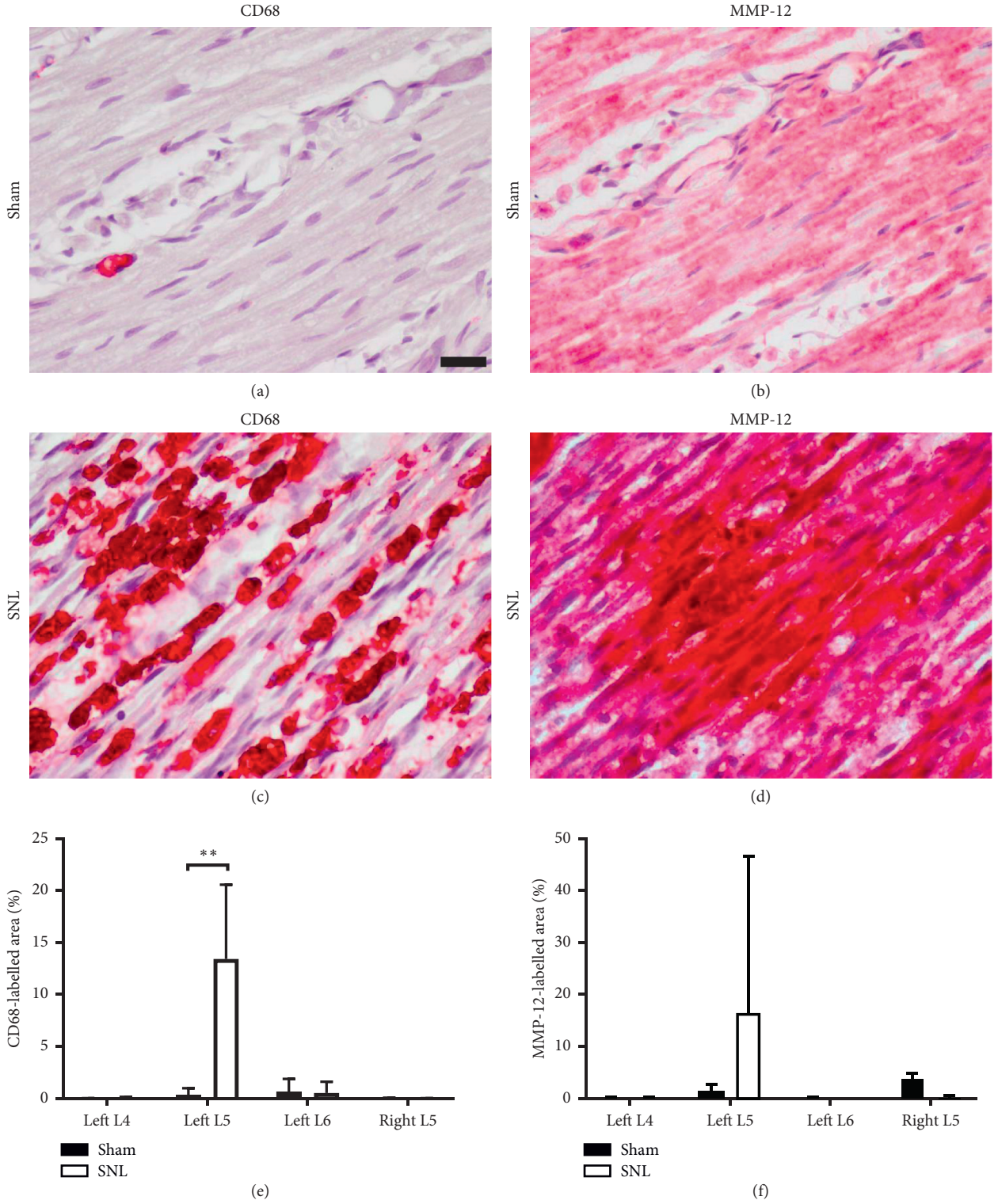


Figure 2: Macrophage infiltration and MMP-12 upregulation occurred in injured nerves. (a–d) Representative images of immunohistochemistry staining on consecutive sections for macrophage marker CD68 and MMP-12, in the left L5 spinal nerves distal to the DRG, 1 week after SNL or sham surgery (CD68 or MMP-12: red, nuclei: purple, scale bar = 20 μm). (e) CD68- and (f) MMP-12-labelled areas were quantified for SNL and sham rats' spinal nerves ($n = 5$ per group). Statistically significant difference in the left L5 spinal nerve CD68-labelled area was determined by Mann–Whitney U test ($^{**}p < 0.01$).

Vector Laboratory, CA, USA) for 20 min. Slides were counterstained in hematoxylin (3801562, Leica Biosystems Inc, IL, USA) for 1 min.

In Verhoeff-van Gieson (ab150667, Abcam, United Kingdom) staining, slides were immersed in working elastic stain solution for 8 min, dipped in differentiating solution 40

times, placed in sodium thiosulfate solution for 1 min, and rinsed in tap water after every reagent. They were then stained with van Gieson's solution for 30 seconds and rinsed in 95% ethanol for 30 seconds.

Luxol Fast Blue staining was carried out after hydrating sections to 95% ethanol. Slides were immersed in 0.1% Luxol Fast Blue (S3382-25G, Sigma-Aldrich, MO, USA) solution for 16 h in a 57°C water bath. After brief washing in 95% ethanol and distilled water, sections were differentiated in 0.05% lithium carbonate (152,537, MP Biomedicals, CA, USA) solution for 1 min and washed with distilled water.

Prussian blue staining was done by immersing slides in a working solution of equal parts of 20% aqueous hydrochloric acid and 10% aqueous potassium ferrocyanide (P-3289, Sigma-Aldrich, CA, USA) solution for 20 min, followed by 0.1% nuclear fast red (60,700, Sigma-Aldrich, CA, USA) solution for 5 min. Slides were thoroughly washed in distilled water after every solution or stain.

All stained slides were dehydrated in graded ethanol and xylene. After mounting slides with DPX (06522, Sigma-Aldrich, CA, USA), bright field images were acquired (Olympus CX41, Japan). For each specimen, 2 sections at least 40 μm apart were selected. For each section, 3 non-overlapping images at the region of interest were taken. Using ImageJ, they were converted to greyscale images and the percentage area that was positively stained was derived. The average percentage area of 6 images per specimen was used for statistical analysis.

2.5. MMP-12 Activity Assay. MMP-12 concentrations in the left L4, L5, and L6, and right L5 spinal nerves, harvested from rats euthanized by carbon dioxide exposure, were determined using an MMP-12 activity assay (AS-71157, AnaSpec, CA, USA). Specimens were homogenized in assay buffer containing 0.1% Triton X-100 and centrifuged at 10000 ×g for 15 min at 4°C. The supernatant obtained was further diluted in assay buffer by 10-fold. MMP-12 concentrations were calculated relative to a human MMP-12 catalytic domain (1 μg/ml, AS-55525, Anaspec, CA, USA) standard curve. 1 mM 5-FAM-Pro-Leu-OH was used as a 5-FAM fluorescence reference standard for instrument calibration. 50 μl of each diluted spinal nerve specimen supernatant, human MMP-12 catalytic domain dilutions, 5-FAM-Pro-Leu-OH dilutions, and a substrate control containing assay buffer only were added to a 96-well plate. 50 μl of MMP-12 substrate was added to each well before incubating at 37°C for 45 min. Thereafter, 50 μl stop solution was added in all wells, and the fluorescence intensity at Ex/Em = 490/520 nm was measured (PHERAstar fluorimeter, BGM Labtech, Germany). Total protein for each sample was measured relative to an albumin standard curve, using a Micro BCA Protein Assay Kit (Micro BCA Protein Assay Kit, Thermo Scientific, MA, USA).

2.6. MMP-12-Targeted IONP Preparation. IONPs were synthesised and coated with dextran, according to the method described by Josephson et al. [27]. Nanoparticles were conjugated with MMP-12 probe linker, via the succinimidyl iodoacetate linker, which acts as a membrane translocator and targeting moiety (Succyl-eeeeeeeee-RPKPVE-Nva-WR-rrrrrrrr-c). Dynamic light scattering and zetapotential measurements were taken (Malvern Zetasizer Nanoseries, United Kingdom).

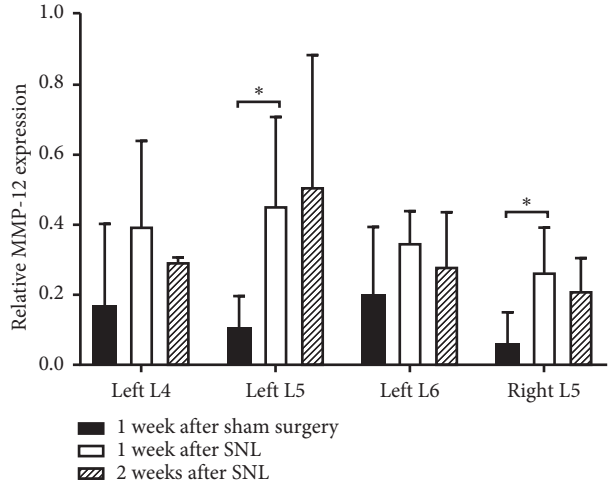


Figure 3: MMP-12 upregulation in ligated left L5 spinal nerve is observed for up to 2 weeks. MMP-12 activity of spinal nerves at 1 ($n = 5$) or 2 ($n = 4$) weeks after SNL and 1 week after sham surgery ($n = 5$) was compared. Statistically significant differences between groups for each spinal nerve were determined by Mann–Whitney U test ($^* p < 0.05$).

To determine iron concentration, the MMP-12-targeted IONP was digested in a mixture of 4 parts of 65% nitric acid to 1 part of 30% hydrogen peroxide. The digests were dried in Perfluoroalkoxy cups on a hotplate, reconstituted, and diluted in 0.4% nitric acid, to a concentration of 10–60 ng/g. Samples were analysed by graphite furnace atomic absorption spectrometry (Varian AA240Z, SpectraLab Scientific Inc., Canada), using standards prepared from Titrisol iron standard (109972, Merck, Germany) for external calibration.

2.7. Probe Cytotoxicity, Cell Uptake, and In Vitro MRI. Probe cytotoxicity was evaluated by methyl thiazolyl tetrazolium (MTT; M2128, Sigma-Aldrich, CA, USA) assay, on MMP-12-expressing U87 glioma cells [28]. A density of 1×10^5 U87 glioma cells were seeded in a 96-well plate and incubated with MMP-12-targeted IONP at different concentrations (20 and 10 μg/ml) for 4 h, followed by incubation with 10 μl of MTT solution (5 mg/ml) for 2 h. Thereafter, the media was aspirated, dissolved in dimethyl sulfoxide, and the absorbance at 570 nm was measured. Cell viability was calculated as a percentage of absorbance in comparison with control cells.

To observe cellular uptake of the probe, U87 glioma cells were seeded into a 48-well plate, at a density of 5×10^3 cells per well. Cells were incubated with 10 μg MMP-12-targeted IONP and fixed with 4% PFA for 40 min. After washing cells with PBS, they were stained using the prussian blue protocol described above.

An *in vitro* MRI was done in a 7T scanner (Bruker Clinscan system, Germany) using U87 glioma cells at a

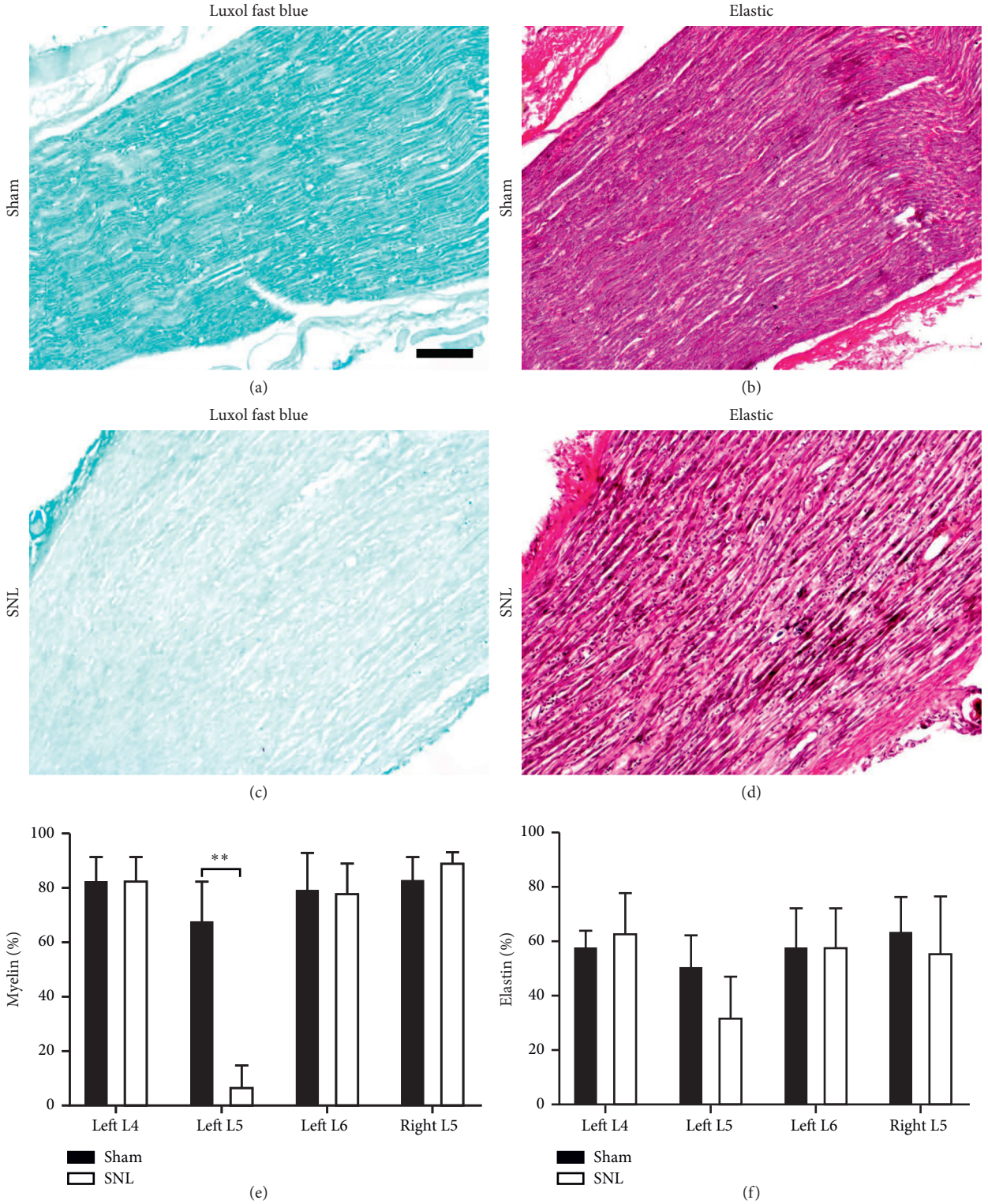
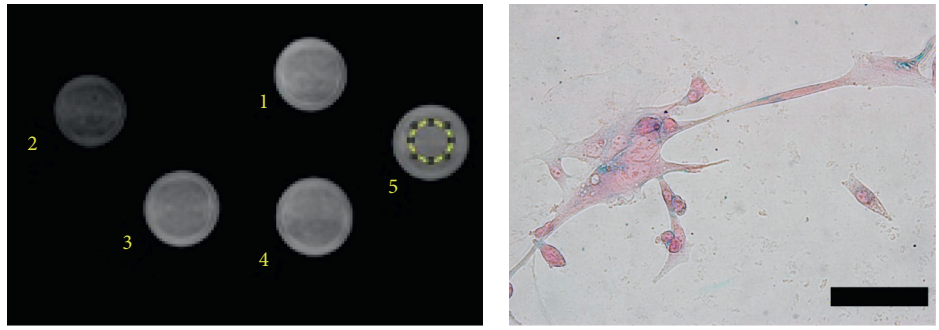


Figure 4: Demyelination and elastin fibre loss occurred at the site of ligation. (a–d) Representative images of Luxol Fast Blue (myelin: blue) and Verhoeff-van Gieson (elastin: black, nuclei: blue, and collagen: red) staining, on consecutive sections of the left L5 spinal nerve distal to the DRG, 1 week after SNL or sham surgery (scale bar = 100 μm). (e) Myelin- and (f) elastin-positive areas of SNL and sham rats' spinal nerves were quantified ($n = 5$ per group). Statistically significant difference in the left L5 spinal nerve myelin content was determined by Mann–Whitney U test ($^{**}p < 0.01$).

density of 1×10^5. They were either left untreated, incubated with MMP-12-targeted IONP for 1 h only, or incubated with the selective MMP-12 inhibitor, MMP408 (CAS 1258003-93-8, Merck Millipore, Germany) [29] for 2 h, followed by a 1 h incubation with the MMP-12-targeted IONP. After their respective treatments, cells were digested with trypsin,



(a) (b)

Figure 5: MMP-12-targeted probe is selectively cleaved by MMP-12 *in vitro*. (a) U87 glioma model MRI phantom showed lower intensity in the ROI (indicated by yellow circle) of (2) cells treated with probe only, compared to (3 and 4) cells treated with probe and MMP408, (5) untreated cells, and a (1) blank. (b) Microscopic observation of U87 cells stained with prussian blue, following incubation with the probe, shows iron-positive areas (scale bar = 100 μm).

centrifuged, fixed with 4% PFA for 1 h at 4°C, and embedded in 1% agarose. T2-WI were acquired with the following parameters: FOV 50 mm, TR 2750 ms, TE 37 ms, and slice thickness 1 mm. The mean grey area within the region of interest (ROI) was measured using ImageJ software. MMP-12 activity of untreated U87 glioma cells, and those incubated with MMP408, was quantified using the assay described above.

2.8. In Vivo MRI. A day after intrathecal administration of MMP-12-targeted IONP, MRI was performed on rats with a 7T scanner (Siemens Magnetom ClinScan syngo, Germany). Rats were deeply anesthetised with isoflurane (5% induction and 2% maintenance in air). Temperature and respiration were monitored during T2-WI acquisition. The following parameters were used: FOV 60 mm, TR 1010 ms, TE 37 ms, slice thickness 0.8 mm, and plane resolution 0.188 × 0.188 mm.

2.9. Statistical Analysis. All data are expressed as mean ± standard deviation (SD) and analysed with Graphpad Prism 7 software. Behavioural, immunohistochemistry, histology, and MMP-12 activity assay data were analysed using Mann–Whitney U test, where $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. SNL Induces Neuropathic Pain. Behavioural assessments (Figure 1(a)) suggest ligation of the left L5 spinal nerve successfully induced neuropathic pain in all animals used in this study. MWL and TWL difference between right and left hind paws were significantly higher at 7 (22.2 ± 2.04 g, 4.57 ± 0.687 s) and 13 days (15.8 ± 2.71 g, 6.11 ± 0.577 s) after SNL, than 3 days before SNL (5.94 ± 2.00 g, −0.389 ± 0.440 s). MWL and TWL difference of sham rats did not differ between the three test points (Figures 1(b) and 1(c)). Thus, mechanical allodynia and thermal hyperalgesia of the left side was evident in SNL rats until their respective endpoints [24].

3.2. Macrophage Infiltration and MMP-12 Upregulation Observed in Ligated Spinal Nerves. One-week postoperative immunostaining for CD68 and MMP-12 showed greater staining in ligated left L5 spinal nerves (CCD68 13.4 ± 7.15%; MMP-12 23.6 ± 18.4%), compared to the left L5 spinal nerves in sham-operated rats (CD68 0.335 ± 0.656%; MMP-12 9.91 ± 9.30%). In SNL rats, CD68 and MMP-12 staining in the left L4, left L6, and right L5 spinal nerves were lower than the left L5 spinal nerve (Figure 2). MMP-12 activity analysis (Figure 3) at 1 week after SNL further confirmed ligation induced significant MMP-12 upregulation in left L5 spinal nerves (0.455 ± 0.253), compared to sham surgery (0.106 ± 0.0900). Moreover, MMP-12 expression remained elevated in left L5 spinal nerves 2 weeks after SNL (0.510 ± 0.374). Hence, the MMP-12-targeted probe was administered 2 weeks after SNL or sham surgery, to ensure animals were fit for intrathecal injection. While sham surgery also induced detectable MMP-12 levels, it is lower than the corresponding spinal nerves in SNL rats. MMP-12 upregulation was observed in spinal nerves contralateral and ipsilateral to the ligated left L5 spinal nerve too. This may be due to local inflammation in response to surgical insult. Nevertheless, MMP-12 levels of nonligated nerves in SNL rats were still lower than ligated nerves. Furthermore, MMP-12 levels in nonligated nerves reduced between 1 and 2 weeks after SNL but increased in ligated nerves, suggesting local inflammation subsidence over time. Taken together, the results suggest that macrophage infiltration occurred primarily at the site of ligation, leading to increased MMP-12 secretion at the pain-generating site [21].

3.3. Demyelination and Elastin Fibre Loss Occurred at the Site of Ligation. Significantly lower myelin and elastin fibre content was noted at the site of ligation 1 week after SNL (myelin 19.6 ± 14.5%, elastin 34.1 ± 11.1%), compared to the corresponding tissues of sham rats (myelin 84.5 ± 6.95%, elastin 60.0 ± 4.78%). Demyelination at the site of ligation only is indicative of successful experimental nerve injury (Figure 4) [30]. MMP-12 is known to be the primary enzyme responsible for elastin degradation [31]. Therefore, elastin

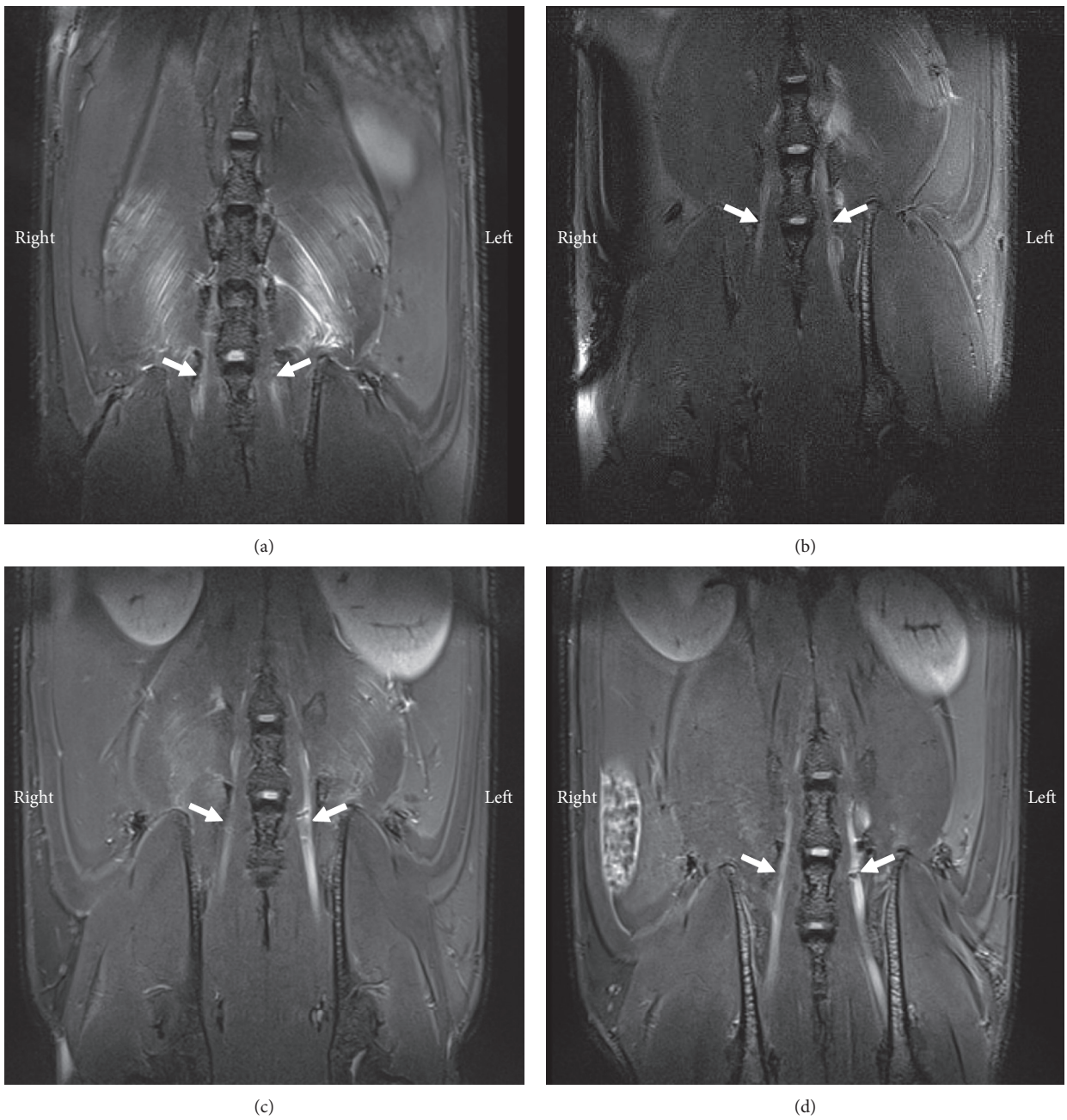


Figure 6: Coronal T2-WI a day after intrathecal injection of MMP-12-targeted probe. White arrows indicate left and right L5 spinal nerves, in sham and SNL rats ($n = 2$ per group). Compared to uninjured nerves, injured nerves are enlarged, and iron-induced signal loss is observed at the approximate site of ligation. (a) Sham 1. (b) Sham 2. (c) SNL 1. (d) SNL 2.

fibre loss at the site of ligation is in line with MMP-12 upregulation observed in ligated left L5 spinal nerves.

3.4. Synthesised Probe Provides Sufficient Contrast In Vitro. The optimised IONP had a diameter of 31.9 nm, iron concentration of 1.85 mg, zetapotential of 6.36 ± 8.74 mV, and U87 glioma cell viability of 107%. Furthermore, the relaxivity of our MMP-12-targeted probe ($211.62\ \text{mmol}^{-1}\text{s}^{-1}$) is comparable to a commercial contrast agent, resovist ($228.83\ \text{mmol}^{-1}\text{s}^{-1}$). Incubating U87 glioma cells with 10 μg/ml MMP-12-targeted IONP resulted in a lower mean grey value (1310 arbitrary units) in the acquired MR image, than cells treated with probe and MMP408 (well 3: 1460 arbitrary units; well 4: 1480 arbitrary units), untreated cells (1460 arbitrary units), and the blank (1500 arbitrary units) (Figure 5). In another set of experiments, 5% MMP408 reduced MMP-12 activity in U87 cells by 40% (0.254 ± 0.0506 ng MMP-12/μg albumin), compared to untreated cells (0.423 ± 0.0315 ng MMP-12/μg Albumin). Hence, the probe is not cytotoxic and is selectively cleaved by MMP-12 *in vitro*, to provide sufficient contrast for MRI [12].

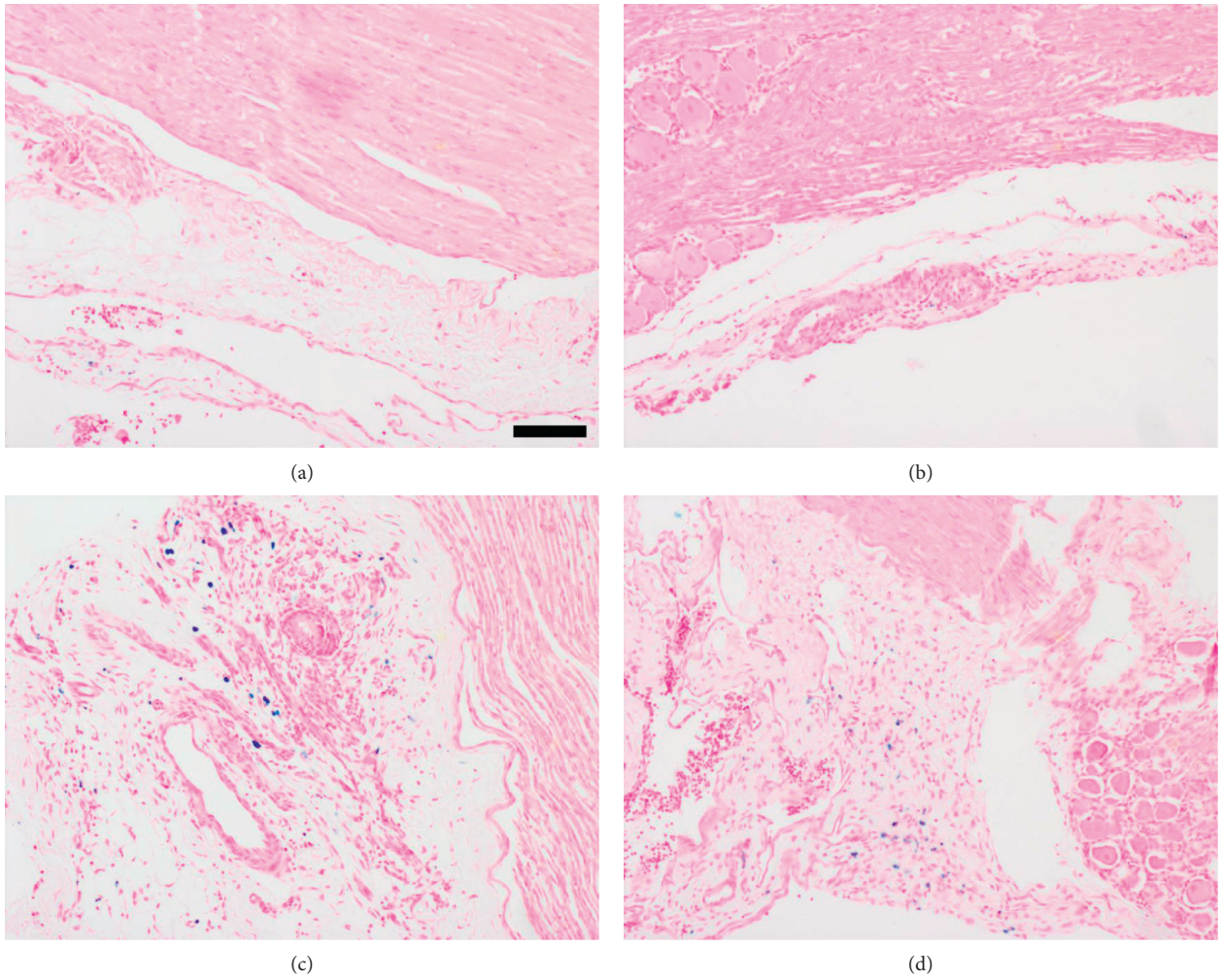


Figure 7: Prussian blue staining verifies MRI observations. Left L5 spinal nerves harvested from SNL rats after MRI show increased iron staining in the perineural tissues, compared to the corresponding tissues in sham rats ($n = 2$ per group; iron: blue, nuclei: red, and cytoplasm: pink; scale bar = 100 μm). (a) Sham 1. (b) Sham 2. (c) SNL 1. (d) SNL 2.

3.5. Low MR Signal Observed at the Site of Ligation. In uninjured left and right L5 spinal nerves, the MR signal was slightly hyperintense to the surrounding soft tissue. In comparison, the left L5 spinal nerves of SNL rats were much brighter, and hypointensive areas were observed at the approximate site of ligation (Figure 6). After these rats were terminally perfused, histology of harvested spinal nerves confirmed the presence of iron in injured nerves only (Figure 7). This result suggests that MR signal increase in left L5 spinal nerves of SNL rats is due to ligation and that surgical removal of the left L5 spinus process or the L5 laminar bone did not damage nerves. Moreover, it suggests that only injured nerve tissues would cleave and absorb sufficient MMP-12-targeted IONPs, to cause MR signal decrease.

MMP-12 is implicated in several inflammatory, vascular, and neurological disease pathogenesis [32]. This self-activating enzyme exacerbates inflammation, by activating pro-MMP-2 and pro-MMP-3. These enzymes then activate other MMPs, leading to the degradation of a several ECM proteins [33]. By degrading the ECM, MMP-12 enables macrophage infiltration into injured tissues, for tissue debris phagocytosis. This is an important process in Wallerian degeneration, which occurs before nerve regeneration can begin [34]. In rodent models of sciatic nerve injury, MMP-12 gene and protein levels are elevated [21, 35, 36]. Similarly, we studied MMP-12 protein expression and enzymatic activity in another model of neuropathic pain. We found that elevated MMP-12 in ligated left L5 spinal nerves is associated with macrophage infiltration, ECM degradation, mechanical allodynia, and thermal hyperalgesia. Thus, this model was aptly used for *in vivo* evaluation of the synthesised MMP-12-targeted magnetic IONP.

MMP-targeted probes for *in vivo* imaging of other inflammatory diseases have been developed too. MMPs are well-known biomarkers for cancer, so MMP-targeted magnetic nanoparticles hold promise for enhanced MRI of malignant cell lines and tumour-bearing murine models [37–40]. Apart from injured peripheral nerves, MMP-12 activity upregulation occurs in hind paws of mice with collagen-induced arthritis. This was detected by near-infrared optical imaging, using an MMP-12-selective Forster resonance

energy transfer probe [41]. MMP-12 is also a promising target for treatment, as local administration of its selective inhibitor reduces mechanical allodynia and thermal hyperalgesia, a week after partial sciatic nerve ligation [36]. Hence, MMP-targeted molecular probes are valuable tools to improve imaging techniques. They may potentially be used for nerve lesion detection and management, as well as drug development for neuropathic pain.

IONP-based MRI is a feasible technique for clinical use. Some IONPs have been approved as MRI contrast agents, and research on other experimental IONPs is mounting. While MMP-targeted IOPNs have been tested on several disease models, they require further development to increase MR signal detection sensitivity [42]. One means of improving reliability is by developing multitargeted probes. The targeting efficiency of IONPs in injured peripheral nerves may be raised by constructing IONPs that can be cleaved by other upregulated MMPs, namely, MMP-9 and MMP-7 [21]. Other proteins with increased expression in injured nerves include aquaporin-4, interleukin 1 receptor-like 1, and periaxin, which may be detected by antibody-conjugated IOPNs [43].

This is the first study to develop an MMP-targeted nanoprobe for enhanced *in vivo* MRI in a neuropathic pain model, albeit with limitations. To be of clinical utility, contrast agents should ideally be systemically administered. However, developing IONPs suitable for intravenous administration remains a challenge. Biological barriers and interaction with blood proteins limit the amount of systemically circulating IONPs that reach target tissues [19]. To achieve sufficient biodistribution at the lumbar spinal nerves, a large volume of the magnetic particle would have to be injected intravenously. However, this was beyond the scope of the current study. Due to the difficulties of generating the left L5 SNL model [23], sample sizes are small and control experiments using nontargeted IONPs were not done.

4. Conclusions

MMP-12 expression is elevated in ligated spinal nerves of a neuropathic pain animal model. Furthermore, MMP-12 is a potential target enzyme for IONP-enhanced MRI of injured spinal nerves.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors have no conflicts of interest to declare with this work or its submission for publication.

Authors' Contributions

Syeda Fabeha Husain and Raymond W. M. Lam contributed equally to this work.

Acknowledgments

The authors would like to thank the Advanced Molecular Pathology Laboratory at the Institute of Molecular and Cell Biology, A ∗ STAR, Singapore, for preparing the paraffin-embedded specimens. The authors also thank the Clinical Imaging Research Centre at the National University of Singapore for their assistance during *in vivo* MRI. This work was supported by the National Medical Research Council, Singapore.

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Hindawi
Pain Research and Management
Volume 2019, Article ID 9758273, 5 pages
https://doi.org/10.1155/2019/9758273

Research Article

Differences in Nonspecific Low Back Pain between Young Adult Females with and without Lumbar Scoliosis

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Received 14 June 2018; Revised 16 November 2018; Accepted 9 December 2018; Published 3 March 2019

Guest Editor: Baogan Peng

Study design. Retrospective characterization of nonspecific low back pain (NSLBP) in young adult female patients with and without lumbar scoliosis. *Background*. There is no consensus as to whether NSLBP in scoliosis patients is related to scoliosis per se or is just a normal symptom that could happen in anyone. *Objectives*. The aim of this study was to compare the differences in NSLBP between young adult female patients with and without lumbar scoliosis and to provide a theoretical basis for differential treatment of NSLBP in patients with and without lumbar scoliosis. *Methods*. Ninety female young adults with NSLBP were divided into scoliosis and nonscoliosis groups. Characteristics of pain, lumbar mobility, muscle strength, Cobb angle, axial trunk rotation (ATR) angle, and surface electromyography (SEMG) signal were compared between the two groups. *Results*. The pain location in scoliotic patients was more concentrated on the left side of the lumbar spine ($P \leq 0.001$). The area affected by pain ($P = 0.028$) and the numerical pain rating scale (NPRS) scores ($P = 0.014$) of scoliotic patients were less than those of nonscoliotic patients. The difference between side-bending in scoliotic patients was greater than that in nonscoliotic patients ($P = 0.001$). Scoliotic patients exhibited a significantly better ability for flexion ($P = 0.001$) and extension ($P = 0.017$) than nonscoliotic patients. The posterior muscles in scoliotic patients were stronger than those in nonscoliotic patients ($P = 0.014$). The ratio of root-mean-square (RMS) on paraspinal muscles in scoliotic patients was greater than that in nonscoliotic patients ($P \leq 0.001$). Scoliotic patients exhibited greater relaxation time during the flexion-relaxation phenomenon (FRP) than nonscoliotic patients ($P = 0.024$). *Conclusions*. The characteristics of NSLBP experienced by patients with lumbar scoliosis were distinct from those of NSLBP experienced by nonscoliotic patients. The treatment of NSLBP in scoliotic patients should be different from that in nonscoliotic patients.

1. Introduction

Idiopathic scoliosis is a common spine deformity. A majority of cases of idiopathic scoliosis occur in adolescents, and the disease progression is much faster and greater in adolescents; therefore, adolescent idiopathic scoliosis (AIS) has received more attention than other kinds of idiopathic scoliosis [1]. Owing to the matured skeleton and typically slow rate of disease progression, young adult idiopathic scoliosis (YAIS) has not garnered much attention, either from a clinical or a societal perspective. However, all AIS patients eventually become YAIS patients, and there will be some new cases diagnosed in young adults; therefore, the number of YAIS patients is much greater than that of AIS patients. Generally, YAIS patients with mild disease experience no functional limitation and their aesthetic appearance is also acceptable; therefore, these patients typically consult a doctor because of low back pain (LBP). Research on the relationship between scoliosis and LBP has largely been focused on adolescent people and most cases of AIS experience nonspecific low back pain (NSLBP). Studies have shown that patients with AIS have a higher prevalence of LBP and experience more severe and longer duration of pain as compared to normal controls [2–4]. However, there is no definitive evidence to suggest that scoliosis is indeed the underlying cause of NSLBP in patients with AIS or whether

the NSLBP is similar to that occurring in nonscoliotic patients [5, 6]. In this retrospective study, we sought to assess the differences between NSLBP experienced by young adult females with and without scoliosis and investigated the associated factors. Our aim was to provide a theoretical basis for a clearer understanding of NSLBP in young adult patients with scoliosis. To the best of our knowledge, this is the first study that compares the NSLBP experienced by scoliotic and nonscoliotic young adults.

2. Materials and Methods

2.1. Subjects. All patients were enrolled at the Department of Physical Therapy and Rehabilitation between January 2016 and May 2017, and were diagnosed as NSLBP by orthopedic surgeons. NSLBP has been widely described as pain or discomfort that is localised below the costal margin and above the inferior gluteal folds, with or without leg pain, but not attributable to a known or specific pathology [7]. Inclusion criteria were as follows: (1) female patients diagnosed as NSLBP by both orthopedic surgeons and rehabilitation physicians; (2) age range, 18–30 years; (3) duration of pain: 1–6 months; no history of treatment (physical or pharmacological); (4) patients with idiopathic scoliosis only had a lumbar curve (apex located between L2 and L4), and the Cobb angle was >10°. The exclusion criteria were as follows: (1) LBP caused by any specific reason; (2) history of spine surgery or injury; and (3) patients with intellectual disability and those unable to understand the instructions. A total of 41 patients with scoliosis suffering from NSLBP (mean age: 24.95 ± 2.90 years; mean height: 162.41 ± 3.82 cm; mean body weight: 55.12 ± 7.41 kg) and 49 nonscoliotic patients with NSLBP (mean age: 24.73 ± 2.83 years; mean height: 162.85 ± 3.72 cm; mean body weight: 55.64 ± 6.42 kg) qualified the study selection criteria and were recruited in the study.

There were no significant differences between the two groups with respect to baseline characteristics (Table 1). All patients with scoliosis had undergone radiographic imaging and standard evaluation. The Institution Review Board of the Peking Union Medical Hospital has approved the study and the consent form.

Table 1: Descriptive analysis of the characteristic of subjects in the two groups in this study (SD, standard deviation).

	Scoliosis group	Nonscoliosis group	*P* value	*t* value
Age (years)	24.95 ± 2.90	24.73 ± 2.83	0.721	−0.358
Height (standing) (m)	162.41 ± 3.82	162.85 ± 3.72	0.578	−0.558
Weight (kg)	55.12 ± 7.41	55.64 ± 6.42	0.722	0.357
BMI (kg/m^2)	20.78 ± 2.66	21.13 ± 2.67	0.538	0.618

2.2. Evaluation and Procedure

2.2.1. Description of Low Back Pain. All subjects were asked to answer the following four questions. First question, where is the location of the pain exactly? The response options were as follows: (1) left side of the lumbar spine; (2) right side of the lumbar spine; (3) middle of the lumbar spine; and (4) both sides of the lumbar spine. Second question, how many square centimeters (cm^2) of the painful area? The response options were as follows: (1) <5 cm^2; (2) 5–10 cm^2; and (3) >10 cm^2. Third question, how severe is the pain? The subjects were asked to rate the intensity of symptoms on 10-point numerical pain rating scale (NPRS), where 0 indicated no pain and 10 indicated the maximum imaginable pain [8]. Fourth question, does the pain happen suddenly or slowly at the very beginning? The response options were as follows: (1) sudden onset and (2) slow onset.

2.2.2. Mobility of the Lumbar Spine. A physical therapist (PT) evaluated the mobility of the lumbar spine in three planes. (1) In the frontal plane, the subject was made to stand straight against the wall and asked to bend towards the left and right sides to the maximum possible extent. The distance from the middle fingertip to the floor in both standing and the bended position were recorded. The difference between the distance in the standing and side bended position denoted the ability of side-bending. (2) In the sagittal plane, the subject assumed the prone position and pushed her upper body up slowly with her arms, while the PT held her sacrum; the subject was asked to stop moving at the point when the PT felt lifting of her sacrum. The distance of the jugular notch from the bed was recorded to denote the extent of extension. The distance from the middle fingertip to the feet in sit-and-reach was recorded to denote the extent of flexion. (3) In the horizontal plane, the subject held the gymnastics rod on her shoulders and rotated her trunk to both the left and the right side without moving her buttocks in the sitting position. The angle of the rotation of the gymnastics rob was recorded to denote the angle of left and right rotation.

2.2.3. Strength of the Core Muscles around the Lumbar Spine. The strength of the anterior and posterior muscles of the lumbar spine was evaluated by a PT. The subject lifted her legs in the supine position, held the thigh at an angle of 45° to the ground, and the calf kept parallel to the ground. The duration of time was recorded to denote the strength of the anterior muscles of the lumbar spine. Subject was asked to undergo a body weight-dependent isometric back extension test (Sorensen Test, ST) whilst lying on a bed [9]. The time duration was recorded to denote the strength of the posterior muscles of the lumbar spine.

2.2.4. Cobb Angle. The Cobb angle was measured from the anterior-posterior X-rays by recording the angle between the upper and lower most-tilted end vertebra by a spine specialist orthopedist (>20 years experience in scoliosis operative treatment) and a PT (>5 years experience in scoliosis conservative therapy) [10, 11]. The average Cobb angle is 26° degree and the maximum angle is 40°.

2.2.5. Axial Trunk Rotation Angle. The subject was in standing position with 30 cm distance between the feet, and the PT sat behind them. The subjects were asked to bend forward slowly until the point when the deformity of the spine was most prominent and the top of the hump was parallel to the PT's line of sight. The scoliometer was laid

across the apical spinous process and the axial trunk rotation (ATR) angle recorded.

2.2.6. Surface Electromyography. The back of the subject was exposed and cleaned with 70% alcohol to reduce skin impedance. For scoliotic patients, the PT palpated the spinous processes, identified the apical spinous process and the intervertebral space between L4 and L5, and marked the skin for placement of electrodes. Six electrodes were placed bilaterally on the marked skin over the erector spinae muscle at the corresponding apical vertebral level and with a 3 cm gap. The other six electrodes were placed bilaterally on the marked skin over the intervertebral space between L4 and L5. For nonscoliotic patients, the electrodes were placed bilaterally on the L2 and L4-L5. Surface electromyography (SEMG) signals were recorded during two movements.

(1) Extension Force. The subject assumed the sitting position with his back to the wall (distance between the back and the wall was 10–20 cm) and extended the trunk until the occiput touched the wall. At that point, the subject was asked to push the occiput against the wall with as much force as possible for 30 seconds. Values of root-mean-square (RMS; microvolt) as the SEMG signal were collected. In the upper segment (apical spinous process or L2), the greater value was the numerator, and the smaller value was the denominator. The ratio of RMS value on bilateral lumbar was used to assess the difference:

$$\text{ratio of RMS} = \frac{\text{RMS value (greater value)}}{\text{RMS value (smaller value)}}. \quad (1)$$

(2) FRP [12]. In the standing position, the subject was asked to bend over to the maximum possible extent on hearing the tone and then to maintain relaxation for 10 s. Subsequently, the subject was asked to straighten up on hearing the tone again; the entire process was performed three times. Values of RMS as the SEMG signal were collected during all the processes. In the lower segment (L4-L5), we recorded the number of times the average RMS value was smaller than 5 mV in the stooped position.

2.3. Statistical Analysis. All statistical analyses were conducted using SPSS (version 19.0) software (SPSS, Chicago, IL). The data were analyzed using the chi-squared test, analysis of variance, Student's t-test, Spearman correlation coefficient, and linear regression. $P < 0.05$ was considered indicative of statistical significance.

3. Results

The distribution of pain in scoliotic patients was largely unilateral. In the scoliosis group, 32 patients had left-sided lumbar pain and 9 patients had right-sided lumbar pain; and 78% of scoliotic subjects had pain on the convex side. In contrast, 83.7% subjects in the nonscoliosis group had midline or symmetrical pain. The painful area in scoliotic patients was smaller than that in the nonscoliotic patients. Nonscoliotic patients had higher NPRS scores than scoliotic patients (Table 2).

Table 2: Descriptive statistics of description of the low back pain in two groups.

	Scoliosis group	Nonscoliosis group	P value	Z value
Pain location	1 (1, 2.5)	3 (3, 4)	≤0.001*	−4.316
Painful area	2 (2, 2)	2 (2, 3)	0.028*	−2.400
NPRS	3.5 (2.5, 6.0)	5.5 (3.5, 7.5)	0.014*	−2.443
Pain onset	2 (1, 2)	1 (1, 2)	0.181	−1.604

*Difference between two groups is significant, $P < 0.05$.

The extent of side-bending in the scoliosis group was significantly greater than that in the nonscoliosis group. The extent of flexion and extension in the scoliosis group were significantly greater than that in the nonscoliosis group. Other movements of the lumbar spine were comparable between the two groups (Table 3).

The posterior muscles in scoliotic patients were significantly stronger than those in nonscoliotic patients. No significant between-group difference was observed with respect to the strength of anterior muscles (Table 4).

Scoliotic patients showed significantly greater Cobb angle and ATR angle as compared to nonscoliotic patients (Table 5).

The ratio of RMS value on bilateral lumbar in scoliotic patients was significantly greater than that in nonscoliotic patients. Scoliotic patients showed significantly greater relaxation times in TFRP than in nonscoliotic patients (Table 6).

4. Discussion

NSLBP and idiopathic scoliosis are two diseases with unclear etiology; currently, the two conditions can only be distinguished based on symptoms and clinical evaluation. Contrary to the findings reported by Gremeaux et al. and Jackson et al. [13, 14], patients with scoliosis showed lesser severity of pain in the present study. The study by Gremeaux et al. found no significant difference between scoliotic and nonscoliotic patients with regard to pain severity. In the study by Jackson et al., pain severity was greater in scoliotic patients. In the present study, most patients in the scoliosis group had unilateral pain especially on the convex side of the lumbar curve, which is different from the results reported by Joncas et al. [15]. These differences could be attributable to different age profile of the study population. The average age of subjects in these studies was >50 years, while the average age of subjects in the present study was 24 years. Younger subjects are less affected by age-related degenerative changes. It is likely that the pain was more closely associated with the scoliosis at the very beginning; with increase in age, the patients gradually experienced pain from NSLBP. With further progression of age, scoliotic patients experience pain due to both scoliosis and NSLBP; therefore, the pain severity was even greater than that in the control group. The location of pain on the convex side is not just because of the uneven biomechanics caused by vertebral deviation and rotation but may also be related to psychological factors [16, 17]. Most

Table 3: Mobility of the lumbar spine in 3 planes in two groups.

	Scoliosis group	Nonscoliosis group	P value	t/Z value
Left side-bending (cm)	17.73 ± 3.91	17.47 ± 3.67	0.744	−0.328
Right side-bending (cm)	19.41 ± 3.85	18.55 ± 3.56	0.273	−1.013
Difference between side-bending (cm)	3 (1, 5)	1 (1, 2)	0.001*	−3.329
Left rotation (°)	57.20 ± 16.43	55.00 ± 18.54	0.558	−0.589
Right rotation (°)	61.95 ± 14.31	57.22 ± 17.82	0.175	−1.368
Difference between rotation (°)	5 (0, 10)	5 (0, 5)	0.103	−1.629
Flexion (cm)	5 (0, 15)	0 (−12.5, 6)	0.001*	−3.462
Extension (cm)	18.22 ± 3.34	16.39 ± 3.76	0.017*	−2.423

*Difference between two groups is significant, $P < 0.05$.

Table 4: Descriptive statistics of strength of the core muscles around the lumbar spine in both groups.

	Scoliosis group	Nonscoliosis group	P value	Z value
Anterior muscle(s)	60 (41, 69)	41 (36, 70)	0.340	−0.955
Posterior muscle(s)	74 (48, 154)	64 (35, 75)	0.014*	−2.469

*Difference between two groups is significant, $P < 0.05$.

Table 5: Descriptive statistics of Cobb angle and ATR angle in two groups.

	Scoliosis group	Nonscoliosis group	P value	Z value
Cobb angle (°)	26 (20, 30)	1 (0, 5)	≤0.001*	−5.508
ATR angle (°)	8 (7, 9)	2 (0, 2)	≤0.001*	−5.555

*Difference between two groups is significant, $P < 0.05$.

Table 6: SEMG activities in two groups.

	Scoliosis group	Nonscoliosis group	P value	t/Z value
Ratio of RMS	1.59 ± 0.44	1.24 ± 0.40	≤0.001*	3.956
Times of FERP	3 (1.5, 3)	2 (0, 3)	0.024*	−2.225

*Difference between two groups is significant, $P < 0.05$.

female young adults with scoliosis attach importance to the aesthetic aspects; therefore, the presence of a hump on the lower back is likely to induce regional pain due to psychological reasons.

In the present study, scoliotic patients exhibited uneven side-bending which is different from the results reported by Veldhuizen and Scholten [18]. From a biomechanical perspective, patients with a left lumbar curve experience restriction of bending towards the left side. However, the left lumbar curve is likely to induce trunk deviation to the left side, which facilitates bending towards the left side. This represents a natural compensatory mechanism. Therefore, in the study by Veldhuizen et al., there was no difference between the extent of bending on the two sides. However, the presence of pain, especially unilateral pain, serves to further exaggerate the uneven side-bending. Studies by Hultman et al. [19] and Taechasubamorn et al. [20] showed that patients with low back pain have significantly lesser sagittal flexibility and endurance of back extensors than healthy people. In this study, patients in the scoliosis group showed significantly greater sagittal flexibility and endurance of back extensor muscles as compared to patients in the nonscoliosis group. This suggests that the NSLBP in nonscoliotic patients caused significantly greater disability than in scoliotic patients. In other words, scoliotic patients showed a less stronger relationship with the restricted flexibility and weak muscle strength.

RMS is the time threshold indicator of SEMG; it was shown to reflect the functional capacity of the muscles and was linked to neuromuscular efficiency [21]. In the present study, the RMS value on the convex side of the apical vertebral region was greater than that on the concave side, which is consistent with the results of previous studies [22–25]. During isometric contraction of homologous muscles under the same load, atrophic muscles were shown to produce greater RMS values than fatigued muscles, and fatigued muscles produced greater RMS values than trained muscles [26]. In patients with scoliosis, the convex side muscles generated greater RMS value than the concave side; therefore, we predict that the convex side muscles were weaker than those on the concave side and that the uneven functional capacity of paraspinal muscles was one of the reasons why a significant proportion of patients in the scoliosis group had unilateral pain. FRP was commonly observed in healthy subjects. In contrast, few patients with low back pain demonstrated FRP [27]. In this study, FRP in nonscoliotic patients with NSLBP was less commonly observed than that in scoliotic patients with NSLBP. These findings imply that the FRP in scoliotic patients with NSLBP was more akin to that in healthy subjects.

In conclusion, irrespective of the pain description or pain-related parameters, NSLBP in young adult females with scoliosis is not the same as that in nonscoliotic patients. These findings suggest that the treatment of NSLBP in scoliotic patients should be different from that in nonscoliotic patients.

Data Availability

The data used to support the findings of this study are restricted by the Institution Review Board of Peking Union Medical College Hospital in order to protect patient privacy.

Data are available from Yuan Wangshu (ywsartemis@126.com) for researchers who meet the criteria for access to confidential data.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Hindawi
Pain Research and Management
Volume 2019, Article ID 3126464, 12 pages
https://doi.org/10.1155/2019/3126464

Review Article

Optimizing the Management and Outcomes of Failed Back Surgery Syndrome: A Consensus Statement on Definition and Outlines for Patient Assessment

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Received 19 October 2018; Revised 18 December 2018; Accepted 26 January 2019; Published 18 February 2019

Guest Editor: Baogan Peng

Failed back surgery syndrome (FBSS) is a controversial term for identifying patients affected by new, recurrent, or persistent pain in the low back and/or legs following spinal surgery. The lack of a comprehensive standardized care pathway compromises the appropriate management of FBSS patients, which is associated with a heavy financial burden. An international panel of spine surgeons, neurosurgeons, and pain specialists with a particular interest in FBSS established the chronic back and leg pain (CBLP) network with the aim of addressing the challenges and barriers in the clinical management of FBSS patients by building a common transdisciplinary vision. Based on literature reviews, additional input from clinical expertise of multiple professional disciplines, and consensus among its members, the network attempted to provide recommendations on the management of patients with FBSS utilizing a multidisciplinary team (MDT) approach. The presentation of this work has been divided in two separate parts to enhance its clarity. This first paper, in favour of selecting appropriate validated tools to improve the FBSS patient assessment, focuses on FBSS taxonomy and its clinical implications for evaluation. Concise recommendations for assessment, treatment, and outcome evaluation using a MDT approach would be an important resource for specialists and nonspecialist clinicians who manage patients with FBSS, to improve decision-making, reduce variation in practice, and optimize treatment outcomes in this difficult-to-treat population.

1. Introduction

Failed back surgery syndrome (FBSS) is a subcategory of a broader group of pain conditions referred to as chronic back and leg pain (CBLP) [1]. The majority of published definitions for FBSS include new, recurrent, or persistent pain in the back and/or legs following spinal surgery [2–8], with an incidence estimated to be around 20% in the most recent publications on this topic [9, 10]. This is a complex condition with a complicated pathophysiology comprising various aetiologies and pain characteristics that negatively impact function, behaviour, and mental and social well-being [1, 5, 11, 12].

Use of the term FBSS has provoked decades of controversy because of a lack of consensus for a single definition and the inherently restrictive and confusing meaning of this

acronym, implying unsuccessful treatment with connotations of blame aimed towards the surgery [12]. A diverse nomenclature has consequently been developed over the last three decades. "Postlaminectomy syndrome" [2, 13], "rebound radicular syndrome" [14], "postoperative persistent pain syndrome" [5], and "chronic postsurgical pain" [15] have been proposed as replacements for FBSS.

The complexity of FBSS suggests that a multidisciplinary strategy to patient assessment, treatment, and therapy evaluation is important for optimization of outcomes [16–19], but no consensus has been clearly defined yet. An international panel of clinicians with a special interest in FBSS established the chronic back and leg pain (CBLP) network and set a list of precise objectives to bridge this gap. The purpose of this paper is to (i) delineate a clear definition of FBSS and specify the criteria for appropriate diagnosis and (ii) suggest recommended treatment evaluation tools to validate and standardize a care pathway for this patient group.

2. Materials and Methods

2.1. The Chronic Back and Leg Pain Network Constitution and Goals. To address the challenges and barriers in the management of patients diagnosed with FBSS, an international panel of clinical specialists with a specific interest in FBSS established the CBLP network in 2012.

The main goals of the network were to provide consensus on (1) a definition of FBSS, (2) recommendations for validated tools to improve FBSS patient assessment and evaluation of treatment outcomes, and (3) a proposal for a standardized care pathway to support clinicians in their decision-making on how to manage patients with FBSS based on a MDT approach.

Since FBSS remains a standardized subjective term assigned by indexers for both MeSH (MEDLINE/PubMed) and EMTREE (Embase) and since the proposition of a replacement term was not an objective of this paper, the CBLP network focused specifically on the definition of FBSS and patient evaluation and treatment.

2.2. Methodology. In order to achieve the set goals, the following methodology was used:

(a) Participants in the CBLP panel were included based on their extensive clinical experience in managing FBSS patients with a focus on representation from the three specialties that are most involved in the treatment of this patient population: spine surgeons, neurosurgeons, and pain specialists, including anesthesiologists. Invitations were sent to potential participants and accepted prior to formal engagement. Formal face-to-face meetings were held annually between 2012 and 2016 with subsequent teleconferences for an additional feedback prior to drafting the manuscript. The meetings were chaired by a trained facilitator to help the consensus process.

(b) Literature searches in PubMed, MEDLINE, LILACS, Embase, and the National Guideline Clearing House were conducted by two separate reviewers: one independent reviewer (GB) and one reviewer on the behalf of the clinical group (NN), on a regular basis up to September 2018, without any restrictions regarding language or year of publication. The search strategy was developed in order to maximise sensitivity of article identification, using controlled vocabulary and title/abstract words combining variations of "Failed back surgery syndrome," "Back pain," "Chronic leg pain" with "Multidisciplinary" OR "Team," "Clinical pathway" OR "Practice guideline" OR "Algorithm" OR "Guideline" OR "Protocol," detailed here after. The independent reviewer (GB) performed a comprehensive electronic search of peer-reviewed full-text papers published between February 2, 2005, and February 21, 2018, in PubMed, MedLine, Embase, and the National Guideline Clearing House. Key words and terms pertaining to the condition (i.e., "failed back surgery syndrome," "low back pain," and "leg pain") were cross referenced with terms pertaining to reports presenting recommendations for MDT involvement in management (i.e., "interdisciplinary communication," "multidisciplinary" OR "multidisciplinary team" OR "multidisciplinary care" OR "patient referral") in relevant combinations. Handsearching of reference lists of identified reports and relevant review articles were also carried out. For the group reviewer (NN), the search strategy varied according to the database as follows:

(i) *Medline* ("Failed back surgery syndrome" OR "Chronic Back pain" OR "Chronic leg pain") AND ("Definition" OR "Characterisation" OR "Characterization" OR "Evaluation")
(ii) *LILACS* ("Failed back surgery syndrome" OR "Back pain") AND ("Definition")

All references retrieved from databases were exported to Zotero where duplicates were discarded using the "find duplicates" tool.

In addition, book chapters dealing with "FBSS," "postoperative low back pain," and the same controlled vocabulary used previously were initially identified from a systematic review of the electronic literature and of all pathophysiology, anatomy, and physiology textbooks available in the following medical libraries:

(i) Paris Medical Library (Université Descartes, Paris 5, rue de l'Ecole de Médecine, 75006 Paris, Fr)
(ii) Paris Anatomy Library (Anatomy Laboratory, Université des Saints-Pères, Paris 6e, Fr)
(iii) Poitiers Anatomy Library (Department of Morphology, Poitiers Medical College, rue de la milètrie, 86000 Poitiers, Fr)
(iv) UIC Library of Health Sciences (University of Illinois at Chicago, 1912 Polk St., Chicago, US)
(v) Dorsch Neuroscience Library (Institute of Neurology and Neuropsychiatry, 712 S Wood St., Chicago, US)

The two literature searches were pooled and converged into one final diagram. The final literature review was conducted to ensure that participants had access to the same body of evidence during the panel discussions. The methodology is summarized in Figure 1.

(c) Additional input was provided by relevant clinical specialists (psychologist, psychiatrist, physiotherapist, and rehabilitation physician) involved in the multidisciplinary evaluation and treatment of patients with FBSS.

(d) Consensus was defined as full agreement among the members of the CBLP network on the set goals which was achieved by face-to-face meetings with facilitated round table discussions focusing on the outcome of the literature overview, each member's personal experience, and input from additional clinical specialists. The consensus process did not include any ranking questionnaires based on the Delphi method since the number of participants was considered to be too small and the purpose of the discussions was not to measure consensus based on specific statements but to develop full consensus (resolve disagreement) on the set tasks [20].

3. Results

3.1. Definition of FBSS. The CBLP network's proposed definition of FBSS is based on the prediction that no further spine surgery is indicated after an appropriate somatic, radiological, and psychosocial assessment [21]. The key elements for definition of FBSS can be summarized in 4 aspects:

(1) Back and/or leg pain that persists for at least six months following the most recent spinal surgery

(2) The patient has undergone a thorough clinical and radiological assessment

(3) There is no clear surgical target on clinical examination and imaging that is concordant with presenting symptoms

(4) There is interdisciplinary agreement that additional surgical intervention (decompression and/or fusion) is not appropriate

It is important to ensure that the temporal relationship between the most recent surgery and the presentation of pain is explored adequately so that complications that are known to occur within the first six months of surgery (e.g., hardware failure, recurrent herniation, and infection, including discitis and abscess) can be identified and taken care of promptly [5]. As a consequence, our definition of FBSS is found on the generally accepted definition of chronic pain in the context of surgery as "pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal" [22].

3.2. Multidisciplinary Approach in the Management of FBSS. Out of 12 pain-related guidelines or health technology assessments that were identified in the literature overview, nine recommended the practice of involving a MDT as the standard-of-care [12, 23–30]. Importantly, a previous meta-analysis of 41 randomized controlled trials (RCTs) ($N = 6{,}858$) yielded by a systematic literature review up to March 2014 revealed that a MDT approach was significantly more effective than usual care in reducing pain and disability in patients with chronic low back pain [31].

In a general statement about pain management, the International Association for the Study of Pain (IASP) recommended that, "clinicians who assess and treat patients in a pain center should include physicians, nurses, mental health professionals (e.g., clinical psychologist and psychiatrist), and physical therapists" [23]. However, many patients do not have access to a pain center, making access to a MDT challenging. To date, recommendations for the composition of a FBSS-specific MDT provided by governments and experts alike suggest the involvement of a neurologist, a rheumatologist, a pain physician, a spine surgeon, a neurospine surgeon, a functional neurosurgeon, a rehabilitation physician, a radiologist, a physiatrist, a pain nurse, and a psychologist/psychiatrist [12, 17, 24].

Based on the literature review (Table 1), additional specialist input and consensus among its members, the CBLP network recommends that a FBSS-oriented MDT should include five types of health professionals, reflecting the continuum of the FBSS patient care pathway:

(i) One or several "pain physician(s)" (i.e., anaesthetist, rheumatologist, and neurologist) representing the cornerstone of professional interactions for the assessment and treatment of pain, focusing on optimizing medical and interventional management within the FBSS care pathway

(ii) One or several rehabilitation physicians, physiotherapist(s), and/or physiatrist(s) to optimize physical examination and review potential rehabilitation strategies

(iii) One or several psychologist(s) and/or psychiatrist(s) to focus on psychosocial aspects and supply ongoing psychological evaluation and support [35, 36]

(iv) One or several "spine surgeon(s)" (i.e., neurosurgeon and orthopaedic surgeon) supported by a radiologist to provide an ultimate spine expertise, making sure that no further surgery is required helping to characterize the pathophysiology of pain generators

(v) One or several member(s) of a "neuromodulation team" (i.e., implanter/anaesthesiologist/neurosurgeon and pain/neuromodulation nurse) to evaluate the eligibility for neurostimulation/intrathecal drug delivery (IDD) therapies in the context of a refractory patient

3.3. Initial MDT Evaluation. The initial stage in the proposed care pathway by the CBLP network is based on MDT evaluation to confirm the FBSS diagnosis. With a specific reference to our definition of FBSS, the clinical work-up of a patient should include the following: (a) history to confirm the occurrence of prior spinal surgeries; (b) precise

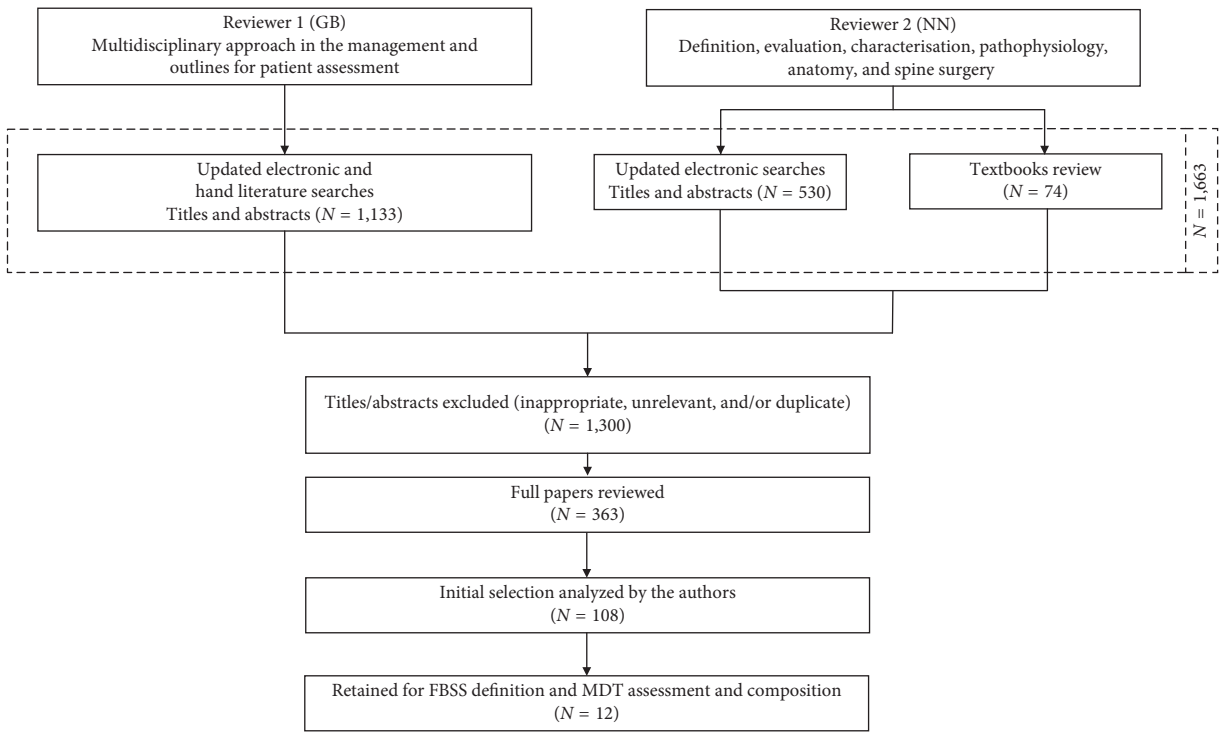

Figure 1: Schematic diagram of steps in the literatures searches: FBSS definition and evaluation. The electronic and hand literature searches yielded 1663 titles and 74 textbooks. Following a review of full-text versions of the 363 residual publications, after discarding duplicates and initial exclusion of 1300 titles/abstracts, 108 papers were finally selected, and 12 were retained for FBSS definition and MDT assessment and composition (Supplementary Material 1).

Table 1: Output of the review of publications with recommendations for specialties to be included in the multidisciplinary team management of failed back surgery syndrome.

Manuscript identification	Design	Management: specialities
Amirdelfan et al. [32]	Evidence-based approach—literature review (guideline)	Physiotherapist Psychologist Interventional pain physician Neurosurgeon trained to implant neuromodulation options
Al Kaisy et al. [12]	Expert consensus (algorithm)	Neurologist Rheumatologist Oncologist Pain physician Psychiatrist Rehabilitation physician Functional neurosurgeon Physiotherapist/physiatrist Psychologist Spine surgeon
Baber and Erdek [18]	Discussion of the literature	Physical therapist Psychologist Pain specialist Spine surgeon Primary care provider
Chan and Peng [8]	Expert consensus	Psychologist Occupational therapist Spine surgeon Physiotherapy
Desai et al. [33]	Literature review	Psychologist Physiotherapist Medical (not defined further)

Table 1: Continued.

Manuscript identification	Design	Management: specialities
Ganty and Sharma [34]	Expert consensus (algorithm)	Pain physician Psychologist Physiotherapist Neuromodulation nurse Spine surgery General physician
Hussain and Erdek [16]	Expert consensus	Physiotherapist Psychologist
Rigoard et al. [5]	Expert consensus	Pain physician Anesthesiologist Surgeon

physical examination; (c) carefully chosen diagnostic tools to assess pain severity and functional incapacity; (d) psychosocial evaluation; (e) appropriate diagnostic radiological assessment.

3.3.1. Pain History. The pain history must be carefully reviewed and pay specific attention to the following items:

(i) New pain, persistent pain, and/or recurrent pain? (if yes, free interval needs to be quantified)

(ii) Circumstances, positions, and movements that improve or exacerbate the symptoms [17]

(iii) Any clinical sign that might be suspicious of underlying infection, neoplasm, and fracture, called "red flag" by the COST B13 group in available European guidelines [37]

3.3.2. Physical Examination. It remains difficult to transpose a "mechanistic" concept based on pathophysiological evaluation of pain into daily practice. Nevertheless, this approach plays a critical role to better understand FBSS management. Several authors have tried to identify, from all of the findings of spine examination, those clinical signs that are predictive of a particular type of lesion (facet joint and discogenic or muscle pain, for example), taking into account pain typology (mechanical/neuropathic) [5]. This type of pathophysiological segmentation might be used to predict the quality and the magnitude of response to the various treatments proposed (classical response to opioids in nociceptive pain and efficacy of antiepileptic drugs or neurostimulation in neuropathic pain, for example). An emphasis on the spatial dimension concerning the topographic distribution of the pain should be incorporated into the concept of pathophysiological pain characterization. Thus, chronic leg pain persisting despite a surgical decompression might be frequently associated to a neuropathic pain component, while the pain characterization becomes much more complex when trying to interpret axial pain, where biomechanical and neuropathic components appear to be inseparable or difficult to isolate [1]. Even though promoting strict dichotomy between the leg pain and the back pain components might be artificial, this clinical strategy can nevertheless guide the physician in the clinical evaluation.

(1) The Leg Pain Component. The first step of leg pain clinical examination aims to confirm a radicular lesion mainly indicative of neuropathic pain and to eliminate pain due to another cause. The presence of sensory dysfunction (hypoesthesia, anesthesia, or allodynia) in the painful territory and/or motor deficit is suggestive of a nerve lesion and thus a neuropathic pain. Several diagnostic tools have been validated for neuropathic pain detection: DN4 (Douleur Neuropathique in 4 questions), LANSS (Leeds assessment of neuropathic symptoms and signs), or S-LANSS (simplified version) [38, 39]. The DN4 questionnaire, published in 2005, is easy to use in daily practice. It is composed of four questions comprising a total of seven items scored during the clinical interview and three items based on physical examination [38]. A score greater than or equal to 4/10 is pathognomonic of neuropathic pain with a sensitivity of 82.9% and a specificity of 89.9%. Shamji and Shcharinsky [40] recently stated that a positive DN4 questionnaire is a powerful predictor of spine (re)surgery failure. The presence of mechanical signs of disc-nerve root conflict (impulse pain, Lasègue's sign) suggests a physical conflict at the level of the disc (disc herniation recurrence and residual conflicting elements) or at the level of the foramen (foraminal stenosis and segmental spine instability) [17] and requires a specific spine expertise. Hip, knee, and sacroiliac joints examination are important to avoid the classical diagnostic traps associated with pain of the anterior surface of the thigh or trunked S1 sciatica. A vascular examination has to be performed in case of intermittent claudication on walking. A careful palpation of the sciatic trunk eliminates a neurinoma and a piriformis syndrome at the gluteal region.

(2) The Back Pain Component. In contrast to leg pain assessment, and before considering any potential neuropathic aspect of the back pain (first described by Attal et al. in 2011) [41], clinical investigation of the back pain component in FBSS patients should be based on meticulous dissection of all potential mechanical triggers that could be a source of the nociceptive pain characteristics [11]. Examination of the spine aims to assess the global posture and stability of the spine in the different planes. Meticulous palpation aims to identify a possible vertebral or paravertebral pain trigger point. The main focus of the back assessment is guided by a somatic diagnostic process using validated diagnostic rules [42]. The key potential spinal pain generators, which need to

be carefully reviewed, are myofascial syndrome, the facets, and the disc complex.

(i) Muscle pain: the muscle trophicity may be compromised by chronic degeneration related to the initial spine pathology, by physical hypoactivity, and by repeated surgery, leading to potential and progressive instability of the vertebral column [43]. A vicious circle can occur when biomechanical overloading (created by disease progression and/or hardware failure) causes displacements of the spine and induces new tensions. Results show increased impulse activity of muscle and tendon nociceptors establishing the neurophysiological basis of postoperative muscle pain.

(ii) Facet joint pain and spinal instability: spine surgery induces major changes in the biomechanical loads on all surrounding structures [44]: muscles, ligaments, discs, facet joints, fat tissues, and fascia. This mechanical loading redistribution occurs particularly in adjacent spinal segments, around the anterior or posterior instrumentation in case of stabilization [11]. Foraminal residual stenosis can be responsible for persistent nerve entrapment, as mentioned above: anteriorly from vertebral spurs and posteriorly from facet arthritic changes. As a consequence, patient's symptoms can be linked to facet compensation syndrome [45, 46], but isolating facets as the specific source of pain is difficult in FBSS patients.

(iii) Discogenic pain: it is predominantly described as a deep midline low back pain with a bilateral metameric irradiation. Mechanical and positional in nature, the pain is generally worse when upright rather than supine [47]. It is thought that this type of pain is generated by the visceral afferents that innervate the intervertebral disc, known as "the sinuvertebral nerve" [48].

3.3.3. Validated Tools for Assessment of Pain and Functional Parameters. In line with the adoption of a uniform MDT approach to the management of FBSS, it is important to utilize recommended validated tools to evaluate treatment outcomes in patients with pain disorders in compliance with IMMPACT recommendations [49, 50]. The aims of a standardized assessment in this context are to facilitate longitudinal patient evaluation, to increase the efficiency, clarity, and quality of patient information during the referral process and to improve dialogue between centers and disciplines in order to optimize treatment decisions. The aims of a common approach to treatment evaluation are therefore relevant to patients, clinicians, payers, and policymakers [51].

The CBLP network recognizes that treatment evaluation should involve previously issued quality standards and guidelines for documentation of outcomes including the patient's subjective assessment of pain severity, function, and health-related quality of life (HRQoL) [49, 52]. Having considered the plethora of existing tools used to evaluate these constructs from the patient's perspective, clinical experience guided the CBLP network to recommend a choice of standardized and validated instruments (Table 2).

For pain severity scales, there is a choice of the visual analogue scale (VAS) or the numeric pain rating scale (NPRS) [53–55]. To assess pain-specific disability/function, either the Oswestry Disability Index (ODI) [56] or the Roland Morris Disability Questionnaire (RMDQ) [57] is recommended. To measure generic HRQoL, either the EuroQol with five dimensions (EQ-5D) [58] or the short form 12/36 (SF-12/SF-36) [59, 60] is recommended. The shorter generic HRQoL instruments, the SF-12 and the EQ-5D, minimize patient burden. It is also recommended that clinicians continuously monitor and evaluate a patient's medication intake.

3.3.4. Psychosocial Assessment. It is well established that psychological factors affect pain perception [61] and clinical outcomes [48, 62–66]. There is no accepted gold standard approach for the psychological screening of FBSS patients. Optional questionnaires can be used to assist the psychological assessment. The most recognized questionnaire in this context is the Minnesota Multiphasic Personality Inventory 2 Restructured (MMPI-2-RF) [67–70]. The Hospital Anxiety and Depression Scale (HADS) allows detection of various states of depression (HADS-D) and anxiety (HADS-A) [71–73], and the Fear Avoidance Beliefs Questionnaire Work and Activity (FABQ) measures patient's fear of pain [74].

Coping strategies may play an important role by determining how patients cooperate with chronic symptoms and with pain management [75, 76]. The Coping Strategies Questionnaire (CSQ) is intended to measure six cognitive and two behavioural coping strategies. Active coping strategies are linked to positive effect, better psychological adjustment, and decreased depression, while passive strategies are linked to poorer outcomes such as depression and increased level of pain [65, 77, 78]. An important subscale of CSQ is catastrophizing. Based on the CSQ, Sullivan and colleagues [79] developed the Pain Catastrophizing Scale (PCS). The PCS is widely used, and elevated scores have been associated with poor treatment outcomes.

The optimization of chronic pain management requires consideration of the social factors that may contribute to people's physical and mental health [80–83]. Factors such as gender, level of education, and working status play a substantial role in pain perception and affect patient compliance and their pain management [65, 84–88]. Medical professionals trained to solve a physical/somatic problem, where there is a potential biopsychosocial comorbidity may fail to anticipate and manage the vicious circle of social exclusion. These arguments support the need for including social assessment in a MDT approach, as it affects clinical outcome in chronic pain management [89].

A proposal for a minimal psychosocial assessment toolbox is presented in Table 3.

3.3.5. Radiological Assessment. In addition to orthopaedic, neurologic, functional, and psychosocial evaluation, spine imaging is essential in order to exclude new indications for

Table 2: Validated questionnaires recommended for completion by patients to assess pain severity, function, and health-related quality of life.

(i) Pain scales
Visual analogue scale (VAS): 10 cm leg VAS and back VAS *OR* the numeric pain rating scale (NPRS) [53–55]
(ii) Pain-specific disability/function
Oswestry disability index (ODI) [56] *OR* Roland Morris disability questionnaire (RMDQ) [57]
(iii) Generic health-related quality of life
EuroQol 5 dimensions (EQ-5D) [58]
Short form 12 (SF-12) *OR* short form 36 (SF-36) [59, 60]

Table 3: Instruments to assess psychological and social well-being among patients with failed back surgery syndrome (FBSS).

	Psychological assessment	Social assessment
Recommended	Minnesota Multiphasic Personality Inventory 2 Restructured (MMPI-2-RF)	Age, gender, educational level, and working status
	The Hospital Anxiety and Depression Scale (HADS)	Social class
	The Fear Avoidance Beliefs Questionnaire Work and Activity (FABQ)	Financial incomes
	The Coping Strategies Questionnaire (CSQ)	Marital status and social withdrawal
	The Pain Catastrophizing Scale (PCS)	

reoperation: recurrent disc herniation (MRI), spine instability (CT, MRI, and bending X-ray), spine imbalance (full-standing lateral and anteroposterior X-ray), EOS® images while the patient is standing (bending X-ray), or nonunion of spinal fusion (plain X-ray, CT, scintigraphy, and positron emission tomography (PET) scan), new-onset stenosis (MRI and CT), and abscess (MRI and CT) [17, 90]. Conditions like discitis, low-grade infections, arachnoiditis, or scar tissue which usually do not require reoperation have also to be identified before being managed conservatively [18].

Following a robust MDT clinical evaluation to define and diagnose a patient with FBSS (Figure 2), a stratification and hierarchization of the various therapeutic options can be constructed through a level approach to optimize management and outcomes. A patient who either does not present with FBSS or presents with FBSS and a significant psychosocial comorbidity, determined by psychological assessment carried out by a clinical psychologist or psychiatrist (ideally with experience in the field of pain), should be excluded from the pathway and referred to the appropriate discipline(s).

4. Discussion

Use of the term FBSS has provoked decades of controversy because of a lack of consensus of a definition and the inherently restrictive and confusing meaning of this acronym. The term hides the challenges associated with selecting appropriate treatment for this patient population due to insufficient identification of the underlying mechanism of pain [4, 5]. In addition, cognitive, affective, and behavioural features of pain are often explanations of the disability as much as or more than abnormal sensory-related pain [4].

In response to the limitations of current practice in managing FBSS patients, an international panel of spine surgeons, neurosurgeons, and pain specialists with a special interest in FBSS established the CBLP network. Based on the broad personal experience of each member of the panel, through literature reviews, additional input from clinical expertise of multiple professional disciplines and consensus among its members, the CBLP network's primary intention is to provide recommendations on how to optimize the management and outcomes of FBSS.

In this paper, we focus on the key elements for defining FBSS and outline how to clinically confirm this diagnosis. The CBLP network's definition of FBSS is found on the prediction that no further spine surgery is indicated after adequate somatic, psychosocial, and radiological assessment have been executed. Management begins with a systematic evaluation of common FBSS aetiologies. Appropriate understanding and identification of the abnormalities most commonly associated with FBSS after a meticulous clinical evaluation is required for adequate caretaking of this often hard-to-treat condition [1, 4]. A growing body of data suggests that the adoption of a multidisciplinary approach is significantly more effective than usual care of patients with chronic low back pain [25, 31, 91, 92]. A MDT-based approach has the potential to improve decision-making, reduce variation in practice, and optimize treatment outcomes. Clinicians should refine pain topographical and topological pain characterization to ensure that clinical evaluation becomes the guiding principle for multidisciplinary assessment. A patient who either does not present with FBSS or presents with FBSS and significant psychosocial comorbidities should be excluded from further inclusion in FBSS care pathways or algorithms and be referred to the appropriate discipline(s).

For many aspects of medical practice, there is a lack of high-quality evidence and a plethora of contradictory information which makes decision-making difficult when trying to optimize treatment outcomes and provide concise recommendations for assessment, treatment, and outcome evaluation. When dealing with a lack of, or conflicting, scientific evidence, consensus statements are seen as a useful tool to establish expert agreement, to define the boundaries of acceptable practice and obtain opinions from different

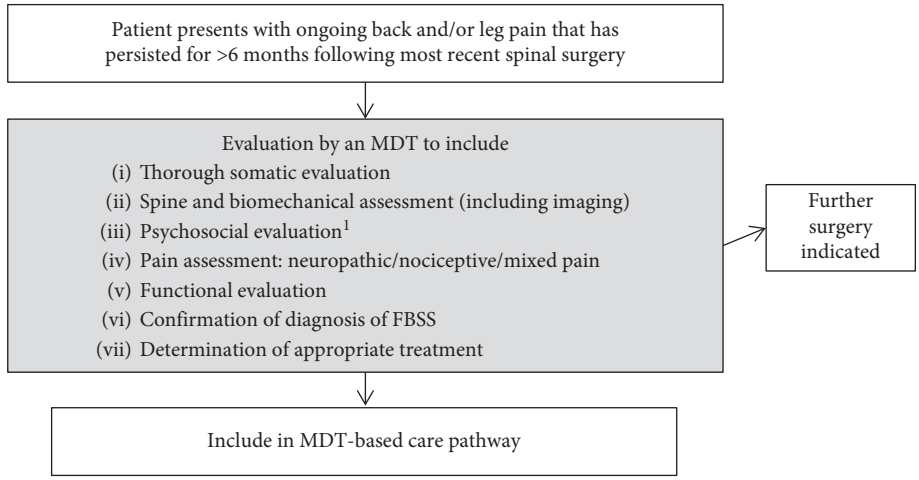

Figure 2: The initial stage of the proposed standardized multidisciplinary team failed back surgery syndrome care pathway, as recommended by the Chronic Back and Leg Pain Network. Clinical evaluation and confirmation of diagnosis. FBSS, failed back surgery syndrome; MDT, multidisciplinary team. [1]Best practice is for the psychosocial evaluation to be performed by a psychologist or psychiatrist with specific experience in the field of pain. Assessment should include the relevant tests and questionnaires that are able to identify patients with major psychological or psychiatric contraindications (Table 3).

countries and healthcare systems [20, 93]. Due to the paucity of evidence-based guidelines in the management of FBSS, the CBLP network chose to adhere to a consensus-based approach to achieve the set goals to define FBSS, design outlines for appropriate patient evaluation, and propose a treatment pathway. One limitation of the chosen method to achieve consensus in the present study is that it was based on round table discussions without involvement of ranking procedures that are used in the two most commonly utilized methods to reach consensus: the Delphi process and the nominal group technique [20]. Although not optimal, we consider the method we adopted to be appropriate based on the complexity of the set tasks which do not fit easily within an evidence-based treatment paradigm. Since personal contact with facilitated discussions among the network members was considered desirable, the Delphi method, the reliability of which rests on anonymity and increases with the size of the group, was not used [94].

5. Conclusions

The complexity of FBSS suggests that a multidisciplinary strategy is most appropriate for patient assessment with the goal to optimize outcomes. This paper focuses on redefining FBSS taxonomy and clinical evaluation in order to improve patient assessment before adequate treatment options can be chosen. It is important for physicians and other healthcare professionals involved in the management of patients with FBSS to expand their knowledge of underlying aetiologies and use of appropriate diagnostic tools to adequately evaluate this difficult-to-treat group affected with chronic pain. In a second paper, a stratification and hierarchization of the various therapeutic options is constructed through a 4 level-approach with a proposal for a standardized treatment pathway for FBSS. The utilization of a MDT approach is emphasized to ensure that care is provided in a uniform manner for optimizing management and ultimately patient outcomes.

Disclosure

The funder did not provide input into the discussions or the consensus. Medtronic manufactures devices indicated for failed back surgery syndrome and may therefore gain from the implementation of the pathway described in this article.

Conflicts of Interest

Philippe Rigoard, Kliment Gatzinsky, Jean-Philippe Deneuville, Wim Duyvendak, Nicolas Naiditch, Jean-Pierre Van Buyten, and Sam Eldabe treat patients with failed back surgery syndrome in the private an/or the public healthcare sectors and therefore may gain from the implementation of the pathway. Philippe Rigoard, Kliment Gatzinsky, Wim Duyvendak, Jean-Pierre Van Buyten, and Sam Eldabe were reimbursed for travel to Chronic Back and Leg Pain Network meetings and received honoraria for Chronic Back and Leg Pain Network meeting participation from Medtronic Inc., and may therefore have a preexisting relationship with Medtronic, the Funder, and may be influenced by beliefs associated with treatments recommended in the pathway. Philippe Rigoard, Kliment Gatzinsky, Sam Eldabe, and Wim Duyvendak have served as consultants to Medtronic Inc., and Boston Scientific and may therefore have a preexisting relationship with them and be influenced by beliefs associated with treatments recommended in the pathway. Kliment Gatzinsky and Sam Eldabe have served as consultants to Abbott and may therefore have a preexisting relationship with them and be influenced by beliefs associated with treatments recommended in the pathway. Sam Eldabe has served as a consultant to Mainstay Medical and may have a preexisting relationship with them and be influenced by beliefs associated with treatments recommended in the pathway. Philippe Rigoard, Wim Duyvendak, and Sam Eldabe have received research funding from Medtronic Inc., and may be influenced by beliefs

associated with treatments recommended in the pathway. Philippe Rigoard and Wim Duyvendak have received research funding from Boston Scientific and Abbott and may be influenced by beliefs associated with treatments recommended in the pathway. Sam Eldabe has received research funding from Nevro and may be influenced by beliefs associated with treatments recommended in the pathway. Nicolas Naiditch and Jean-Philippe Deneuville declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The authors thank Gillian Barnett of Gillian Barnett and Associates Limited for support in manuscript preparation and literature review. Medtronic provided sponsorship and logistical support in the form of meeting services and project coordination.

Supplementary Materials

Supplementary Material 1 (with a reference list) presents a description of the 12 reports yielded by literature searches relating to recommendations for the management of failed back surgery syndrome involving multidisciplinary teams. (*Supplementary Materials*)

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Hindawi
Pain Research and Management
Volume 2019, Article ID 9161906, 4 pages
https://doi.org/10.1155/2019/9161906

Research Article

Pain Clinic in Tibet, China: A Single-Center Retrospective Study

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Received 19 October 2018; Revised 20 November 2018; Accepted 29 November 2018; Published 14 January 2019

Guest Editor: Baogan Peng

Pain disease is a worldwide problem.The prevalence of chronic pain in developed and developing countries has been reported in some published research. However, little knowledge of situation of pain clinic in Tibet is known. Tibet Autonomous Region People's Hospital established the first pain clinic in Tibet. This study collected and analyzed the data of medical records of pain clinic in Tibet Autonomous Region People's Hospital from September 2017 to August 2018. The results showed that the total amounts of patients visiting pain clinic were very small, the most common pain diseases were postherpetic neuralgia and sciatica, and more female patients visited the pain clinic than male patients. All these results indicate that the hospital and government need to pay more attention to the development and promotion of pain medicine in Tibet to make Tibetans being accessed to high-quality pain clinic service.

1. Introduction

Chronic pain is a worldwide problem, which creates huge burden on patients and society. The prevalence of chronic pain in Europe, America, and Australia is 12%–30%, 11%, and 17.1%–20%, respectively [1–3]. In China, some similar studies had been performed in recent years. Zhang et al. did a cross-sectional study between the prevalence of chronic pain and academic pressure in adolescents in Shanghai, and the results showed that the prevalence of headache, abdominal pain, neck and shoulder pain, and low back pain was 30.3%, 20.9%, 32.8%, and 41.1%, respectively, which indicated that the high-school students were experiencing huge academic pressure [4]. Jackson et al. designed a study to assess the prevalence of chronic pain among adults in Chongqing. Their investigation found that 25.8% interviewees suffered from chronic pain [5]. In the Chaoyang district of Beijing, the prevalence of chronic pain was 52.99% [6], much higher than the data mentioned above. However, little is known about the epidemiology of pain diseases in some special area, for example, Qinghai-Tibet plateau of China.

The Qinghai-Tibet plateau of China is a plateau region with an average elevation of 3,000 meters above the sea level, and it is the highest region on earth. For Tibet Autonomous Region (TAR), China, it occupies 1.23 million square kilometers with a population of about 3.3 million. According to the worldwide data, there might be at least 350,000 chronic pain patients in TAR. However, altogether about 150 anesthesia practitioners, including anesthesiologist and nurse anesthetists, are providing anesthesia and pain medical services in Tibet Autonomous Region now. So, the diagnosis and management of chronic had been underestimated or ignored for years.

On September 28, 2017, the first pain clinic of Tibet Autonomous Region was set up in Tibet Autonomous Region People's Hospital (TARPH), Lhasa. TARPH is one of the biggest class A tertiary general hospitals in Tibet Autonomous Region and committed to the medical services,

medical education/teaching, research, and prevention of the whole area of Tibet. Therefore, we conducted this study to understand the situation of pain clinic in TAR, China, in three aspects: first, the pain disease categorization of outpatients; second, the risk factors for pain; and third, comparing the situation of pain diagnosis and treatment with other areas of China.

2. Materials and Methods

This investigation was a retrospective hospital-based, case series study approved by the TARPH Institutional Review Board. All the chronic pain patients of TARPH pain clinic from September 2017 to August 2018 were enrolled retrospectively. The outpatient records including demographic data, clinical manifestation, diagnosis, and treatment were collected.

For statistical analysis, continuous data were expressed as mean (±standard deviation). Histogram was used to check the normality of data. Statistical analysis was performed using SPSS 19.0.

3. Results

3.1. Basic Information of the Pain Clinic Records. Totally, 37 medical records of pain clinic of TARPH from September 2017 to August 2018 were collected. Among them, 29 patients visited the pain clinic only once, 6 patients for two times, and 2 patients for three times. The average age of these 37 patients was 54.8 years, with the male to female sex ratio of 16/21.

3.2. Pain Disease Categorization and Demographic Characteristics of the Pain Clinic Records. We divided the patients into four groups according to the locations of pain. Some patients suffered from pain of multiple sites. (Table 1). Pain of trunk and lower extremity consisted of majority of the cases. Except the abdominal pain, low back pain, and lower extremity pain, more females suffered from pain diseases than males.

After analyzing all the cases of the medical records, we found that postherpetic neuralgia and sciatica consisted of nearly half of the cases. However, the etiological factors of some patients were still not clear. The detail categorization of these records is shown in Figure 1.

3.3. Patients Diagnosed with Postherpetic Neuralgia. Totally, 11 (29.7%) patients were diagnosed with postherpetic neuralgia in TARPH pain clinic. The average age of these 11 patients was 70.4 years, with the male to female sex ratio of 5/6. Almost all the patients came to see pain physicians more than one month after the onset of herpetic zoster. Only one patient received treatment of gabapentinoids from dermatologists. Six out of eleven postherpetic neuralgia patients visited the pain clinic for more than one time (Table 2).

4. Discussion

Medical aid for Tibet Autonomous Region is an important strategic decision of the country. The government gives top priority to the improvement of Tibetan's livelihoods. The medical experts coming to Tibet not only saved the life of Tibetans but also contributed to the unity and stability of the country. As anesthesiologists, we should try the best to support this strategy in our subject areas. Despite the aid of clinical anesthesia for Tibet, we should also pay attention to pain medicine in Tibet. The pain clinic of Tibet Autonomous Region People's Hospital is the first pain clinic in Tibet area. This is the first study in China to investigate the situation of pain clinic in the Qinghai-Tibet plateau. Tibet Autonomous Region People's Hospital is a class A tertiary comprehensive hospital and established the first pain clinic in Tibet; therefore, these data could represent the situation of pain clinic in Tibet area. Comparing with the pain clinics of other provincial capital hospitals in China, the outpatient amounts of Tibet Autonomous Region People's Hospital were so small. Some reasons may explain this phenomenon. Firstly, the inhabitants of Tibet may not be aware of the existence of pain clinic, so they may choose other departments as their first consultation departments. Secondly, the pain medicine is not the focus of the development of this hospital, and it was short of professionally trained pain physicians. Thirdly, the hospital may lack fund to introduce some necessary equipment to carry out pain diagnosis and treatment.

As all the cases were outpatients, we cannot estimate the prevalence of chronic pain in Tibet. The data of these medical records showed that the mean age of these patients was 54.81 ± 15.66, older than the data (39.5 ± 15.67) presented by Jackson et al. [5]. It may indicate that the inhabitants of Tibet have tolerated pain diseases for a long time before they visited the pain clinic for the first time. It may delay treatment and cause more consumption of medical resources. However, this phenomenon may also indicate that the Tibetans are more physically healthy. Further study needs to be done to confirm the reason why the mean age of pain clinic patients in Tibet was older than the data presented by Jackson et al.

From the data of this study, we could find that more females visit the pain clinic than males. This phenomenon coincides with some published articles [5–8]. The underlying mechanism is not clear. Some animal research indicated that ovarian hormones may contribute to the pain development [9, 10].

We found that postherpetic neuralgia and sciatica are the most common diagnosis of pain clinic. These two kinds of diseases could significantly influence the daily life of patients and make the patients to seek for medical help. The frequency and severity of PHN increase with advancing age, occurring in 20% of people aged 60–65 years who have had acute HZ, and in more than 30% of people aged >80 years [11]. The effect of female gender seemed protective in studies in which the mean age was ≥60 years, compared with among studies with mean age <60 years, for which female gender increased the risk of PHN [12]. Our results also show that most PHN patients in Tibet are older than 70 years (7/11), but no gender association was found. The first-line analgesic

Table 1: Subgroup analysis of different pain diseases.

Pain diseases	Number	Age (mean ± SD)	Sex (male/female)
Pain of anterior and posterior aspects of the thorax	17	64.06 ± 15.46	7/10
Abdominal pain, low back pain, and lower extremity pain	13	47.08 ± 11.64	8/5
Joint pain	8	44.63 ± 9.04	2/4
Upper extremity pain	2	53 ± 4.24	1/1

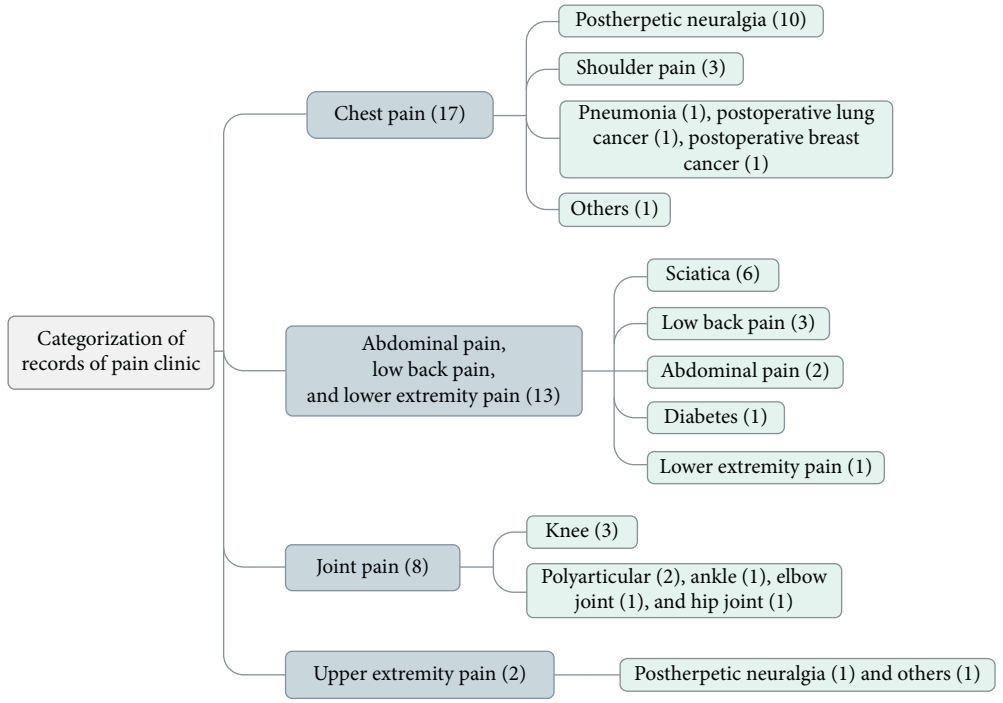

Figure 1: Categorization of medical records of pain clinic.

Table 2: Summary of postherpetic neuralgia patients.

No.	Gender	Age	Spinal cord level	Duration from onset to pain clinic	Previous treatment	Follow-up
1	M	56	C8-T1	9 m	Vitamin B6, Vitamin B12	1
2	F	82	T levels	Not known	No	No
3	F	75	T6-T8	4 m	No	1
4	F	77	T8	40 m	No	1
5	F	62	T11-T12	1.5 m	Antiviral gabapentin	2
6	F	71	T levels	Not known	COX-2	No
7	M	75	T levels	Not known	COX-2	No
8	M	62	T10-T12	3 m	No	1
9	F	82	T levels	Not known	No	No
10	M	63	T8-T9	1 m	Antiviral	1
11	M	70	T10	1.5 m	Antiviral	No

medication for PHN is gabapentinoids [13]; however, patients diagnosed with postherpetic neuralgia had not been effectively treated before they visited the pain clinic. Therefore, the pain physicians should pay more attention to the update of diagnosis and treatments of these pain conditions, and on the other hand, local physicians should receive more training in pain medicine. Local hospital should supply the basic drugs and equipment to ensure whether the clinical practice is going well.

Small sample size is the major limitation of this study. However, it suggested that the hospital and the government should establish some policy to develop and promote pain medicine in Tibet and let more Tibet inhabitants know that they can seek help from pain clinic if they are suffering from pain symptoms.

Another limitation is that the data that we could use are age, sex, and diagnoses and we could not perform deep analysis of the data. This fact also reflects the urgency of

promotion of pain medicine, supplying the relative drugs, equipment, and tests in this hospital to enrich the data of medical records. If the hospital has a pain ward, we could also collect much more data than before.

5. Conclusions

This study revealed the situation of pain medicine in Tibet. Both the government and the hospital should make efforts to develop pain medicine to make Tibetans being accessed to high-quality pain clinic service.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Both Le Shen and Xin Zhang contributed equally to this work.

Acknowledgments

This study was supported by Tibet Natural Science Funding Committee Grant (XZ2017ZR-ZYZ06) and CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-3-024).

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Hindawi
Pain Research and Management
Volume 2019, Article ID 6924941, 12 pages
https://doi.org/10.1155/2019/6924941

Research Article

Comparison of Transforaminal Percutaneous Endoscopic Lumbar Discectomy with and without Foraminoplasty for Lumbar Disc Herniation: A 2-Year Follow-Up

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Received 18 October 2018; Accepted 29 November 2018; Published 2 January 2019

Guest Editor: Baogan Peng

Background. Both transforaminal percutaneous endoscopic lumbar discectomy with foraminoplasty (TF PELF) and transforaminal percutaneous endoscopic lumbar discectomy without foraminoplasty (TF PELD) were developed for lumbar disc herniation (LDH) patients. However, the safety and effectiveness between the TF PELF and TF PELD have not been investigated. *Methods*. Of the included 140 LDH patients, 62 patients received TF PELF (PELF group) and 78 patients received TF PELD (PELD group). The operation time, the duration of staying at the hospital, and complication incidences were recorded. All patients were followed up for 2 years, where low back and leg visual analogue scale (VAS) pain ratings and Oswestry Disability Index (ODI) were compared between the 2 groups before and after surgery. Modified Macnab criterion was estimated for all patients at postoperative 2 years. *Results*. There were no significant difference of the operation time, number of days staying at the hospital, and the incidence of complications between the 2 groups ($P > 0.05$). Two cases in the PELF group and 1 case in the PELD group received a second surgery due to unrelieved symptoms postoperatively. Low back and leg VAS and ODI scores decreased in both groups after operation ($P < 0.01$), respectively, but were not significant between the 2 groups over time ($P > 0.05$). Six patients in the PELF group and 3 patients in the PELD group did not continue the follow-up; thus, only 131 patients completed Macnab evaluation. The satisfactory rate was reported as 80.4% in the PELF group and 90.7% in the PELD group ($P > 0.05$). *Conclusions*. This study suggested that the safety and effectiveness of TF PELF are comparable to TF PELD for LDH patients.

1. Introduction

Low back pain was reported affecting up to 80% of the population during their lifetime [1], disabling 5–10% of the people, which is a major concern and accounts for up to 75–90% of the cost [2], and was the top source of disability and lost productivity in the United States [3]. Lumbar disc herniation (LDH) is a widespread medical problem, closely associated with low back and leg pain mostly affecting 30- to 50-year-old people. It was also reported that 80% adults suffered from low back and/or leg pain at least once in their life time, and of these patients in China, around 20% were caused by LDH [4].

Open lumbar discectomy was implemented as a standard surgery for LDH therapy, firstly described by Dandy and Peltier [5] The improvement of minimally invasive methods

was achieved after introduced with the microscope, and microscope discectomy has been the predominant surgical approach for LDH during past decades.. However, minimally invasive surgery is gaining increasing attention, including in the area of spinal surgery. The anatomic neural foramen described by Kambin with the purpose for endoscopic access was seemed as a cornerstone in the development of a fully endoscopic transforaminal approach, which was followed by the endoscopic spine system introduced by Yeung [6]. After that, three different operative approaches of percutaneous endoscopic lumbar discectomy (PELD) were mainly developed gradually, including interlaminar, TF, and posterolateral discectomy. The TF approach is the most popular, used with the advantage of ensuring safety in "Kambin's" triangle [7].

The overall success rate of conventional microdiscectomy ranged from 75 to 100% [8] and that of transforaminal PELD was 69–90% [9–12]. Therefore, transforaminal PELD might be an important alternative to conventional open microdiscectomy, and their clinical outcomes were reported to be comparable [13–15]. Moreover, transforaminal PELD can be operated under local anesthesia. Hence, this procedure is possible for elderly patients with poor general conditions and provides better feedback to avoid potential nerve root damage from manipulation during operation [16] with advantages of small incision size, limited blood loss, less surrounding tissue injury, rapid recovery, short hospital stay, and less postoperative pain [14].

Recently, the significance of foraminoplasty has been widely emphasized. It was defined as "widening the foramen by undercutting the ventral part of the superior articular process (SAP) with ablation of foraminal ligament with the use of bone trephines, endoscopic drill, and side-firing laser to visualize the anterior epidural space and its contents" [17]. The working place can be enlarged, and the cannula can be navigated through a very narrow space, allowing the removal of the herniated mass completely without injuring the exiting nerve root [18]. Transforaminal PELD with foraminoplasty (TF PELF) was reported safe for the patients and reached a satisfactory rate of 92.5% [12]. Whereas, in addition to the disadvantages of bleeding, pain, and extended operation time, foraminoplasty also would cause postoperative flares with an incidence of 19% [19]. Furthermore, 6.1% patients complained of dysesthesia [20], which might be attributed to increasing temperature when using a side-firing laser or high-speed drill, hence, leading to nerve inflammation and deterioration of nerve conduction to some extent [21].

Upon the development of PELD, a technique of transforaminal PELD without foraminoplasty (TF PELD) was adopted on treating LDH. However, whether the injury during the TF PELF procedure would deteriorate the clinical outcomes compared with TF PELD on LDH treatment is an open question. In the present study, 140 patients with LDH who underwent TF PELF (62 cases, PELF group) or TF PELD (78 cases, PELD group) were recruited. The authors comprehensively compared the postoperative clinical outcomes between the two groups with a 2-year follow-up.

2. Materials and Methods

2.1. Patients. With approval from the Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, the study population comprised 140 consecutive patients with LDH who underwent TF PELF or TF PELD surgery in our department from July 2014 to August 2016. All of the patient met the inclusion criteria and were followed up to 2 years postoperatively. All the patients provided the informed consents and protocols that described the details of the follow-up.

Inclusion criteria were as follows: (1) preoperative imaging evidence of LDH at L1-2, L2-3, L3-4, L4-5, and L5-S1 (monosegmental or double segmental), with or without canal and/or lateral recess stenosis caused by herniated mass on magnetic resonance images (MRI) and computed tomography (CT) (Figures 1 and 2). (2) Presented with symptoms of lumbar radiculopathy with low back pain, leg pain, decreased motor function, and/or dysesthesia, which was in accordance with the presentation of MRI and CT. (3) Dynamic flexion-extension radiographs, the neutral anterior-posterior, and lateral radiographs were checked for every patient. Only the patients with spondylolisthesis of grade I (1–24% of the vertebral body has slipped forward over the body below), segmental angulation <10°, and segmental movement less than 3 mm that was measured with flexion-extension radiographs were recruited, if any segmental instability was found. (4) Agreed to elect TF PELF or TF PELD over other spinal surgeries. (5) Failure to conservative treatment for at least 12 weeks, including but not limited to oral medication, epidural steroid injection, and physical therapy. Exclusion criteria were as follows: (1) patients who had significant spinal deformity or spinal instability and needed fusion or transferred to open surgery or lumbar interbody fusion. (2) Patients who cannot tolerate or did not agree to the surgery or did not agree to be followed up. (3) Patients with systematic infection, bleeding diathesis, or a high risk of bleeding. (4) Patients who cannot accept MRI scanning because of contraindication. (5) Patients with mental illness and who were uncooperative.

2.2. Surgical Technique. All the surgeries were performed by two senior and experienced surgeons (Dr. Zhan and Dr. Xu) in TF PELD and foraminoplasty. All procedures were performed following the standard TF PELF and TF PELD technique with the transforaminal endoscopic spine system (Joimax GmbH, Karlsruhe, Germany). Patients were on the lateral position on an operating table on the contralateral side. The C-arm fluoroscopy technique was used to help surgeons determine the affected discs and pedicle and to draw a line from the midpedicular annulus to the facet lateral margin and the extension to the body surface. The skin entry point from the midline was 10–12 cm. After subcutaneous infiltration of local anesthesia with 1.0–1.5 mL 0.5% lidocaine, the subsequent steps were performed sequentially: (1) An 18-gauge needle was inserted to reach the lower segmental SAP under fluoroscopic guidance with a puncture angle of about 15° until the needle tip reached the posterior

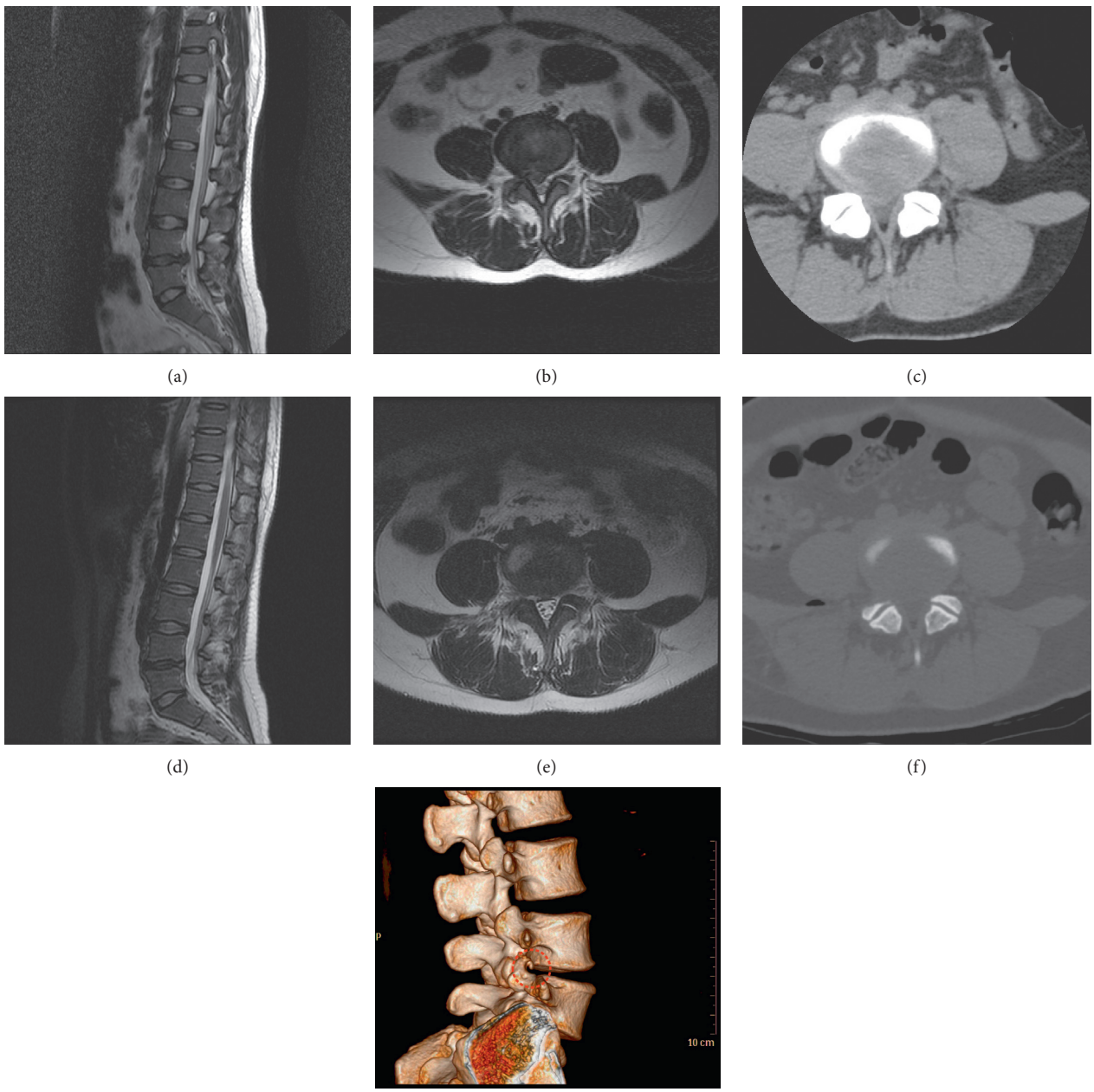
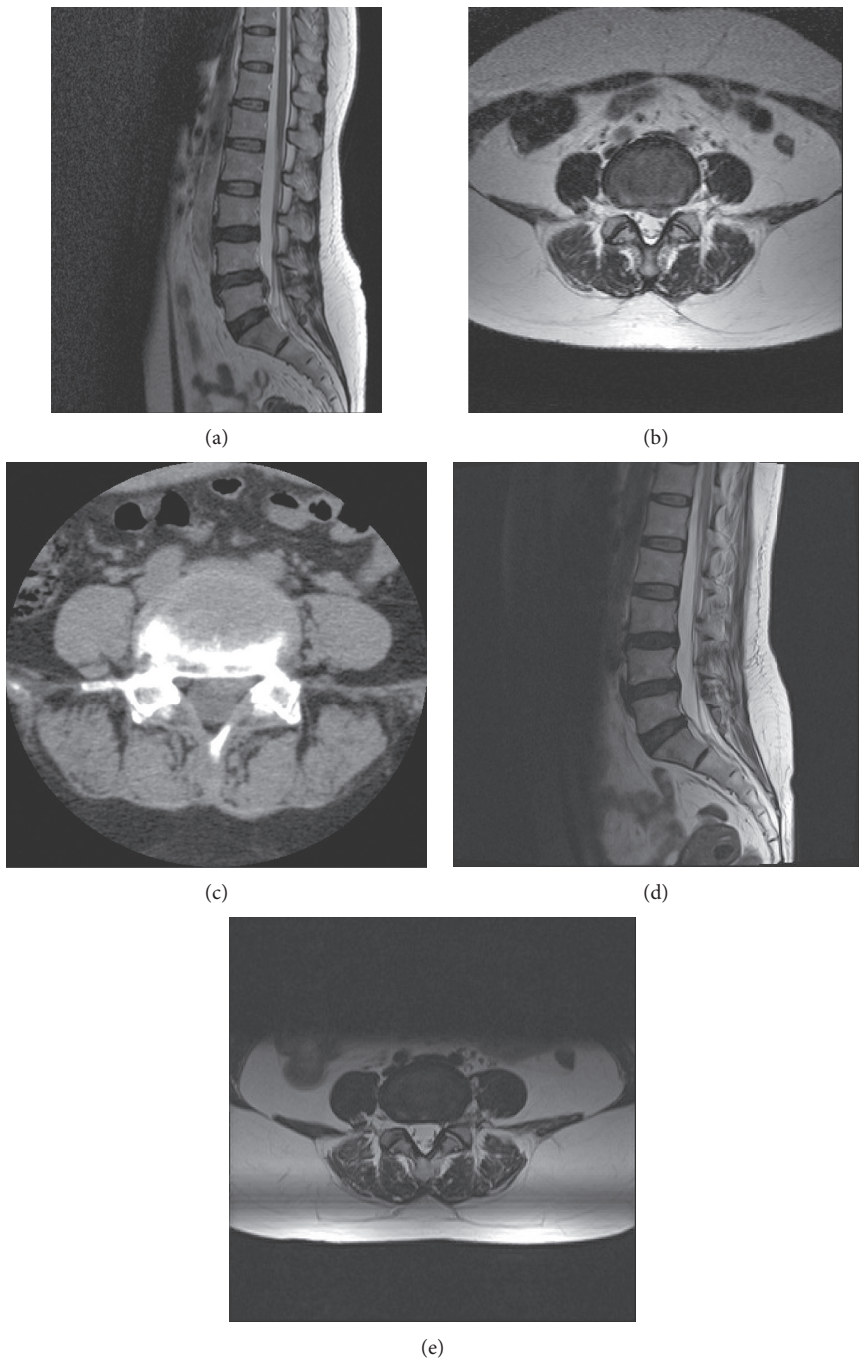


Figure 1: The preoperative and postoperative imaging data of patient who received TF PELF. (a and b) A preoperative MRI image shows the sagittal and coronal views of a patient diagnosed with LDH. (c) A preoperative CT image of the same patient. (d and e) The postoperative MRI sagittal and coronal views of the patient after TF PELF. (f) A postoperative CT image. (g) The postoperative 3D CT imaging result. The red round denotes foraminoplasty.

rim of the SAP of the distal vertebrate at the lateral view and the medial pedicle line at the anterior-posterior view. (2) After the stylet was retreated, another 20 mL 0.5% lidocaine was injected through the needle for adequate anesthesia. A guide wire was inserted on the same direction of the needle and a 0.8 cm in diameter incision was made, followed by a serial dilation, and a working channel was rotated into the guide wire in succession. (3) Replacing the guide wire and dilation with a guide bar (Figures 3(a) and 3(b)).

The foraminoplasty was individualized for each situation, and the surgeons decided to perform foraminoplasty depending on the operation location and experience. In cases where the working cannula could not be placed near the disc fragment due to the anatomical barrier, especially the SAP, leading to the inability of transforaminal endoscopic access to the dural sac or nerve root in the spinal canal, foraminoplasty also would be carried out to allow the working cannula access near the herniated disc [22].



(a) (b) (c) (d) (e)

Figure 2: The preoperative and postoperative imaging data of patient who received TF PELD. (a and b) A preoperative MRI image shows the sagittal and coronal views of a patient diagnosed with LDH. (c) A preoperative CT image of the same patient. (d and e) The postoperative MRI sagittal and coronal views of the patient after TF PELD.

Furthermore, less than 1/3 of cartilage of the SAP would be removed to maintain stability [23]. If no foraminoplasty was needed, the surgeons navigated the guide bar over the SAP of the distal vertebrate, and the working channel was accessed through the foramen. Otherwise, the foraminoplasty would be performed as follows: a tapered cannulated obturator was inserted along the guide wire, and a cannula was placed outside the foramen and lateral border of SAP; then an endoscopic trephine was used to remove the superior part of the SAP (Figure 3(c)), undercutting facet joint, ablation of osteophytes, and partially removing the foraminal ligament from outside to inside of the foramen with an endoscopic drill, bone remears, cutting forceps, and firing laser (joimax GmbH, Karlsruhe, Germany), thus, helping the surgeons access the epidural space and allowing complete decompression of foraminal or lateral recess stenosis. After the guide bar reached the position of the operation area, the working channel was rotated in the direction of the guide

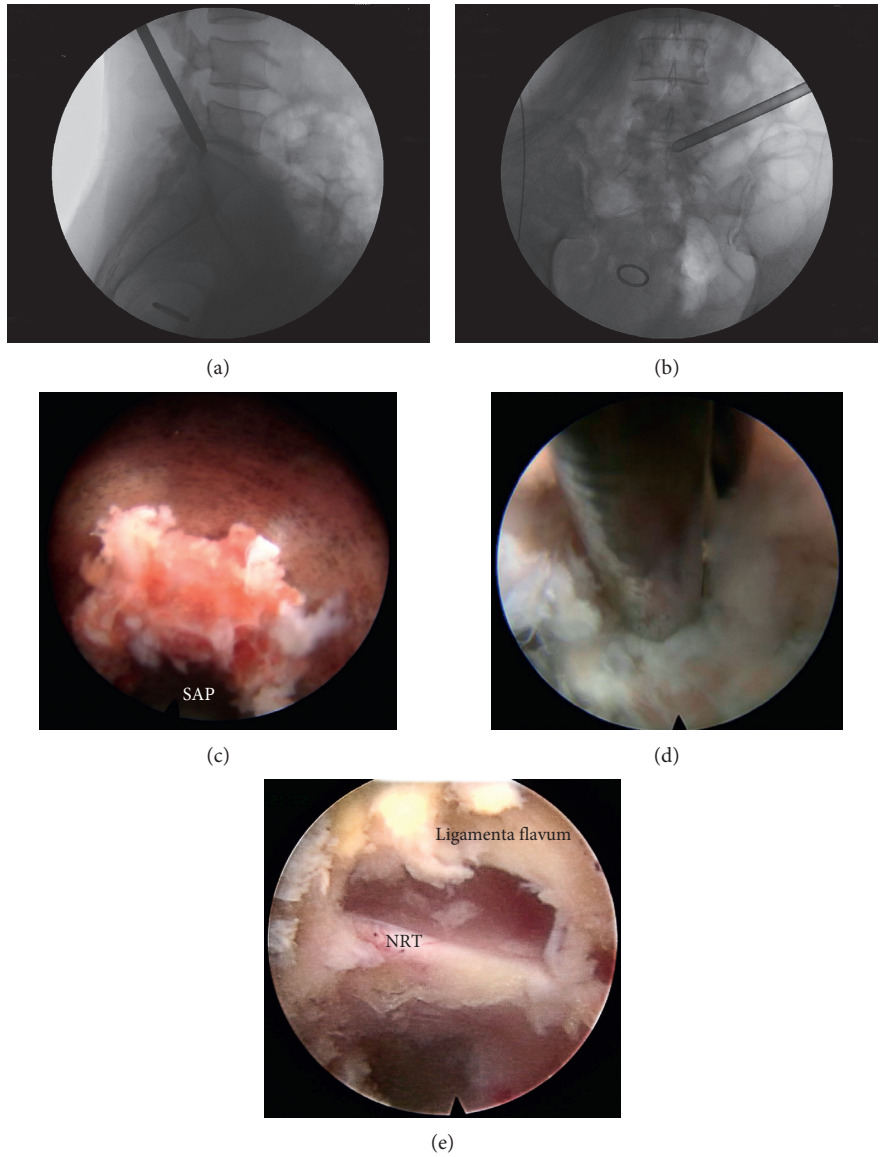


Figure 3: Imaging data during surgeries. (a) The tip of the guide bar lay at the posterior rim of the upper endplate of the SAP facet of the distal vertebrate in the lateral view. (b) The tip of the guide bar lay at the medial pedicle line in the anterior-posterior view. (c) Cutting SAP with a trephine under endoscope. (d) Removing the herniated lumbar disc mass under endoscope during procedure. (e) The operation area after the herniated mass was removed. SAP = superior articular process, NRT = nerve root.

bar. To remove the herniated mass (Figure 3(d)), the endoscope was introduced through the cannula, and navigation was used for all cases to confirm that compression had been cleared across to the contralateral pedicle. If dural tear occurred, a small piece of gelatin sponge would be used to seal the rip. The operation area was copiously irrigated and meticulous hemostasis was achieved at the end of all surgeries (Figure 3(e)). For postoperative management, all the patients were required to wear a lumbar back brace for approximately 3-4 weeks to limit lumbar rotation.

2.3. Evaluation of Postoperative Outcomes and Radiography. Postoperative symptomatic improvement was evaluated by the surgeons on the operation day, and the radiography was further examined by MRI (Figures 1 and 2). Visual analogue scale (VAS) pain rating is used for estimating pain [24], and the Oswestry Disability Index (ODI) is currently considered as the gold standard for measuring life quality along with the degree of disability with low back and/or leg pain and LDH [25]. The authors adopted VAS and ODI to estimate low back and leg pain, the disability of the patients before surgery and at postoperative day 1, day 7, month 1, month 3, month 6, year 1, and year 2, respectively. In addition, the recovery of all the patients was estimated with modified Macnab criteria at postoperative 2-year follow-up.

2.4. Data Analysis. Quantitative data were presented as mean ± standard deviation, and qualitative data were

presented as frequency (%). The normality of the data was analyzed. Mann–Whitney U test was utilized for nonnormal distributed data analysis between PELF and PELD groups. The Wilcoxon test was used for the nonnormal distributed data analysis within the PELF and PELD groups and the *post hoc* test for multiple comparisons. The Macnab outcomes and incidence comparisons between the 2 groups were done with χ^2 test. All data were analyzed with statistical software SPSS 19.0, and P value <0.05 was considered significant.

3. Results

3.1. Patients' Demographic Characteristics. Eighty-six males and fifty-four females were included in this study, and the mean age was 54.5 years in the PELF group and 54.6 years in the PELD group ($P = 0.973$). The pain duration in the PELF and PELD groups was 52.1 ± 89.34 and 22.9 ± 39.67 months, respectively ($P = 0.051$). Operation time was 121.7 ± 46.39 minutes in the PELF group and 108.9 ± 37.70 minutes in the PELD group ($P = 0.237$). The average hospital stay was 11.06 ± 9.18 days in the PELF group and 9.08 ± 3.75 days in the PELD group ($P = 0.458$). The data are presented in Table 1.

Because of the loss of contact, death resulting from other diseases, or refusal to continue the follow-up, 2 patients were lost to follow-up at postoperative month 1, 2 patients at month 3, 1 patient at month 6, and 1 patient at year 2 in the PELF group. In the PELD group, 2 patients were lost to follow-up at postoperative month 1 and 1 patient at month 3 (Table 2). Thus, the average follow-up duration was 22.0 ± 6.38 months in the PELF group and 23.1 ± 4.55 months in the PELF group (Table 1, $P = 0.181$).

3.2. Complications. Of all included patients, 2 cases had herniation at L2-3, 1 was included in the PELF and 1 in the PELD group; 6 cases had herniation at L3-4, 5 were included in the PELF and 1 in the PELD group; 76 cases had herniation at L4-5, 29 were included in the PELF and 47 cases in the PELD group; 43 cases had herniation at L5-S1, 25 were included in the PELF and 18 in the PELD group; 3 cases had herniation at both L3-4 and L4-5 levels, 1 was included in the PELF and 2 in the PELD group; 2 cases had herniation at L3-4 and L5-S1 levels, both were included in the PELD group; and 8 cases had herniation at L4-5 and L5-S1 levels, 1 was included in the PELF group and 7 in the PELD group. The distribution of the surgery sides is also presented in Table 3. Nerve root injury occurred in 1 patient herniated at L5-S1 in the PELD group ($P = 0.908$) who complained postoperatively of moderate leg pain and recovered after conservative treatment for 30 days. Another 2 patients who developed dural tears received TF PELF surgery at L4-5 ($P = 0.378$), but no special postoperative complaint from the patient was reported. Other 2 cases in the PELF group and 1 case in the PELD group received the second PELD within 3 months postoperatively ($P = 0.840$) due to the unrelieved symptoms and imaging data indicating residuals, and no patient required conversion to an open surgery during the 2-year follow-up.

3.3. Comparison between Preoperative and Postoperative Clinical Outcomes within the PELF and PELD Groups. VAS and ODI were utilized to estimate the surgery clinical outcomes. Compared with those preoperatively, the postoperative low back and leg VAS pain ratings and ODI scores significantly decreased over time in both groups (Figures 4–6, $P \leq 0.001$, $P \leq 0.001$, $P \leq 0.001$). To further analyze the postoperative recovery of the patients, VAS and ODI scores at postoperative day 7, month 1, month 3, month 6, year 1, and year 2 were compared with postoperative day 1. We found that the postoperative change of low back VAS was not significant in the PELF group ($P = 0.948$). However, low back VAS score increased at postoperative day 7 ($P = 0.046$), month 1 ($P = 0.001$), month 3 ($P = 0.001$), and month 6 ($P = 0.014$) in the PELD group. Leg VAS decreased significantly at nearly all time points postoperatively in the PELF group ($P < 0.01$) and decreased at postoperative month 6 ($P = 0.013$) and year 1 ($P = 0.004$) in the PELD group. ODI score increased at postoperative month 1 ($P = 0.007$) in the PELF group and was increased at postoperative day 7 ($P = 0.007$) and month 1 ($P = 0.001$) in the PELD group.

At the final stage of the follow-up, modified Macnab criteria were used to evaluate the recovery at postoperative year 2 for the remaining 131 patients. In the PELF group, 24 cases reported "excellent" (42.9%), 21 cases reported "good" (37.5%), 6 cases reported "fair" (10.7%), and the other 5 cases reported "poor" (8.9%). In the PELD group, 38 cases reported "excellent" (50.7%), 30 cases reported "good" (40.0%), 5 cases reported "fair" (6.7%), and the remaining 2 cases reported "poor" (2.6%). Hence, the satisfactory rate reached 80.4% in the PELF group and 90.7% in the PELD group (Table 4).

3.4. Comparison of Clinical Outcomes between the PELF and PELD Groups. To further determine whether the injury from the TF PELF procedure would deteriorate the clinical outcomes compared with TF PELD for LDH patients, low back and leg VAS pain ratings, ODI and Macnab outcomes were compared between the 2 groups (Figures 4–6). No significant difference of low back and leg VAS pain rating was found between the PELF and PELD groups ($P = 0.654$, $P = 0.722$) before and after operation. Moreover, no statistical significance of ODI ($P = 0.238$) and Macnab (Table 4, $P = 0.310$) outcomes was found between the 2 groups.

4. Discussion

This is a retrospective study to explore a clinical question of whether the damage during the TF PELF procedure would deteriorate the clinical outcomes compared with the TF PELD. Sixty-two LDH-diagnosed patients who received TF PELF and 78 patients who received TF PELD were included for the 2-year follow-up. We found that low back and leg pain VAS pain ratings and ODI scores significantly decreased in both the PELF and PELD groups after surgery, although a fluctuation was observed during the follow-up

Table 1: Comparisons of basic information between PELF and PELD groups.

Values	PELF group ($n = 62$)	PELD group ($n = 78$)	P
Female	28	26	0.153
Male	34	52	
Mean age (year)	54.5 ± 15.26	54.6 ± 13.63	0.973
Pain duration (month)	52.1 ± 89.34	22.9 ± 39.67	0.051
Operation time (minute)	121.7 ± 46.39	108.9 ± 37.70	0.094
Hospital stay (day)	11.06 ± 9.18	9.08 ± 3.75	0.458
Follow-up duration (month)	22.0 ± 6.38	23.1 ± 4.55	0.181

Table 2: Time points of the patients lost to follow-up.

Time	PELF group	PELD group
1 month	2	2
3 months	2	1
6 months	1	0
2 years	1	0
Total	6	3

Table 3: The distribution of surgery levels and sides.

Groups	PELF		PELD	
Levels	Sides			
	Left	Right	Left	Right
L2-3	1	0	1	0
L3-4	4	1	1	0
L4-5	13	16	23	24
L5-S1	17	8	10	8
L3-4 and L4-5	1	0	2	0
L3-4 and L5-S1	0	0	0	2
L4-5 and L5-S1	1	0	5	2
Total	37	25	42	36

period. The satisfactory rate was evaluated with modified Macnab criteria at postoperative year 2, which reached 80.4% in the PELF group and 90.7% in the PELD group. However, no significant difference between the two groups of low back and leg VAS, ODI, or satisfactory rate was recorded.

The transforaminal PELD procedure is being developed these years, and the indications of transforaminal PELD are being expanded with the invention and development of the instruments, such as ultrathin high-speed surgical drill, bone remears, cutting forceps, and firing laser. In addition to LDH, this technique can also be utilized to treat lumbar disc stenosis [26], spondylolisthesis [27], migrated recurrent disc herniation, foraminal and extraforaminal LDH [28, 29], and large disc herniations at high levels under local anesthesia [30]. The PELF is a second stage following PELD, which is used to enlarge the foramen with high-speed drill and/or trephine [16]. Both transforaminal PELD and PELF have been reported safe and effective for LDH patients, and the satisfactory rate reached over 90% in some studies [11, 12], but no study compared the effectiveness of PELD with and without foraminoplasty to determine whether foraminoplasty would severely affect clinical outcomes. The satisfactory rate of the PELD and PELF groups in the present study was 80.4% and 90.7%, which was lower than the data reported above, but was in accordance with the study reported by Nellensteijn et al. [9]. Moreover, 3 patients received a second surgery because of residuals, 2 cases in the PELF group and 1 case in the PELD group, whereas in this study, the residual rate was 2.1%, which is higher than that reported as 1.2% [8].

Recurrent herniation was defined as (1) patients with a successful PELD confirmed by a pain-free interval of at least 1 month; (2) reappearance of the initial symptoms and MRI evidence of recurrent herniation on the same level [31]. Two patients acquired dural tear in the PELF group, but no recurrence was revealed in all patients, so the incidence was lower than the previously published data [8, 9, 32, 33].

Despite the evolution, transforaminal PELD cannot be adopted in all patients due to narrow foraminal area and high iliac crest hindered by the L5 transverse process. It was reported that transforaminal PELD could be performed at the L4-5 level in 94.4% (right) and 90.4% (left) patients and only 24.1% and 19.2% at the L5-S1 level [34]. The patients who performed the interlaminar approach were not included here. However, foraminoplasty was performed in 30 cases who had herniation at the level of L4-5 and in 25 cases who had herniation at the level of L5-S1 because of high iliac crest in this study; thus, 65.1% patients who had herniation at L4-5 received TF PELD, and 46.8% patients needed foraminoplasty for larger space for endoscope navigation at L5-S1.

The disadvantages of PELF were reported as more bleeding and pain, longer operation time, prolonged postoperative recovery time, needing more expensive equipment, and higher risk of heat-damage to the surrounding spinal nerves, including neural injury [14, 21, 35]. However, we did not find any statistical difference of operation time, number of days staying at the hospital, or incidence of complications between the two groups, which might relate to both surgeons being skilled at the procedures. Therefore, we consider that foraminoplasty might extend the operation time or have a higher risk of injuring the nerve root but was not significant in this study. Although some studies reported open or closed CSF, fistulas did not readily occur in PELD because of limited access and was not recommended to attempt any dural repair after dural tear occurred [8]. The surgeon in this study sealed the dural rip with gelatin sponge intraoperatively for the patients who had dural tear to prevent postoperative hypocranial pressure symptoms. Besides, because of the irrigation during the procedure, the authors could not record the bleeding volume accurately, so the bleeding volume was not analyzed.

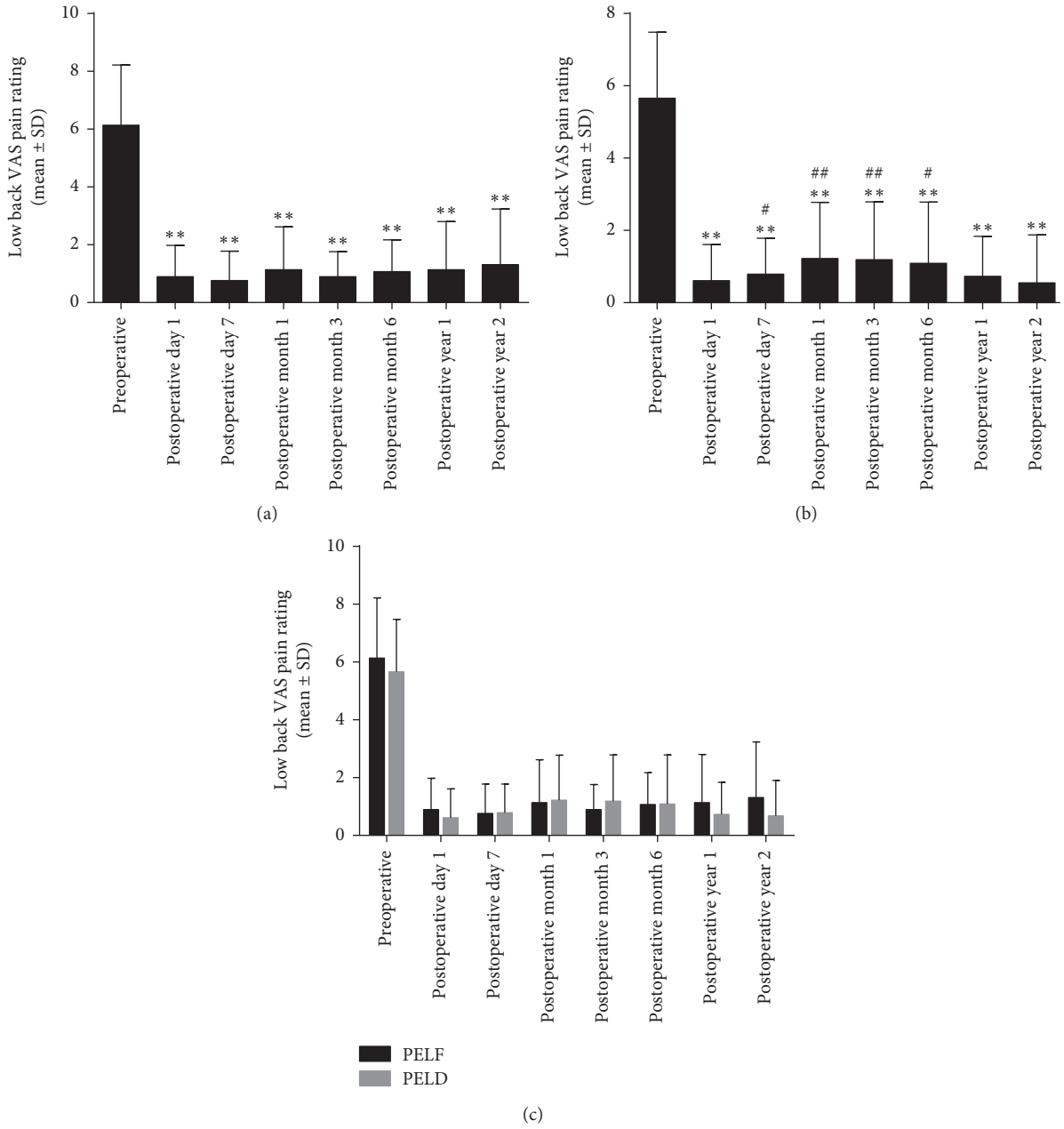


Figure 4: The low back pain VAS pain rating before and after TF PELF and PELD. (a) Low back pain was significantly decreased at all time points postoperatively compared with that preoperatively in the PELF group ($P < 0.01$), and no statistical difference was found between postoperative time points compared with postoperative 1-day ($P > 0.05$). (b) Low back pain decreased after TF PELD ($P < 0.01$), but increased at postoperative day 7, month 1, month 3, and month 6 compared with postoperative day 1 in the PELD group ($P < 0.05$). (c) No significant difference between the 2 groups over time ($P > 0.05$). $^{**}P < 0.01$, compared with that preoperatively, $^{\#\#}P < 0.01$, compared with postoperative 1-day.

VAS and ODI were evaluated for all patients at each visit during the follow-up. We found that low back and leg VAS pain ratings and ODI scores decreased at postoperative day 1 compared with those preoperatively in both PELD and PELF groups, but both VAS and ODI changed significantly compared with postoperative day 1, suggesting that the symptoms of the patients would fluctuate during postoperative recovery. Low back VAS pain rating increased within 6 months postoperatively compared the first day after operation was observed in the PELD group but not in the PELF group. We postulated that it might be related with a greater range of working channel motion during the procedure in the PELD group, thus causing more damage of the peripheral spinal muscle and even local edema of nerve root, which may extend the recovery period. Nerve root injury occurred in 1 patient in the PELD group, and dural tears

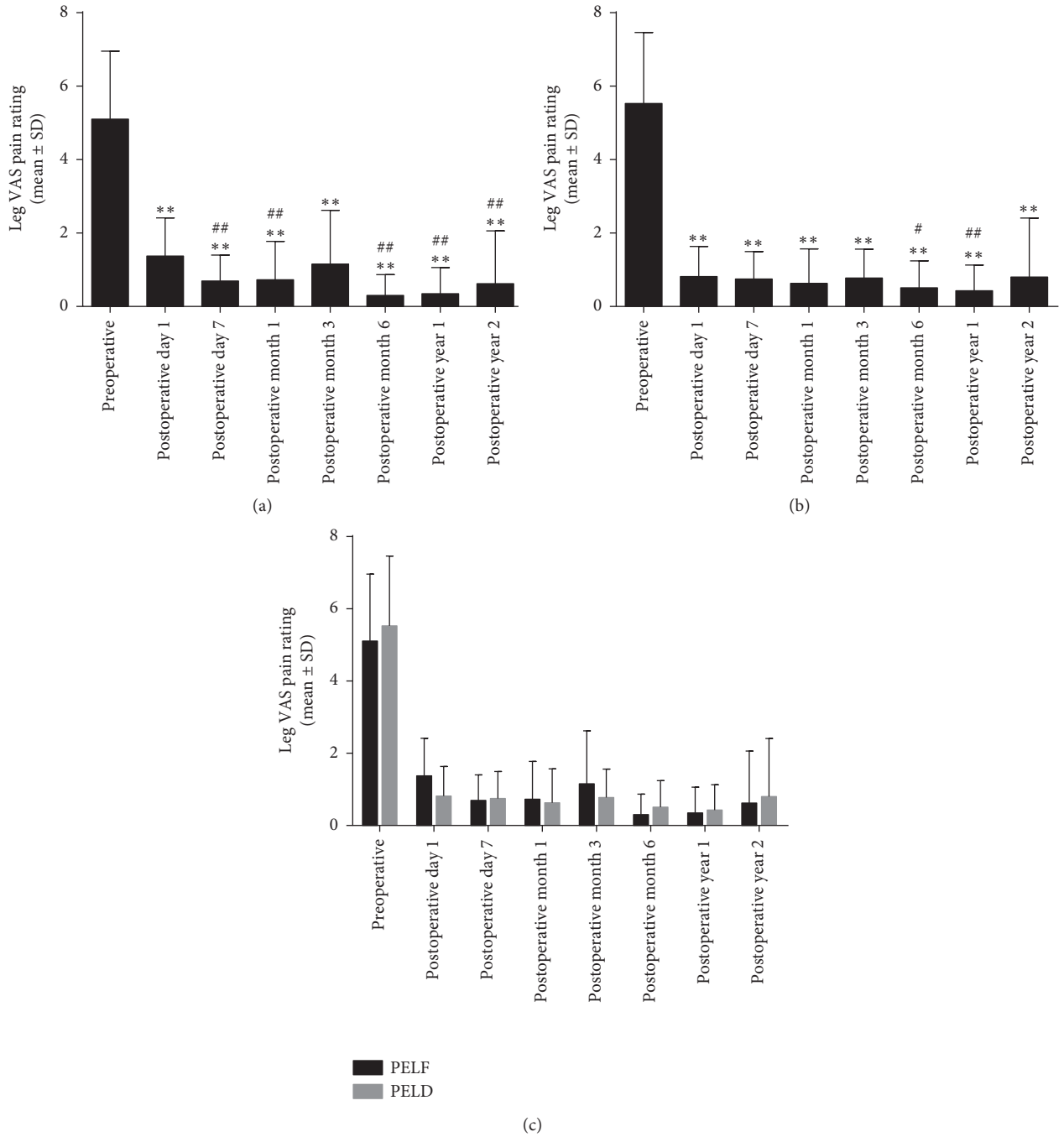


Figure 5: Leg VAS pain rating before and after TF PELF and PELD. (a and b) Leg VAS pain rating decreased significantly at postoperative all time points compared with that preoperatively in both PELF and PELD groups ($P < 0.01$). Compared with postoperative day 1, VAS score decreased at postoperative day 7, month 1, month 6, year 1, and year 2 in the PELF group ($P < 0.01$), and at postoperative month 6 ($P < 0.05$) and year 1 ($P < 0.01$) in the PELD group. (c) No significance between the 2 groups ($P > 0.05$). $^{**}P < 0.01$, compared with that preoperatively; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, compared with postoperative day 1.

occurred in 2 patients in the PELF group, indicating that foraminoplasty did not result in more nerve root or ganglion, but caused complications such as dural tears, but the difference was not significant. No difference was found in Macnab outcomes between the two groups. Therefore, we considered that both TF PELD and PELF were effective and comparable for LDH treatment.

This study has some limitations. (1) Dynamic flexion-extension radiographs were not used to assess stability and hidden dynamic instability after surgeries, especially in the foraminoplasty group. (2) This is a retrospective study without controls from open discectomy, and no valid evidence from randomized controlled trials on the effectiveness of TF PELD and PELF was provided. (3) Randomized

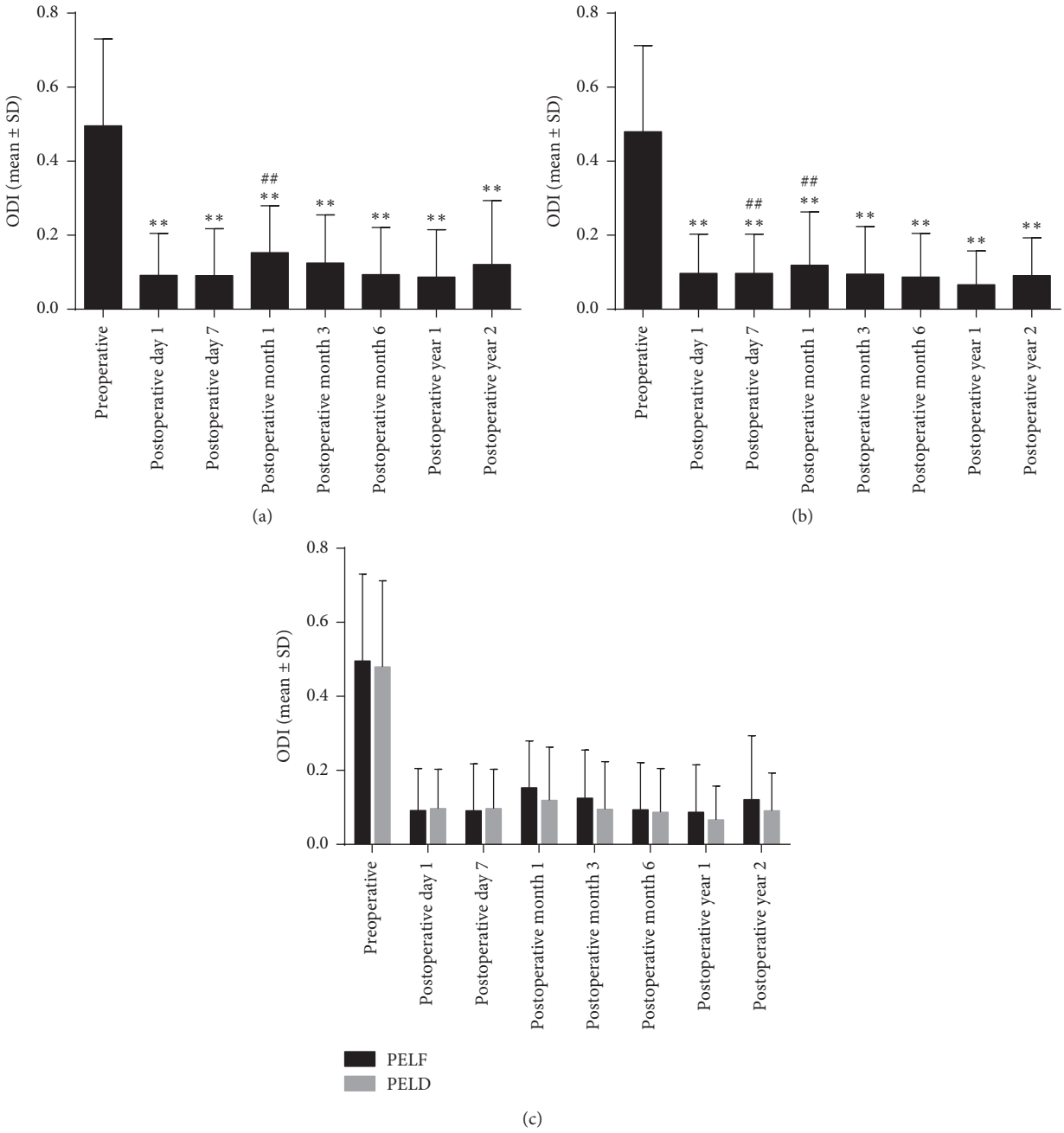


Figure 6: ODI before and after surgery in PELF and PELD groups. (a and b) ODI in both PELF and PELD groups significantly decreased after surgery compared with that preoperatively ($P < 0.01$). ODI at postoperative month 1 increased compared with postoperative day 1 ($P < 0.01$) in the PELF group, and increased at postoperative day 7 and month 1 in the PELD group ($P < 0.01$). (c) No significance between the 2 groups at all time points ($P > 0.05$). $^{**}P < 0.01$, compared with that preoperatively; $^{\#\#}P < 0.01$, compared with postoperative day 1.

controlled trials with longer-term follow-ups compared with other surgical techniques are needed in the future. (4) Despite the LDH-diagnosed patients who reached the inclusion criteria were included in this study, the indication for accepting PELF and PELD is different, the surgeons decided to perform foraminoplasty mainly depending on operation location and experience. If the working cannula could not access the disc fragment due to the anatomical barrier, the foraminoplasty would also be performed. (5) The dimension of foramens of PELF and PELD groups were not recorded in this study, and most of the patients did not receive postoperative CT examine besides MRI, so the authors did not compare pre and postoperative foramens.

5. Conclusions

Both procedures are demonstrated as safe and effective for the treatment of LDH, and the clinical outcomes of TF PELF and PELD are comparable for LDH treatment. TF PELF would not deteriorate prognosis compared with PELD.

Table 4: Macnab outcome evaluated at the final visit (postoperative year 2) of the follow-up.

Groups	Excellent	Good	Fair	Poor	Total	P
PELF	24 (42.9%)	21 (37.5%)	6 (10.7%)	5 (8.9%)	56 (100%)	0.329
PELD	38 (50.7%)	30 (40.0%)	5 (6.7%)	2 (2.6%)	75 (100%)	

Excellent: free of pain and deficit, without restriction of mobility; good: residual symptoms or deficits not impeding a normal life; fair: some improvement in functionality but remained handicapped; poor: no improvement at all.

However, because of the limitations of the present study, further randomized controlled trials are needed to explore the prognosis of the two procedures in future.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the National Science Funding of China (81801320) and Wenzhou Science and Technology Project (Y20160392 and Y20130292).

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Hindawi
Pain Research and Management
Volume 2018, Article ID 5192814, 8 pages
https://doi.org/10.1155/2018/5192814

Research Article

Low-Concentration Oxygen/Ozone Treatment Attenuated Radiculitis and Mechanical Allodynia via PDE2A-cAMP/cGMP-NF-κB/p65 Signaling in Chronic Radiculitis Rats

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Received 26 September 2018; Accepted 22 November 2018; Published 13 December 2018

Guest Editor: Ke Ma

Background. Oxygen/ozone therapy is a minimally invasive technique for the treatment of radiculitis from lumbar disc herniation. This study aimed at investigating whether intrathecal administration of low-concentration oxygen/ozone could attenuate chronic radiculitis and mechanical allodynia after noncompressive lumbar disc herniation and at elucidating the underlying mechanisms. *Methods*. First, we transplanted autologous nucleus pulposus into dorsal root ganglions to establish chronic radiculitis in rats. Then, filtered oxygen or oxygen/ozone (10, 20, or 30 μg/mL) was intrathecally injected on day 1 after surgery. The ipsilateral paw withdrawal thresholds (PWTs) to mechanical stimuli were tested daily with von Frey filaments. The expression of the tumor necrosis factor- (TNF-) α, interleukin- (IL-) 1β, IL-6, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), phosphodiesterase 2A (PDE2A), and nuclear factor- (NF-) κB/p65 in spinal dorsal horns was measured by enzyme-linked immunosorbent assay, polymerase chain reaction, and western blot on day 7 after surgery. *Results*. Chronic radiculitis was established in rats. Intrathecal administration of 10 μg/mL, 20 μg/mL, or 30 μg/mL oxygen/ozone significantly attenuated the decreased mechanical PWTs, downregulated the overexpression of spinal TNF-α, IL-1β, and IL-6, and increased the expression of cGMP and cAMP in chronic radiculitis rats. In addition, the effects of treatment with 20 μg/mL oxygen/ozone were greater than the effects of the 10 μg/mL or 30 μg/mL doses. Moreover, intrathecal administration of 20 μg/mL oxygen/ozone reversed the increased levels of spinal PDE2A and NF-κB/p65 mRNA and protein expressions in rats with chronic radiculitis. *Conclusion*. Intrathecal administration of low-concentration oxygen/ozone alleviated mechanical allodynia and attenuated radiculitis, likely by a PDE2A-cGMP/cAMP-NF-κB/p65 signaling pathway in chronic radiculitis rats.

1. Introduction

Radiculitis induced by lumbar disc herniation (LDH) is a very widespread and disturbing disease all over the world. A great deal of research has focused on LDH, and it has been clearly proven that radicular inflammation plays a key role in radicular pain in LDH patients [1–4]. Administration of epidural glucocorticoids and local anesthetics is a common treatment for radiculitis in pain management [5, 6]. However, the use of epidural glucocorticoids is limited by adverse effects. In the past decade, O_3 therapy has gradually become one of the minimally invasive treatments available for radiculitis [7, 8]. A study by Melchionda et al. found that paravertebral oxygen/ozone (O_3) therapy was safe and effective in patients with lumbar radiculitis compared to nonsteroidal anti-inflammatory drugs (NSAIDs) [9, 10]. O_3 therapy is deemed to be an effective minimally invasive therapeutic strategy for LDH, radiculitis, and other chronic painful disorders.

However, ozone is a controversial gas. In previous studies, many researchers have found that ozone is toxic to some organs. Additionally, chronic inhalation of ozone

upregulates proinflammatory cytokines in the respiratory system [11]. Some professors thought that ozone might always be toxic due to worsening of chronic oxidative stress, while on the contrary, others thought that the proper concentration of ozone could be atoxic and activate antioxidative systems [12, 13]. In previous studies, Li et al. found that 40 μg/mL or 60 μg/mL O_3 treatments are neurotoxic to spinal neurons, whereas 20 μg/mL or 30 μg/mL O_3 treatment decreased the levels of methane dicarboxylic aldehyde (MDA) and TNF-α [14]. Carlo demonstrated that low concentration of O_3 prevented the development of mechanical allodynia and decreased the overexpression of caspase 1, 8, and 12 in the orbitofrontal cortex in spared nerve injury (SNI) mice [15]. However, the underlying mechanisms of O_3 therapy in radiculitis are not yet clear [12, 13, 16]. The current study aimed at exploring the mechanisms of a single intrathecal administration of low-concentration O_3 in the rat with chronic radiculitis.

Phosphodiesterases (PDEs) are the only enzymes that hydrolyze cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP) and are divided into 11 families (PDE1 to PDE11). Recent studies have demonstrated that inhibitors of PDEs inhibit the release of proinflammatory cytokines by cAMP/cGMP signaling pathways in depression, pulmonary hypertension, erectile dysfunction, and sepsis [17, 18]. Wiebke and Ruirui et al. found transient PDE2A mRNA upregulation after hind paw inflammation that was accompanied by enhanced acute mechanical paw withdrawal latencies, which indicated that PDE2A likely contributed to acute radicular inflammation and pain [19]. PDE2A can hydrolyze both cAMP and cGMP and preferentially hydrolyzes cAMP after activation by cGMP [20]. In our previous study, we found that PDE2A was significantly increased in the spinal cord of chronic radiculitis rats and was dramatically inhibited by the PDE2A inhibitor, BAY 60-7550, which decreased the spinal tumor necrosis factor- (TNF-) α, interleukin- (IL-) 1β, and IL-6 levels and also alleviated radiculitis and mechanical allodynia in noncompressive lumbar disc herniation (NCLDH) rats [21]. However, the relationship between PDE2A and O_3 therapy has not yet been thoroughly studied.

In the present study, we investigated whether intrathecal injection of low-concentration O_3 improved radicular pain in chronic radiculitis rats. Furthermore, we gained insights into whether PDE2A is involved in the underlying mechanisms of the treatment of pain by low-concentration O_3 therapy.

2. Materials and Methods

2.1. Animals. Adult male Wistar rats (250–350 g) were purchased from the Experimental Animal Center of Shandong University in Shandong, China. All rats were housed in controlled environmental conditions (12 h light/12 h dark cycles and room temperature at 20–22°C) for 1 week prior to the experiment with ad libitum access to food and water. The experimental procedures were approved by the Institutional Animal Care and Use Committee of Shandong University. All endeavors were made to minimize animal suffering and the number of animals.

The investigator was blinded, and the rats were randomized into five groups (n = 8 per group), as follows:

(a) Sham group: sham operation, with a single intrathecal administration of filtered air

(b) Control group: NCLDH rats, with a single intrathecal administration of filtered air

(c) O_3 10 μg/mL group: NCLDH rats, with a single intrathecal administration of 10 μg/mL O_3

(d) O_3 20 μg/mL group: NCLDH rats, with a single intrathecal administration of 20 μg/mL O_3

(e) O_3 30 μg/mL group: NCLDH rats, with a single intrathecal administration of 30 μg/mL O_3

2.2. Establishment of NCLDH Rats and Intrathecal Catheter Implantation. These procedures were completed as previously described [1, 21]. Rats were anesthetized with 10% chloral hydrate (3.0–3.5 mL/kg, i.p.) and fixed in the prone position. Using sterile procedures, right L5 vertebral laminae were exposed by a longitudinal incision at the midline. The right L5 dorsal root ganglion (DRG) and nerve root were exposed after cutting the right L5 vertebral laminae. The epineurium of the L5 DRG was then punctured to create a 2-3 mm opening. Following this, approximately 0.5 mg of the tail nucleus pulposus (NP) was obtained from between two coccygeal intervertebral discs and placed on the right L5 DRG, without mechanical compression. After that, a PE-10 cannula was inserted in the right L5 intervertebral foramina into the intrathecal space, approximately 0.5 cm caudal to the head. Cerebrospinal fluid flowed out of the cannula after placement. Proper intrathecal cannula placement was confirmed by the bilateral hind limb dragging or weakness after intrathecal administration of 10 μL of 2% lidocaine [2, 22]. The catheter was fixed and sealed.

In the sham group, a right L5 hemilaminectomy was performed and then an intrathecal catheter was placed, without the implantation of NP or damage to the DRG.

2.3. O_3 Administration. Filtered air or O_3 was injected 24 h after surgery after evaluating mechanical paw withdrawal thresholds (PWTs). A single dose of filtered air (20 μL) or O_3 (10, 20, or 30 μg/mL O_3, 20 μL) was administered over a period of 20 s by the microsyringe. O_3 mixture was created by a medical ozone generator (CHY-31, Yuehua Company, China). The concentration was measured by the concentration detector on the medical ozone generator.

2.4. Mechanical Paw Withdrawal Thresholds (PWTs). It has been confirmed that NCLDH rats have significant ipsilateral mechanical allodynia, but not thermal hyperalgesia [21–23]. Based on these previous findings we only evaluated ipsilateral mechanical paw withdrawal thresholds (PWTs) before surgery (day 0) and daily for 7 days after the operation (days 1–7). The mechanical PWTs in the right hind paw were measured by an experimenter blinded to treatment groups

using von Frey monofilaments (0.41, 0.70, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 g; Stoelting, Wood Dale, IL, USA). Ipsilateral mechanical PWTs were tested by the "up-down" method. A sudden withdrawal of the right hind paw after stimulation was seen as a positive response. The responses were then converted to a 50% threshold (50% threshold = $10^{(X-\kappa d)}/10^4$) as previously published [20].

2.5. Spinal Specimen. All animals were euthanized after PWTs were tested on day 7 after the operation. Rats were anesthetized with 10% chloral hydrate and then received cardiac perfusion with phosphate-buffered saline (PBS). The right spinal dorsal horns from L4–L6 were exposed, rapidly separated, and then stored in a −80°C freezer.

2.6. Enzyme-Linked Immunosorbent Assay (ELISA). TNF-α, IL-1β, IL-6, cAMP, and cGMP levels in the spinal cord were measured by ELISA. The tissues were homogenized in PBS solution (pH 7.4, containing 1% Triton-X100, 1 mM PMSF, 10 g/mL aprotinin, and 1 g/mL leupeptin). The homogenized samples were subsequently centrifuged at 10000 g for 30 minutes at 4°C. Then, the supernatant was aliquoted and stored at −80°C. Supernatants were assayed using the manufacturer's instructions for the rat TNF-α, IL-1β, IL-6, cAMP, and cGMP ELISA kits (R&D Systems, Minneapolis, MN, USA).

2.7. Real-Time Polymerase Chain Reaction (RT-PCR). PDE2A and NF-κB/p65 mRNA were measured by RT-PCR. Following the manufacturer's protocol, total RNA was isolated from homogenized ipsilateral L4–L6 spinal dorsal horns using the TRIzol reagent (Invitrogen Corp., Carlsbad, CA, USA). Total RNA was then reversely transcribed into cDNA, with the MML-V reverse transcriptase kit (Western Biotechnology, Chongqing, China). PDE2A and NF-κB/p65 mRNA were examined by a PCR system (FTC2000q PCR System; Conrem, Canada) with real-time PCR master mix kit (Fermentas, Glen Burnie, MD, USA). PDE2A and NF-κB/p65 mRNA level were quantified relative to β-actin using the relative quantification $2^{-\Delta\Delta CT}$ method.

2.8. Western Blotting. The protein expressions of PDE2A and NF-κB/p65 were analyzed by western blotting. Ipsilateral spinal dorsal horn tissue from L4–L6 were homogenized by radio immunoprecipitation assay (RIPA) lysis buffer (Western Biotechnology, Chongqing, China) at 100 mg tissue per mL and centrifuged. Then, the samples were separated on a 10% sodium dodecyl sulfate- (SDS-) polyacrylamide gel electrophoresis (PAGE) gel for 45 minutes and electrophoretically transferred onto a polyvinylidene difluoride (PVDF) membrane (Millipore, USA) for 1 hour at 37°C. The membranes were blocked with 5% fat-free milk in Tris buffer solution (TBS-T) with 0.01% Tween 20 (TBS-T) (Sigma-Aldrich) for 2 hours at 37°C to eliminate nonspecific binding. The membranes were washed in Tris-buffered saline (TBS-T) and incubated with primary PDE2A and NF-κB/p65 antibody (1 : 1000 dilution, Western Biotechnology, Chongqing, China) and rabbit-anti-GAPDH (1 : 3000 dilution, Western Biotechnology, Chongqing, China). The membranes were then incubated at 4°C overnight, washed with TBS-T, and incubated with anti-rabbit secondary antibody (1 : 5000 dilution; Western Biotechnology, Chongqing, China) for 1.5 hours at 37°C. After adequate washing with TBS-T, the protein bands were visualized by enhanced chemiluminescence according to the manufacturer's instructions. Signals were quantified by the UVP gel Imaging System (BioSpectrum, USA), and values were normalized to GAPDH.

2.9. Statistical Analysis. SPSS software (SPSS 20.0, Chicago, IL) was used. Data are presented as the mean ± SEM. The data were measured by Student–Newman–Keuls post hoc test for normal distributions, and analyses between groups were performed using one-way analysis of variance (ANOVA). Results were considered statistically significant if the P value was less than 0.05.

3. Results

3.1. 10, 20, or 30 μg/mL O_3 Treatment Improved the Mechanical PWTs in Chronic Radiculitis Rats. Mechanical PWTs were not significantly different between groups before the operation ($P > 0.05$). There was no significant difference in the sham group PWTs after the operation compared to before the operation ($P > 0.05$). Ipsilateral mechanical PWTs were significantly reduced after operation in the control group ($P < 0.05$) and in the 10, 20, and 30 μg/mL O_3 groups ($P < 0.05$) compared to the sham group and the within-group measurements prior to operation. Ipsilateral mechanical PWTs were significantly improved in the 10, 20, and 30 μg/mL O_3 groups from days 2 to 7 after operation ($P < 0.05$) compared to the control group. In addition, mechanical PWTs on days 2–7 were increased significantly in the 20 μg/mL O_3 group ($P < 0.05$) compared to the 10 or 30 μg/mL O_3 groups (Figure 1).

3.2. 10, 20, or 30 μg/mL O_3 Reversed the Increased Spinal TNF-α, IL-1β, and IL-6 Protein Expression Levels in Chronic Radiculitis Rats. There were significant increases in spinal TNF-α, IL-1β, and IL-6 protein expression levels ($P < 0.05$) in the control group compared to the sham group on day 7 after operation. However, the protein expressions of spinal TNF-α, IL-1β, and IL-6 were significantly lower in the 10, 20, and 30 μg/mL O_3 groups ($P < 0.05$) compared to the control group. Furthermore, the expression levels of spinal TNF-α, IL-1β, and IL-6 in the 20 μg/mL O_3 group were significantly decreased ($P < 0.05$), compared to the 10 or 30 μg/mL O_3 groups (Figure 2).

3.3. Effects of 10, 20, or 30 μg/mL O_3 on cAMP and cGMP in the Spinal Cord of Chronic Radiculitis Rats. There was a significant increase in the expression level of cGMP in the control group ($P < 0.05$) compared to the sham group.

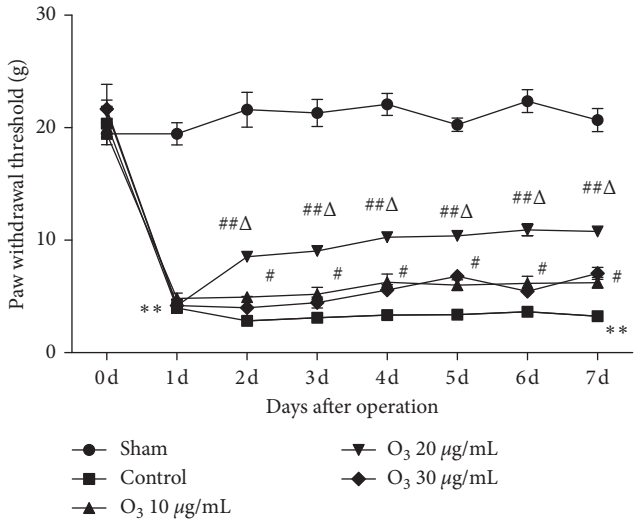

Figure 1: Treatment with low-concentration O_3 improved mechanical allodynia in chronic radiculitis rats. Implanted autologous nucleus pulposus (NP) led to ipsilateral radicular inflammation. There was no significant difference in paw withdrawal thresholds (PWTs) between groups to mechanical stimuli prior to operation. Ipsilateral PWTs in the control group and 10, 20, and 30 μg/mL O_3 groups were significantly reduced on day 1 after NP implantation ($P < 0.05$) compared to the PWT before the operation and to the sham group. After intrathecal O_3 administration, the ipsilateral PWTs were significantly elevated in the 10, 20, and 30 μg/mL O_3 groups ($P < 0.05$) from day 2 to day 7 after NP implantation. Compared with the 10 μg/mL and 30 μg/mL O_3 groups, the ipsilateral PWTs were significantly increased in the 20 μg/mL O_3 group. The values are expressed as mean ± SEM. $^*P < 0.05$ vs. sham group; $^{\#}P < 0.05$ vs. control group; $^{\Delta}P < 0.05$ vs. 10 μg/mL and 30 μg/mL O_3 groups.

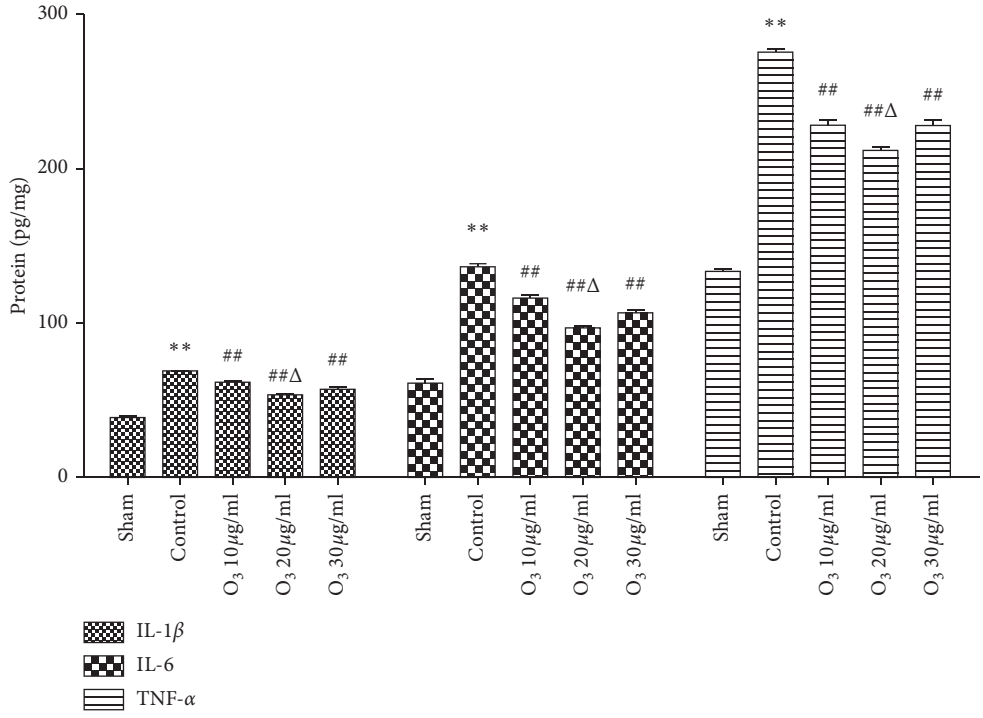

Figure 2: Low-concentration O_3 treatment reversed the overexpression of tumor necrosis factor- (TNF-) α, interleukin- (IL-) 1β, and IL-6 in chronic radiculitis rats. TNF-α, IL-1β, and IL-6 proteins were all significantly increased in the control group ($P < 0.05$) on day 7 compared to the sham group. Compared to the control group, TNF-α, IL-1β, and IL-6 proteins were significantly decreased in the 10, 20, and 30 μg/mL O_3 groups ($P < 0.05$). These effects were most noticeable in the 20 μg/mL O_3 group ($P < 0.05$) compared to those in the other O_3 groups. The values are expressed as mean ± SEM. $^*P < 0.05$ vs. sham group; $^{\#}P < 0.05$ vs. control group; $^{\Delta}P < 0.05$ vs. 10 μg/mL and 30 μg/mL O_3 groups.

However, cAMP expression was not significantly different between the control and sham groups ($P > 0.05$). The protein expression levels of both cAMP and cGMP were significantly increased in the 10, 20, and 30 μg/mL O_3 groups ($P < 0.05$) compared to the control group. Furthermore, the increases of cAMP and cGMP were the most significant in the 20 μg/mL O_3 group ($P < 0.05$), compared to the 10 or 30 μg/mL O_3 groups (Figure 3).

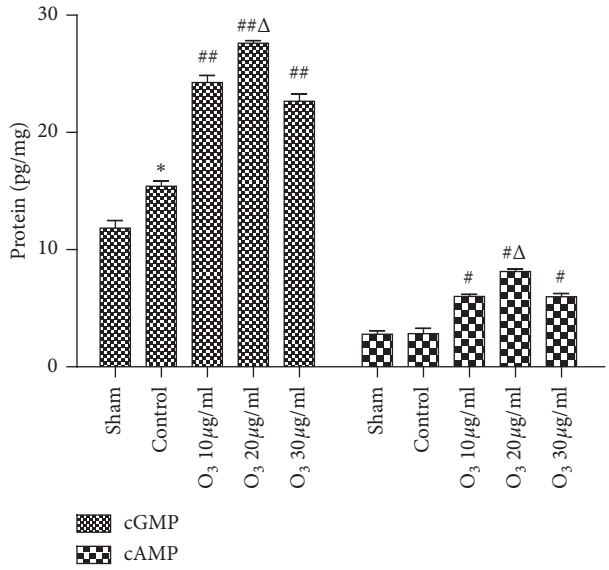

Figure 3: Low-concentration O_3 upregulated the expressions of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), but especially cGMP, in chronic radiculitis rats. cGMP was significantly increased in the control group after nucleus pulposus implantation on day 7 ($P < 0.01$). Both cGMP and cAMP were significantly increased to a greater extent in the 10, 20, and 30 μg/mL O_3 groups ($P < 0.05$) at day 7; this effect was especially pronounced for cGMP. These effects were most noticeable in the 20 μg/mL O_3 group ($P < 0.05$). The values are expressed as mean ± SEM. $^{*}P < 0.05$ vs. sham group; $^{\#}P < 0.05$ vs. vehicle group; $^{\Delta}P < 0.05$ vs. O3 10 μg/mL and 30 μg/mL groups.

3.4. 20 μg/mL O_3 Downregulated the Overexpression of Spinal PDE2A and NF-κB/p65 in Chronic Radiculitis Rats. The mRNA and protein expression levels of PDE2A and NF-κB/p65 in the spinal cord on day 7 after operation were significantly upregulated in the control group ($P < 0.05$) compared to the sham group. However, the expression levels of PDE2A and NF-κB/p65 in the 20 μg/mL O_3 group were significantly downregulated ($P < 0.05$) compared to the control group (Figure 4).

4. Discussion

LDH is one of the most familiar diseases that are commonly accompanied by severe radiculitis. Radiculitis causes immense suffering for patients with LDH. Radicular inflammation is one of two common reasons for pain induced by lumbar disc herniation, the other reason being the direct compression of the herniated disc [15, 24, 25]. Many different drugs and minimally invasive techniques, such as nonsteroidal anti-inflammatory drugs (NSAIDs), epidural injection of steroid hormones [26], and/or O_3, have been used for the treatment of radiculitis in LDH. Among these treatment methods, O_3 therapy is a common, minimally invasive technique used in some countries, including Italy, China, and Canada, where it has recently been widely applied in the clinical management of pain [24, 25].

Ozone is an unstable gas with a pungent smell, which has a dual role. To date, O_3 therapy has been widely used in oncology, gynecology, skin and mucosal infections, pain management, and other medical conditions because of its anti-inflammatory, antioxidant, antiseptic, and disinfectant properties [26, 27]. Furthermore, O_3 treatment has been shown to have therapeutic effects in patients with lumbar disc herniation [25, 28]; Giurazza et al. found that O_3 therapy used for the treatment of low back pain was safe and effective and that the benefits lasted for up to 10 years after treatment [29]. Melchionda et al. reported that paravertebral injections with oxygen-ozone could induce a direct improvement in radicular inflammation and pain [10]. Bocci found that different concentrations of ozone have different and even contradictory effects [30]. In our previous studies, we also found that intrathecal injection of high concentration ozone (40–60 μg/mL) could induce neurotoxicity, whereas intrathecal injection of low-concentration ozone (<40 μg/mL) is a rarely induced neurotoxicity. [14]. Although O_3 therapy is now used worldwide, there are very few studies aimed at investigating the mechanisms underlying the use of intrathecal injection of low-concentration O_3 for the treatment of radiculitis caused by LDH.

TNF-α, IL-1β, and IL-6 are potent proinflammatory factors, which play an important role in radicular pain [3–5]. Some scholars found that a single subcutaneous injection of O_3 could decrease the overexpression of IL-1β in SNI models [15]. In other studies, O_3 was found to decrease levels of TNF-α and IL-1β and also prevent demyelination [31–33]. In the present study, we confirmed that mechanical PWTs decreased significantly during the 7 days following NCLDH operation and that spinal levels of TNF-α, IL-1β, and IL-6 increased significantly in radiculitis rats. Furthermore, intrathecal injection of 10, 20, or 30 μg/mL O_3 reduced mechanical allodynia and suppressed the overexpression of TNF-α, IL-1β, and IL-6 in the spinal cord. We speculate that intrathecal administration of low-concentration O_3 diminishes radicular inflammation by reducing TNF-α, IL-1β, and IL-6 in radiculitis rats. We found that intrathecal injection of 20 μg/mL O_3 led to the most significant reduction of mechanical allodynia and the largest decreases in the spinal TNF-α, IL-6, and IL-1β levels. These results are consistent with the opinion that ozone with proper concentration could be atoxic and therapeutic [12, 13].

PDEs are enzymes that regulate the physiological function by hydrolyzing cAMP and/or cGMP and are classified into 11 families, PDE1 to PDE11. There is general consensus that PDE2A is abundant in the central nervous system of mammals, especially in the laminae I and II of spinal dorsal horn in rats [20, 34]. In addition, PDE2A might contribute to acute inflammatory pain processing [19]. Recent experiments have detected that an inhibitor of PDE2A had anti-inflammatory and analgesic effects [35]. In a previous study, we found that the expression of PDE2A was upregulated in NCLDH rats, and that the PDE2A inhibitor, BAY 60-7550, could suppress the release of spinal TNF-α, IL-6, and IL-1β and also improve the mechanical allodynia by increasing the levels of cAMP and cGMP [21]. However, the signaling pathways between PDE2A and low-concentration O_3 are not clear. In the present study, we

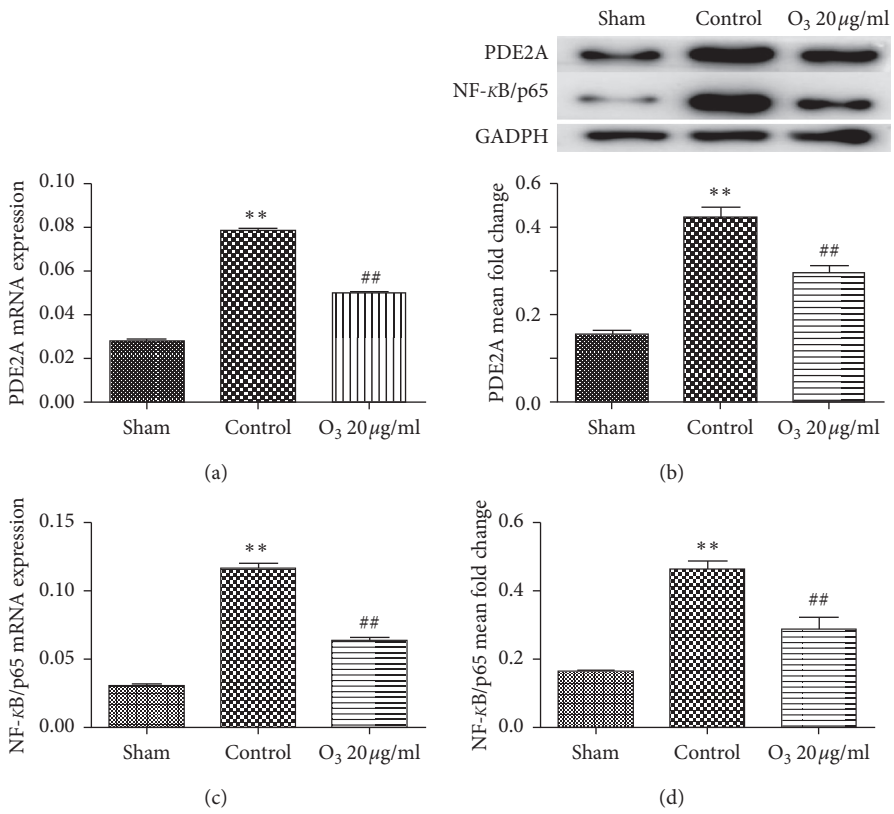

Figure 4: 20 μg/mL oxygen/ozone suppressed the expression of phosphodiesterase 2A (PDE2A) and nuclear factor- (NF-) κB/p65 mRNA and protein on day 7 in chronic radiculitis rats. The expression of both PDE2A mRNA (a) and protein (b) in the ipsilateral spinal cord was significantly increased on day 7 in the chronic radiculitis control group ($P < 0.05$). 20 μg/mL O_3 significantly reversed the overexpression of PDE2A that was induced by autologous nucleus pulposus implantation ($P < 0.05$). The expressions of both NF-κB/p65 mRNA (c) and protein (d) in the spinal cord were also elevated on day 7 in the control group ($P < 0.05$). Both NF-κB/p65 mRNA and protein expressions were significantly decreased in the 20 μg/mL O_3 group ($P < 0.05$) compared to the control group. The values are expressed as mean ± SEM. $^{*}P < 0.05$ vs. sham group; $^{\#}P < 0.05$ vs. control group.

found that 20 μg/mL O_3 could downregulate the overexpression of PDE2A and upregulation of cGMP and cAMP. Therefore, we inferred that low-concentration O_3 decreased the overexpression of spinal PDE2A, which lessens the hydrolysis of cAMP and cGMP, which leads to alleviation of radiculitis and mechanical allodynia.

Some scholars found that both cAMP and cGMP, as well as nuclear factor-kappa B (NF-κB), are components of downstream signaling pathways of PDEs [11, 20, 26]. Moreover, researchers discovered that inhibition of NF-κB induces increased levels of cGMP [36]. Additionally, cGMP and NF-κB are involved in antioxidative and anti-inflammatory treatments for cancer, neurodegenerative diseases, and low back pain [37–39]. The NF-κB/p65 heterodimer is an important transcription factor in the development of inflammation and pain and is widely expressed in the central nervous system [36]. Luo et al. found that NF-κB/p65 in the spinal cord was activated in chronic arthritic models and that inhibiting the NF-κB/p65 pathway could reduce painful inflammatory disorders [35]. In the current study, we found that the level of NF-κB/p65 in the spinal cord significantly increased after NP implantation; furthermore, 20 μg/mL O_3 downregulated the expressions of NF-κB/p65 and increased cGMP and cAMP in chronic radiculitis rats. Therefore, we speculate that low-concentration O_3 inhibits inflammation by modulating the PDE2A-cAMP/cGMP-NF-κB/p65 signaling pathway.

5. Conclusion

Intrathecal injection of low-concentration O_3 (10, 20, or 30 μg/mL) reduces the overexpression of TNF-α, IL–6, and IL-1β and also significantly alleviates mechanical allodynia in chronic radiculitis rats. Furthermore, 20 μg/mL O_3 decreases the overexpression of PDE2A and NF-κB/p65 while also upregulates cGMP and cAMP. We believe that radiculitis and mechanical allodynia might be attributed to the PDE2A-cAMP/cGMP-NF-κB/p65 signaling pathway in chronic radiculitis rats and that low-concentration O_3 attenuates radiculitis and mechanical allodynia by altering this signaling pathway.

5.1. Study Limitations. Although 20 μg/mL O_3 produced the strongest anti-inflammatory effects in the present study, we cannot infer that 20 μg/mL O_3 is the best concentration to use in the treatment of radiculitis patients. However, our results indicate a potential clinical application of low-concentration O_3 in the treatment of patients with radiculitis from LDH.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This study was funded by the National Natural Science of China (Grant nos. 81271346 and 81771199) and Natural Science Foundation in Shandong Province of China (ZR2010HM097).

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Hindawi
Pain Research and Management
Volume 2018, Article ID 2010129, 14 pages
https://doi.org/10.1155/2018/2010129

Review Article

The Diagnosis and Therapy of Degenerative Knee Joint Disease: Expert Consensus from the Chinese Pain Medicine Panel

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Received 21 June 2018; Accepted 19 November 2018; Published 13 December 2018

Guest Editor: Baogan Peng

At present, there are many constantly updated guidelines and consensuses on the diagnosis and treatment of osteoarthritis both at home and abroad. The recommendations established using methods of evidence-based medicine has experienced strict research on controlling bias and promoting reproduction rate. As a result, the previous evidence was reevaluated, and a lot of changes were provoked in the diagnosis and treatment concept of osteoarthritis. However, several methods not recommended by foreign guidelines are still in use in the current clinical practice in China. On the one hand, Chinese experts have not reached extensive consensus on whether it is necessary to make changes according to foreign guidelines. On the other hand, almost all the current relevant guidelines are on osteoarthritis, but the lesions around knee joints which, as a whole, bear the largest weight in human body, cannot be ignored. For this purpose, Chinese Association for the Study of Pain (CASP) organized some leading experts to formulate this Chinese Pain Specialist Consensus on the diagnosis and treatment of degenerative knee osteoarthritis (DKOA) in combination with the guidelines in foreign countries and the expert experience of clinical practice in China. The consensus, which includes the definition, pathophysiology, epidemiology, clinical manifestation, diagnostic criteria, and treatments of DKOA, is intended to be used by first-line doctors, including pain physicians to manage patients with DKOA.

1. Overview

Degenerative knee osteoarthritis (DKOA) refers to a group of diseases caused by the degenerative changes and chronic cumulative damage of the knee joint, with knee articular cartilage denaturation and destruction, subchondral bone sclerosis or cystitis, hyperosteogeny of joints margin, synovium lesions, and/or the decompensated changes in

surrounding tendons, ligaments, and other structures as the main pathological manifestations, knee joint pain, and movement restriction as the main clinical manifestations [1]. At present, there are many constantly updated guidelines and consensuses on the diagnosis and treatment of osteoarthritis both at home and abroad. The recommendations established using methods of evidence-based medicine have experienced strict research on controlling bias and promoting reproduction rate. As a result, the previous evidence was reevaluated, and a lot of changes were provoked in the diagnosis and treatment concept of osteoarthritis. For example, the Guideline on Evidence-Based Medicine for Knee Osteoarthritis (2nd edition) promulgated by American Academy of Orthopaedic Surgeons (AAOS) in 2013 pointed out that there is clear evidence that patients are not recommended for intra-articular injection of sodium hyaluronate, arthroscopic lavage, etc. However, such methods are still in use in the current clinical practice in China. On the one hand, Chinese experts have not reached extensive consensus on whether it is necessary to make changes according to foreign guidelines. On the other hand, almost all the current relevant guidelines are on osteoarthritis, but the lesions around knee joints which, as a whole, bear the largest weight in human body cannot be ignored. For this purpose, Chinese Association for the Study of Pain (CASP) organized some leading experts to formulate this Chinese Pain Specialist Consensus on the diagnosis and treatment of degenerative knee osteoarthritis (DKOA) in combination with the guidelines in foreign countries and the expert experience of clinical practice in China. The consensus is mainly to guide first-line doctors, including pain physicians, in the clinical diagnosis and treatment of DKOA.

2. Etiology and Pathogenesis

(1) Risk factors such as age, obesity, gender, region, occupation, ethnicity, hormonal status, and genetic factors are associated with the morbidity of DKOA, among which age and obesity are of special importance. The specific pathogenesis of DKOA remains unclear. At present, it is generally agreed that the imbalance of anabolic and catabolic changes in chondrocytes, extracellullar matrix, and subchondral bone caused by both biomechanical and biological factors is one of the important pathogenic factors [1]. The main pathological changes are apoptosis of chondrocytes and abnormal extracellullar matrix. The type II collagen provides a meshwork that parallels to the articular surface, proteoglycans, and water are embedded within this framework, providing compressive resistance. As the joint is subjected to repeated and excessive loads, these meshwork changes and anticompression ability will be weakened, abnormal proliferation and apoptosis of the chondrocytes will be abnormally proliferated and apoptotic, and various cytokines, free radicals, and enzymes will be released. As a result, the pathological changes will be aggravated [2], causing cartilage damage and injury of the supporting structure [3]. Besides, metabolic factors such as hypertension, dyslipidemia, osteoporosis, and impaired glucose tolerance also affect the occurrence and development of the DKOA [4]. COL2A1 was the first mutant gene that has been found to be associated with the pathogenesis of DKOA [5], and after that, 10 more mutations were reported in succession [6].

(2) Acute and chronic knee injuries substantially increase the risk of DKOA [7, 8], and it is considered that the severity of synovitis is associated with the progression of DKOA [9]. Anatomical abnormalities of the joint such as varus and valgus deformity may facilitate the development of DKOA and functional incapacitation [10], as a result of imbalance distribution of stress caused by anatomical changes [11]. Muscle weakness and ligamentous laxity which give rise to joint instability are also deemed to be the risk factors of DKOA [12], so exercise is beneficial to the treatment and remission of DKOA [13].

(3) Periarthritis of knee is essentially an adaptive change after long-term load and damage, and this change can hardly compensate the original function. During the procedure, aseptic inflammation could be induced, that is why nonsteroidal anti-inflammatory drugs are effective. Within limits, adaptive change of the joint structure like tendon and ligament can increase the capability of the withstanding load. However, pathological changes will appear when the load is beyond compensation [14]. In the area with poor blood supply, ischemia and hypoxia can cause degeneration and necrosis, and at the same time, the expression of inflammatory mediators, enzymes, and vascular growth factors is upregulated, which lead to angiogenesis and tissue damage, inducing pain [15].

3. Epidemiology

The prevalence of symptomatic knee osteoarthritis (KOA) diagnosed by the clinician ranges from 4.2%–15.5%, increasing with ageing, and is associated with region, ethics, etc [16]. In Chinese population, the prevalence of symptomatic KOA was 8.1%, presenting a difference in sex (10.3% in women and 5.7% in men) and region (2 times higher in rural areas than in urban areas) [17]. The prevalence of KOA based on radiography is much higher, about 80% of the population above 65 years reveals radiographic evidence of KOA, and only 60% of those have symptoms [18, 19]. KOA, the leading cause of pain and disability worldwide, ranked 11th among 291 disease for disability globally [18, 19]. Almost 1/4 of KOA patients will suffer severe joint pain. Periarticular lesions and inflammation arose from synovium ligament, tendon, and muscle are major causes of knee osteoarthrosis, existing alone or coexisting with KOA. In population with the painful knee, the prevalence of gonarthromeningitis reached 67%, while bursal synovitis reached 0.2%–0.7% [20–22].

4. Classification and Clinical Characteristics of Degenerative Knee Osteoarthritis

According to the position of lesions, the classification and clinical characteristics of degenerative knee osteoarthritis are as follows:

(1) Degenerative knee osteoarthritis [23]
(2) Chondromalacia patellae [24]
(3) Patellar tendonitis [25]
(4) Subpatellar fat pad inflammation [26]
(5) Medial collateral ligament inflammation [27]
(6) Lateral collateral ligament inflammation [28]

5. Clinical Manifestation (Includes Symptom, Sign, Laboratory Examination, and X-Ray Examination)

5.1. Degenerative Knee Osteoarthritis

5.1.1. Clinical Manifestation. DKOA is commonly seen in wrinkly and elderly people, and the main clinical symptom is arthralgia, which is manifested by recent recurrent knee joint pain [29]. Arthralgia is aggravated after moving or bearing weight, while relieves after rest. Local tenderness is an obvious symptom. Some patients have morning stiffness, but the symptom is no more than 30 minutes. With the disease progressing, the knee joint would be swollen, articular cartilage destruction, articular surface roughness, and bony crepitus (sense) may occur with joint activity. Joint deformity may appear as the patient's condition is further aggravated.

5.1.2. Auxiliary Examination. Laboratory examinations show that the level of C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) are normal or slightly elevated. Articular cavity effusion (at least 2 times) is clear and sticky, and the leukocyte count is less than 2000 mL. The X-ray examination in standing or weight-bearing position shows that the joint space appears asymmetrical narrow, the subchondral bone appears sclerosis and cystic degeneration, and the joint marginal appears osteogenesis and forms osteophyte, and the joint may even appear deformity.

5.2. Chondromalacia Patellae

5.2.1. Clinical Manifestation. Chondromalacia patellae is common in sports enthusiasts, most of whom has a history of trauma. Initial pain appears in the patella or knee. It is obvious at the beginning of activity, while alleviated quickly. But the pain will aggravate with prolonged exercise and then disappears after rest. When the condition is aggravated, the pain time is longer than that of the remission time. In severe cases, patients cannot be squatted and have trouble in step movement. Sometimes, patients appear lower extremity weakness suddenly and fall down. Physical examinations suggest that the prevalence of patellar edge tenderness in these patients is more than 90%. Grinding the patella in extending the position may result in patella friction and associated pain [30].

5.2.2. Auxiliary Examination. In the early stage, there is no abnormality in the X-ray film. In the advanced stage, osteophyte would be formatted at the edge of the patella, the patella joint surface would be unsmooth, and the joint space would be narrow. Radionuclide bone imaging examination can reveal the localized radionuclides of the patella, which is essential for early diagnosis.

5.3. Patellar Tendinitis

5.3.1. Clinical Manifestation. Pain and tenderness appear in the tibial tuberosity and the patellar ligament. When the illness state is slight, knee movement is normal, only with weakness and pain. With the illness state aggravating, patients feel difficult to go up and downstairs, and often keep knee joint in the flexed position because of straightening pain [31].

5.3.2. Auxiliary Examination. X-ray shows sclerosis, roughness, and bone hyperplasia on patellar articular surface. MRI examination has a specific diagnostic value.

5.4. Subpatellar Fat Pad Inflammation

5.4.1. Clinical Manifestation. Subpatellar fat pad inflammation most commonly occurred in mountain-climbing enthusiasts and long-term squatting position workers, who have a long history of knee joint strain. The disease develops slowly, and is manifested as pain in the knee joint and asthenia at the anterior inferior side of the knee. The tenderness appears in the lower margin of the patella and both sides of the patellar tendon. The knee joint pain aggravates with activity and alleviates after rest. With the patients condition worsened, the pain will be persistent and aggravated when squatting or going up and downstairs [32, 33].

5.4.2. Auxiliary Examination. Knee joint X-ray examination can help exclude knee osteoarthritis, and MRI examination can help exclude knee joint meniscus and other injuries.

5.5. Knee Joint Medial Collateral Ligament Inflammation

5.5.1. Clinical Manifestation. Knee joint medial collateral ligament inflammation is common in ball and snow athletes because of more jumping activities. Pain appears in the medial part of the knee when medial accessory ligament is damaged. When medial accessory ligament is partly ruptured, the pain sharpens and walking will be affected. When the ligament is completely ruptured, the pain will be significantly aggravated, and there will be muscle spasm, limitation of knee flexion or extension, and walking

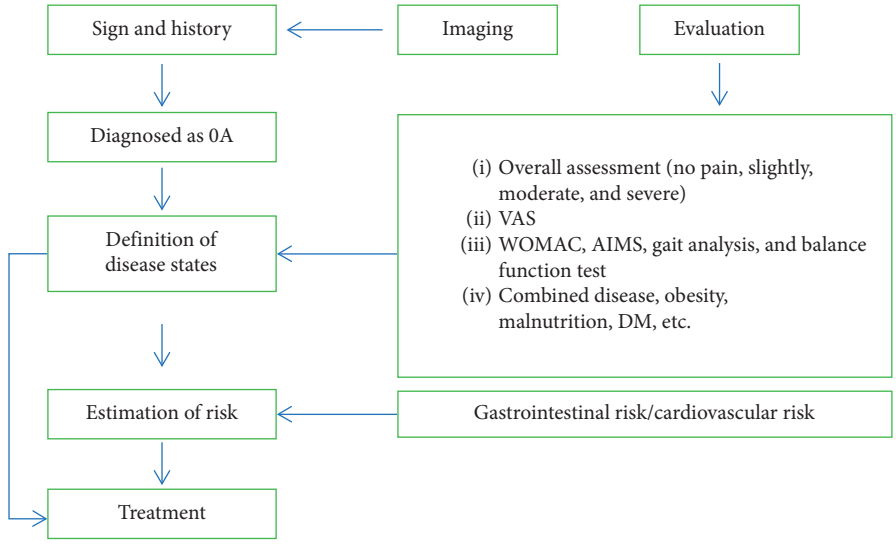

Figure 1

difficulties. Patients with medial accessory ligament inflammation have signs of tenderness at both starting and ending points of medial accessory ligament.

5.5.2. Auxiliary Examination. The X-ray film shows normal findings. MRI could help to determine the degree of injury in the ligament and knee.

5.6. Knee Joint Lateral Collateral Ligament Inflammation

5.6.1. Clinical Manifestation. The patients and their clinical manifestations are the similar to those people with knee medial accessory ligament injury. Knee joint lateral accessory ligament inflammation normally happens after injury. However, because of lateral accessory ligament disconnecting with joint cavity, it rarely causes joint effusion. The tenderness is obvious at both starting and ending points of lateral accessory ligament.

5.6.2. Auxiliary Examination. The MRI examination could help to reflect the damage degree of ligament and effusion in the knee joint.

6. Diagnostic Criteria

6.1. Degenerative Knee Osteoarthritis

(1) Recurrent episodes of genual arthralgia for one month [23, 34, 35]

(2) X-ray examination shows asymmetric arthrostenosis, subchondral bone sclerosis and (or) cystic degeneration, and osteophytes of the joints

(3) Synovial fluid (at least 2 times) is clear and viscous, and the leukocyte count is less than 2000 ml

(4) Middle-aged patients (over 40 years of age)

(5) The time of morning stiffness is less than 30 min

(6) Bony crepitus occurs with joint activity

(7) The level of ESR or CRP is normal or slightly high [36]

Degenerative knee osteoarthritis can be diagnosed by fulfilling following conditions: (1) + (2) or (1) + (3) + (5) + (6) or (1) + (4) + (5) + (6). (7) is for reference.

Imaging classification (Kellgren–Lawrence level).

Grade 0: normal

Grade I: doubtful narrowing of the joint space with possible osteophyte formation

Grade II: possible narrowing of the joint space with definite osteophyte formation

Grade III: definite narrowing of joint space, moderate osteophyte formation, and some sclerosis

Grade IV: large osteophyte formation, severe narrowing of the joint space with marked sclerosis, and definite deformity of bone ends

Diagnostic and evaluation flow chart is shown in Figure 1 [23].

6.2. Chondromalacia Patellae

(1) Pain at the anterior knee or posterior patella, obviously in the squat position [37, 38]

(2) Asthenia of the knee joint was obvious when walking up or downstairs

(3) Patellar tenderness

(4) Patella pressure test (+)

(5) Single leg squat test (+)

(6) X-ray examination shows hyperostosis. Axis examination shows patellar tilt or subluxation, narrowing of lateral joint space

Chondromalacia patellae can be diagnosed by following conditions: meeting (1) + (2) + (3) + (4) + (5) or (2) + (3) + (4) + (5) + (6).

6.3. Patellar Tendonitis

(1) Pain at jumping or squatting and no pain at walking [39]

(2) Pain at the beginning of movement, reduced or disappeared after activities, and feeling fatigued pain after exercise

(3) Patellar tendon tenderness

(4) Local swelling

(5) B-mode ultrasonography shows the signs of patellar tendon inflammation [40]

Patellar tendonitis can be diagnosed by fulfilling following conditions: (1) + (2) + (3) + (4) or (1) + (2) + (3) + (5).

6.4. Subpatellar Fat Pad Inflammation

(1) Genual pain, aggravated when straightening the knee. Have difficulty to go downstairs, with the feeling of asthenia [41]

(2) Xiyan (EX-LE4,5) swelling

(3) Patellar tendon and patellar tip surface tenderness

(4) Hyperextension test of the knee joint (+)

(5) Patellar tendon relaxation test (+)

(6) The X-ray film shows normal finding or a moderate degree of hyperostosis

Subpatellar fat pad inflammation can be diagnosed by fulfilling the following conditions: (1) + (2) + (3) + (4) or (1) + (2) + (3) + (5). (6) is for reference.

6.5. Medial Collateral Ligament Inflammation

(1) Medial of knee joint pain, obviously at walking or squatting [42]

(2) Medial collateral ligament tenderness (+)

(3) Medial collateral ligament local swelling

(4) Lateral compression test (+)

(5) X-ray examination will show specific finding only when calcification of ligament and ossification are formed

Medial collateral ligament inflammation can be diagnosed by fulfilling the following conditions: (1) + (2) + (3) + (5) or (1) + (2) + (4) + (5) conditions can diagnose medial collateral ligament inflammation.

6.6. Lateral Collateral Ligament Inflammation

(1) Lateral of knee joint pain [42]

(2) Lateral collateral ligament tenderness (+)

(3) Lateral compression test (+)

(4) X-ray examination shows calcification of ligament and ossification

Medial collateral ligament inflammation can be diagnosed by fulfilling the following conditions: (1) + (2) + (3) or (1) + (2) + (3) + (4).

It is recommended to use MRI for auxiliary examination, and MRI combined with clinical symptoms and signs can help definitive diagnosis and staging of disease.

7. Differential Diagnosis

7.1. Knee Rheumatoid Arthritis. Knee rheumatoid arthritis is a synovial inflammation disease of the knee caused by various causes. Chronic inflammation of the synovial membrane leads to hyperplasia of the knee joint, erosion of articular cartilage and ligaments, etc., eventually resulting in deformity and loss of function. Knee rheumatoid arthritis usually affects middle-aged women, and its typical symptoms are symmetrical polyarthritis, morning stiffness, and rheumatoid nodules around the knee joints in severe patients. A laboratory test reveals continuing positive in the rheumatoid factor. Magnetic resonance imaging is more sensitive in the early diagnosis of rheumatoid arthritis due to its high tissue resolution [43].

7.2. Rheumatoid Arthritis. Rheumatoid arthritis is closely related to human hemolytic streptococcal infection. The most common clinical manifestations of rheumatoid arthritis are knee pain, myalgia, muscle weakness, increased muscle enzymes, myogenic damage, etc. Irregular fever without chills appears before rheumatism and reveals insensitive to antibiotic therapy, and there are some abnormities in the blood test of autoantibody, such as anti-ENA antibodies, anti-ds-DNA antibodies, anti-platelet antibodies, anti-nuclear antibodies, and anti-cardiolipin antibodies. In the acute phase of the disease, blood sedimentation rate can reach 90 mm/hr or more; the level of C-reactive protein exceeds 30 mg/L (30 μg/mL) and then gradually returns to normal after 1-2 months. The proportion of males and females is nearly equal, and the initial episode affected is more common in 9–17-years-old. The musculoskeletal ultrasound for rheumatic osteoarthropathy in the children can provide an accurate theoretical basis for the diagnosis of the disease [44].

7.3. Posttraumatic Knee Arthritis. The knee joint is the site most susceptible to injury. Posttraumatic knee arthritis is a disease with main clinical manifestations of joint pain and dysfunction, which may occur in any age group, with a history of knee trauma, pain, and even swelling. Its main pathological changes cover traumatic degeneration of articular cartilage and secondary cartilage hyperplasia, ossification. There are no specific laboratory tests for traumatic arthritis. Some X-ray findings of the knee joint include fractures or malunion lines, space narrowing, subchondral articular sclerosis, and bone spur formation, and at late phase, unsmooth joint surface, bone deformation, and intracapsular corpus liberum [45]. Pain may be induced by activities, and patients may feel a sensation of rough friction

when moving the knee joint. However, X-ray imaging shows joint deformation and locked joint.

7.4. Tuberculosis of the Knee Joint. The majority of tuberculosis of the knee joint are secondary to pulmonary tuberculosis, and however, some of them are primary [46]. Generally tuberculosis of the knee joint is of bone type, and the synovium type may exist when the synovial membrane is attacked by hematogenous infections. X-ray imaging of bone type of joint tuberculosis is characterized by asymmetry of the joint space narrowing or destruction of the joint bone and periarticular soft tissue swelling. Synovium type of joint tuberculosis progresses slowly, with bone destruction limited to the edge of the articular surface, which gradually affects the weight-bearing part of knee. The early X-ray examination shows swelling of the joint capsule and articular soft tissue, increased density, normal or widened joint space, and osteoporosis. All these changes are attributed to the formation of granulation tissue and joint effusions arose from swelling and thickening of the synovial membrane. High-frequency ultrasound can show the degrees of synovial thickness, effusion, cartilage, and bone damage in the tuberculosis of the knee joint, having an important value for the diagnosis [47].

7.5. Infectious Arthritis of the Knee. The clinical manifestations of warmth, pain, swelling, and redness and the microbiological examination of the infection site are helpful for diagnosis. In most cases, laboratory tests reveal ESR accelerating, white blood cell count, and C-reactive protein level increasing. WBC count in the synovial fluid sample of the acute infected swollen joint was >20000 μl, and the neutrophils rate was >95%. The viscosity and sugar concentration of synovial fluid decreased. Gram-negative and Gram-positive bacteria in 50% to 75% of the infected joint can be identified by Gram staining. Synovial fluids also require anaerobic and aerobic cultivations. Anaerobic infection can be confirmed from the odor in synovial fluid, gas shadows in joints, or periarticular soft tissue under X-ray imaging. The latest literature proved that procalcitonin has a good efficacy in the diagnosis [48].

8. Prevention and Health Education

Patient education of knee osteoarthritis has been carried out to make patients fully aware of the natural progression of the disease, the purpose of the treatment, the usage and side effects of the medication as well as to minimize psychological burdens. By strengthening self-management, we can significantly improve the quality of life for these patients.

8.1. Self-Management and Countermeasures. To facilitate chronic care management for degenerative knee osteoarthropathy [49, 50], it is essential to emphasize the coparticipation of doctors and patients. This supports patients in developing an efficient self-management scheme. It is furthermore important to educate patients about the disease's etiology, prevention, and treatment. Through the general clinic, standardized telephone follow-up, consulting [51], health examination etc., a high risk population for knee osteoarthropathy will be selected for dynamically tracking the current situation and trend of health change in order to achieve the best preventative care measures.

8.2. Daily Care. It is important to pay attention to the protection of hurt joints at an early stage in order to avoid further damage. Lifestyle changes such as avoiding stair-climbing and crawling for long periods of time can occur. It is advisable to choose a combination of exercises to reduce the frequencies and lasting time of pain. Furthermore, since changes of weather may increase pain, damp as well as cold should be avoided.

8.3. Keeping a Healthy Weight. Patients with BMI > 25 should adopt a low caloric diet as well as get into the habit of performing aerobic exercise [52]. Excessive knee bearing should be avoided in order to reduce the risk of joint degeneration.

8.4. Walking with an Electronic Monitor. Slow walking under guidance of an electronic monitor is advised to activate cartilage metabolism and prevent muscular atrophy [53].

8.5. Psychological and Social Support. Health care staff may give psychological and social support to release the psychological burden of elderly people and increase the compliance of disease treatment.

8.6. Doctor-Patient Communication. Full communication between health care staff and patients on etiology and prognosis of their disease, and comprehensive information about the purpose, curative effect, and rehabilitation measures before and after the treatment with drugs or surgical operations, can greatly improve the compliance of the patients and the prognosis of the disease treatment.

9. Therapies

9.1. Nonpharmaceutical Therapies. Individualized rehabilitation evaluation, including the items of knee joint activity, lower limb muscle and muscle strength, degree of pain, and local soft tissue condition, should be implemented for patients with degenerative knee joint disease, through which comprehensive rehabilitation treatment plan can be formulated.

9.1.1. Physiotherapeutics. Physiotherapy for degenerative knee joint disease may reduce pain and joint stiffness, eliminate inflammation, enhance the stability of muscles and joints, and improve joint function and the ability of daily activities [54, 55].

(1) Ultrashort Wave Therapy. The treatment of degenerative knee joint disease with ultrashort wave therapy can help reduce knee joint pain but has little effect on knee function improvement. Microheat and tepid are commonly chosen in ultrashort wave treatment.

(2) Medium- and Low-Frequency Electric Therapies. Medium- and low-frequency electric therapies are used to treat chronic inflammation, adhesion, muscular atrophy, and joint stiffness. Transcutaneous electrical neural stimulation is an effective way to control pain.

(3) Ultrasound Therapy. Ultrasound therapy can significantly relieve knee pain and partially improve the knee joint function in DKOA patients. Ultrasound therapy is used for the treatment of joint swelling and adhesion.

(4) Shockwave Therapy. Extracorporeal shockwave therapy for degenerative knee joint disease can help relieve knee pain and improve the knee function. The efficacy of moderate energy is better than that of low energy.

(5) Infrared Treatment and Magnetic Therapy. Low energy red light and infrared-ray therapy can help relieve pain and improve knee functions in patients with DKOA. Magnetic therapy is used to treat chronic inflammation such as arthritis and soft tissue inflammation around the joints [56].

(6) Millimeter Wave Therapy. Millimeter wave therapy reduces knee pain score and improves joint activity.

9.1.2. Rehabilitation Therapy. Rehabilitation therapy relieves pain and improves joint activity [57]. Patient education, exercise, and body mass reduction are the economic first-line treatment programs [58, 59].

(1) Exercise Therapy. Exercise therapy mainly focuses on the function of muscle and joint activity [60], which is an important measure to prevent joint degeneration [61, 62]. Exercise therapy includes the following: (1) muscle strength training: strength training for quadriceps, hamstring, hip abductor group, and hip adductor group; (2) joint activity training: from nonweight-bearing to weight-bearing joint activity training; (3) body fitness training (aerobic exercise); (4) walking under the monitoring system.

(2) Spa. Arthritis of different ages can be treated with warm water for rehabilitation, which has obvious advantages and great safety [63, 64].

(3) Application of Walking Aids. Walking aid instrument can be appropriately used to alleviate the knee load for patients suffering from degenerative bone joint disease of the lower extremities.

9.2. Pharmacological Treatment. The main purpose of pharmacological therapy is to relieve pain, reduce inflammatory response, and improve joint function and the quality of life in the patients with degenerative knee osteoarthritis. The commonly used drugs are divided as follows:

9.2.1. Acetaminophen. As a kind of acetanilide antipyretic analgesics, acetaminophen only relieves a mild-moderate pain. This product has no obvious anti-inflammatory effect, and the patients with mild pain can be used as the preferred drug for short-term use. Major adverse reactions include gastrointestinal symptoms and hepatotoxicity. Patients with severe liver and kidney dysfunction and patients allergic to acetaminophen are prohibited to use it [65–67].

9.2.2. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). NSAIDs can be recommended as the first-line drugs in the treatment of DKOA. Of note, NSAIDs should be used with caution in patients who are the elderly or has a history of asthma induced by aspirin, hepatorenal impairment, and coagulative dysfunction. NSAIDs are contraindicated and should be avoided in patients with upper gastrointestinal hemorrhage or perforation. Therefore, the patients should be fully evaluated before using these medicines and following the principle with minimum effective dosage, short course of treatment, and individualization as well.

(1) Oral NSAIDs. The selective NSAIDs could be more targeted to inhibit COX-2 enzyme, and the risk of adverse reaction of the digestive system was lower than that of nonselective NSAIDs. The representative drug is celecoxib.

(2) Topical NSAIDs. Topical NSAIDs could directly be used in the pain site and can quickly exert analgesic effect by penetrating into the local tissue, which can get a high local analgesic dose. Also, compared with Oral NSAIDs, topical NSAIDs have slighter systematic adverse reaction risks. The common adverse reactions for topical NSAIDs are erythema, itching, dryness, etc. These symptoms can be self-relieved [65–70].

(3) Intravenous NSAIDs. Intravenous NSAIDs could be used in patients who are unable to take oral medication or need intravenous fluids. The representative drug is ibuprofen injection.

9.2.3. Opioids. It will be applied for the patients with no response to other analgesics or for the patients with moderate to severe acute and chronic pain. The use of opioids should follow the principle of individuality. Common adverse reactions include dry mouth, nausea, vomiting, dizziness, lethargy, and constipation. The overdose of opioids can cause respiratory depression. Tramadol should not be used in conjunction with 5-hydroxytryptamine drugs in order to avoid the occurrence of 5-hydroxytryptamine syndrome [68, 69].

9.2.4. Glucosamine and Chondroitin Sulfate. Glucosamine is often used in dietary adjuvant therapy for osteoarthritis and can be combined with nonsteroidal anti-inflammatory drugs

[71, 72]. However, the efficacy remains controversial. Some patients may experience gastrointestinal discomfort, lethargy, headache, and skin response. Patients allergic to shellfish are prohibited to take glucosamine.

Chondroitin sulfate can be used as an adjuvant for chronic pain. However, chondroitin sulfate can increase the risk of hemorrhage. Therefore, the patients taking anticoagulant should use such drugs with caution [73].

9.2.5. Glucocorticoid. Intra-articular or pain points glucocorticoids injection may be used to manage acute pain and localized inflammation associated with DKOA, or the pain which is unresponsive to oral or external analgesics. Glucocorticoid can inhibit the protein polysaccharide synthesis in articular cartilage, and long-term use in the articular cavity can aggravate the damage of articular cartilage and aggravate the symptoms. Thus, using articular cavity injection of glucocorticoid arbitrarily is not recommended. As a general rule, the number of injection is limited to three for a single joint per year. The patients with severe mental history, active gastrointestinal ulcer, recent gastrointestinal anastomosis, severe osteoporosis, diabetes, hypertension, and infection are prohibited to use glucocorticoid [65, 74, 75].

9.2.6. Sodium Hyaluronate. Its efficacy is still in controversial. However, it is recommended for early and medium to use for the patients with DKOA.

9.2.7. Vitamins. Due to the antioxidation effect, Vitamins A, C, and E are beneficial for the treatment of DKOA. By the way, vitamin D exerts the therapeutic effect by bone mineralization and cell differentiation [76].

9.3. Traditional Medicine. Traditional medicine includes traditional Chinese medicine, Tibetan medicine, needle knives, silver needles, internal thermal needles, acupuncture, and massage.

Chinese medicine doctors believe that osteoarthritis is a "bone impediment." The main reason is the deficiency of liver, spleen, and kidney, causing the local joints and tendons affected by wind, cold, and wet. Clinically, they often fall into the category of marrow depletion due to kidney deficiency, yang deficiency due to yin excess, and blood stasis [77]. Traditional medicine therapies can be listed as follows:

(1) Internal application of traditional Chinese medicine. Commonly used proprietary Chinese medicines include Huoluo Pills, Duhuojisheng Pills, Zhuangyao Jianshen pills, and Zhuifeng Tougu Pills [78]. Clinically, patients taking Chinese patent medicines orally are advised to regularly test liver and kidney functions to ensure the safety of medication.

(2) External application of traditional Chinese medicine. External application of traditional Chinese medicine, with rare adverse reactions, can significantly relieve mild-to-moderate joint pain. Commonly used methods include Chinese herbal fumigation and washing therapy, Chinese herbal iontophoresis, and Chinese herbal plaster. As herbal analgesics, several Tibetan medicines like Qizheng pain-relieving plaster and Qingpeng ointment exert anti-inflammatory and analgesic effects to help alleviate osteoarthritis pain and discomfort effectively [79]. The main mechanism is that those herbal analgesics can inhibit the abnormal immune activity of the pain pathway [80], inhibit the proinflammatory effects of various cytokines, and delay the destruction of the cartilage matrix.

(3) Cupping therapy. Cupping can alleviate joint pain and stiffness and improve the quality of daily life and general condition [81, 82]. Especially when induration and cords in joints can be palpable, or ache, tenderness, numbness, and other pathological features are existed, cupping therapy combined with stabbing is effective.

(4) Acupuncture therapy. Acupuncture, a non-pharmacological treatment, with few side effects, great safety, and effectiveness, is recommended as a basic therapy for osteoarthritis [83]. Ashi points and local acupoints are often chosen to implement warm acupuncture moxibustion, direct moxibustion, or suspended moxibustion. For severe joint pain, especially in cold cases, warm needle or fire needle therapy is recommended.

(5) Needle knives therapy. Needle knife is a kind of therapeutic tool integrated traditional Chinese medicine and western medicine. The main mechanism of needle knife therapy is to relieve the local myofascial attachment points. By relieving the dynamic imbalance and restoring the mechanical balance of joint, the therapeutic effect can be achieved. For the muscle fascia adhesion, joint function limitation, and obvious deformity, acupuncture treatment is recommended. The choice of the site of administration is at the junction of pain points or tender points around the joints, or at sites of hyperosteogeny of the joints. The treatment was performed once a week, up to 3 times [84, 85].

(6) Silver needles therapy. The silver needle originates from the ancient "Nine-Needles", and it has the function of "treating other areas" and is "good for joints." On account of the unique acupuncture and heat transfer diffusion effect of deep tissue, it produces anti-inflammatory and analgesic effects, improves blood supply, and relaxes muscle contracture. It has a significant long-term effect on chronic pain. Myofascial start and end points, fascial space, and local acupoints around the joints can be selected as the treatment sites of osteoarthritis. The treatment was performed once per week, and two or three times constituted one course of treatment [86, 87].

(7) Internal thermal needles therapy. The internal thermal needle is made on the basis of traditional acupuncture and silver needles, and its mechanism of action is similar to silver needles. Due to the stainless steel material, the thermal conductivity

diffusion effect in the deep soft tissue is not as good as that of the silver needle. The efficacy and mechanism remain to be observed.

(8) Massage therapy. Massage has the effect of activating the circulation, relaxing the muscles and promoting blood circulation, reducing swelling and pain, smoothing the joints, and improving the muscle strength and joint function. It can be combined with other methods.

9.4. Minimally Invasive Therapy. Minimally invasive treatment guided by imaging is an effective method for the treatment of knee osteoarthropathy.

9.4.1. Injection Therapy. Injection is a common method for the treatment of knee osteoarthropathy. For moderate and severe pain, trigger point injection, nerve block, and intra-articular injection can be used. Trigger point injection (local anesthetics + corticoid) can quickly relieve pain in patients with degenerative knee osteoarthritis accompanying ligament and tendon injury or inflammation but is not recommended to be used frequently or for a long time and as a first-line treatment method [88–92]. The injection of glucocorticoid and sodium hyaluronate into a point injection has been controversial. Most guidelines recommend the former [93–96]. Glucocorticoid is recommended when it is joint effusion or resting pain [97]. PRP [98–100] and ACS [101–103] have been used more in recent years and can be used in articular injection [97, 104]. Especially, it is safe and effective for PRP to be injected into the articular cavity for the treatment of osteoarthritis [105]. The more mature methods of nerve block for knee osteoarthritis are mainly femoral nerve [106], adductor canal, and saphenous nerve block [107–110]. Contraindications should be strictly controlled in injection therapy, especially in intra-articular injection [111]. Patients with local skin diseases at the injection site, diabetes mellitus, high blood pressure, and mental illness should be implemented with caution. The local or total body infection and low immune function are contraindications. If trigger point injection has been implemented for 2~3 times and the pain was not relieved, alternative treatment strategies should be considered.

9.4.2. Radiofrequency Therapy. Indications are as follows: (1) knee OA with moderate to severe pain and no response to at least 3–6 months of conservative treatment; (2) persistent pain after total knee arthroplasty (TKA) and conservative treatment [112, 113].

Contraindications are as follows: acute knee pain, bleeding tendency, localized infection, systemic infections, neurologic or psychiatric disorders, pregnancy, and pacemakers.

Procedures and adverse reactions:

(1) RFS (standard radiofrequency): RFS can be performed under X-ray or ultrasonic imaging guidance, with a cannula advanced into the joint towards the area connecting the shaft to the epicondyle. The area is stimulated to identify the nerve position and to ensure that no motor nerves are activated, as evidenced by absence of fasciculations. The RF electrode is then advanced through the cannula to the target area. The electrode tip heats up targeted local tissue within a few millimeters to a temperature typically greater than 65~90°C for 120~130 seconds. Adverse effect is as follows: prolonged (2–6 weeks) hypoesthesia in the medial aspect of the knee was observed.

(2) RFP (pulsed radiofrequency): The pulse generator produces pulses with an amplitude of 45 V lasting 20 milliseconds every 500 milliseconds (twice per second). The tissue temperature reaches a maximum of 42°C. Targets are as follows: (a) intra-articular: the entry point for the RF cannula was the anterolateral aspect of the knee midway between the femoral and tibial surfaces. RFP lasts for 10–15 min. (b) Major nerves or their main branches: femoral and sciatic nerves or their main branches (saphenous, tibial, and common peroneal nerves) were targeted. RFP lasts for 4–8 min. No adverse reactions were reported.

9.4.3. Intra-Articular Ozone Injection Therapy. Indications are as follows: knee OA pain, Kellgren–Lawrence grade 2-3 [114–117].

Contraindications are as follows: ozone allergy, hyperthyroidism, G-6-PD deficiency, recent myocardial infarction, bleeding tendency, and pregnancy. Be cautious when hepatic and renal insufficiency were present.

Procedure and adverse reactions are as follows: intra-articular applications with an ozone concentration of 20–30 mg/L and volumes between 5 and 15 mL once a week for 3-4 weeks. Adverse reactions like transient pain when injecting was reported.

9.4.4. Cryotherapy. Cryotherapy following total knee replacement (TKR): application of cold temperatures to the skin around the knee following surgery by means of ice packs, cooling pads, or other commercial devices within 48 hours after surgery, either continuously or replacing ice packs every 1.5–4 hrs [118]. Blood loss and pain could be improved mildly. Adverse reactions include discomfort, local skin reactions, superficial infection, cold injury, and venous thrombosis.

Cryoneurolysis of infrapatellar branch of the saphenous nerve (IPBSN): (1) indication: knee OA with moderate to severe pain, Kellgren–Lawrence grade 2-3, ≥50% reduction in VAS pain score when performing the activity that elicited the worst pain following a diagnostic lidocaine block of the IPBSN; (2) contraindication: gross deformity of the knee and body mass index (BMI) ≥35 kg/m^2; (3) procedure and adverse effects: inject nitrous oxide with iovera device to form a highly localized cold zone via the Joule–Thompson effect. Low temperatures (−20°C to −100°C) to peripheral nerves cause Wallerian degeneration. Adverse effects include

altered sensation, bruising, crusting, hyperpigmentation, itching, local pain, numbness, redness, swelling, tenderness on palpation, and tingling.

9.5. Surgical Management. Patients with severe lesions and obvious dysfunction of the knee who failed the treatments above may be considered to have surgical management, which includes the following: (1) knee arthroscopy [119, 120]: arthroscopic intra-articular lavage is performed to remove fibrin, cartilage residues, and other impurities if other minimally invasive treatments were invalid; arthroscopy with partial meniscectomy, joint debridement, or a combination of both techniques may be effective in patients who had mild-to-moderate osteoarthritis of the knee with a varus or valgus angle <5°; and however, the conventional application of arthroscopy was not supported by most of the literature evidences. There are adverse reactions such as deep vein thrombosis, pulmonary embolism, infection, and even death. (2) Osteotomy [121]: it can improve the balance of the joint force line and effectively relieve the knee pain in patients. (3) Arthroplasty [122–124]: progressive degenerative knee osteoarthritis in patients over 60 years with poor conservative management may be treated with joint replacement, which can significantly alleviate pain and improve the physical function of the knee. (4) Arthrodesis [125].

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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