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ABOUT COVER

Editor-in-Chief of *World Journal of Clinical Cases*, Bao-Gan Peng, MD, PhD, is Professor and Director of the Department of Orthopedics at The Third Medical Center of PLA General Hospital. Professor Peng's research interest is spinal surgery. His career work has generated a multitude of new academic viewpoints and theories, and more than 200 academic papers, published both at home and abroad. In practice, he has systematically elucidated the pathogenesis of discogenic low back pain and established a new minimally invasive treatment method: The intradiscal methylene blue injection. He also revealed and characterized a new pathogenesis of Schmorl's nodes, which is a now a famous concept. Finally, he was the first to discover that ingrowth of Ruffini corpuscles into degenerative cervical disc is related to dizziness of cervical origin. (L-Editor: Filipodia)

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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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EDITORIAL

Editorial for the special issue of the Chinese Association for the Study of Pain

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Abstract

The Ministry of Health of China officially issued a document, adding the first level diagnosis and treatment discipline "Algology" in the list of diagnosis and treatment subjects of medical institutions on July 16, 2007. As the most important pain academic organization in China, the Chinese Association for the Study of Pain has made outstanding contributions in promoting the development of pain discipline and in establishing pain standards and disease diagnosis and treatment guidelines. In this special issue, under the leadership of Yan-Qing Liu, Chairman of the 7th Committee of the Chinese Association for the Study of Pain, nine consensus and one guideline were included.

Key Words: Chinese Association for the Study of Pain; Algology; Pain; Consensus; Guidelines; Recommendations

Core Tip: Pain medicine has developed rapidly in China and accumulated rich Chinese experience in the diagnosis and treatment of various pain diseases. Under the leadership of Yan-Qing Liu, Chairman of the 7th Committee of the Chinese Association for the Study of Pain, this special edition contains nine consensus and one guideline.

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INTRODUCTION

On July 16, 2007, the Ministry of Health of China officially issued a document, adding the first level diagnosis and treatment discipline "Algology," code: "27" in the list of diagnosis and treatment subjects of medical institutions. In the past 13 years, pain medicine has developed rapidly in China and accumulated rich Chinese experience in the diagnosis and treatment of various pain diseases. The Chinese Association for the Study of Pain (CASP) is the most important pain academic organization in China. In recent years, it has made outstanding contributions in promoting the development of the pain discipline and in establishing pain standards and disease diagnosis and treatment guidelines.

Under the leadership of Yan-Qing Liu, Chairman of the 7th Committee of CASP, this special edition contains nine consensus and one guideline.

GUIDELINES

Expert panel's guidelines on cervicogenic headache: The CASP recommendation[1]

Cervicogenic headache was recognized as a unique form of headache that is difficult to diagnose and treat. Pharmacologic treatment is recommended as the first-line therapy for cervicogenic headache. C2-3 posterior medial branch radiofrequency (RF) intervention is conditionally recommended for patients with persistent cervicogenic headache. Imaging technologies (ultrasound, X-ray and computed tomography) are recommended to guide invasive therapies[2].

CONSENSUS

Chronic pain

Expert consensus of CASP on the diagnosis and treatment for lumbar disc herniation[3]**:** Lumbar disc herniation is one of the most common and recurrent diseases. This consensus from CASP points out that: Individualized treatment regimen should be taken according to the course, clinical manifestations, the location of the disc herniation and the severity of the corresponding nerve root compression. The routine strategies used for lumbar disc herniation treatment include medicine, minimally invasive interventional therapy, surgery and rehabilitation[4].

Expert consensus of CASP on the diagnosis and treatment of myofascial pain syndrome[5]**:** Myofascial pain syndrome refers to a type of chronic pain syndrome that recurs in muscles, fascias or related soft tissues and can be accompanied by obvious emotional disorders or dysfunctions. Acupuncture and moxibustion therapy are based on the theory of human meridians. The treatment of silver needle combined with heat conduction and acupotomy (a combination of Chinese acupuncture and Western surgery) are both effective methods for the treatment of persistent myofascial pain syndrome. Moreover, local anesthetic, corticosteroid and botulinum toxin, oxygen-ozone injection and RF therapy can relieve pain and remarkably improve function[6,7].

Expert consensus of CASP on chronic postsurgical pain[8]**:** Although there are many improvements in surgical procedures, acute pain interventions and the application of multiple preventive measures, chronic postsurgical pain is still one of the most common surgery-related complications[9]. Optimized surgical procedure, multiple analgesia, psychological intervention and rehabilitation are the four most important factors. The people closely related to chronic postsurgical pain are surgeons, anesthesiologists and pain physicians. The cooperation among the three can maximize the patient's benefit[10].

Pharmacologic therapy

Analgesics are the first choice in the treatment of pain. The guidance and suggestions of the expert consensus and guidelines should be followed to prescribe medicine safely

and effectively.

Expert consensus of CASP on the non-opioid analgesics for chronic musculoskeletal pain[11]: In recent years, the "opioid crisis" has been a topic of interest. More and more doctors realized that they should pay more attention to non-opioid analgesics. This special issue covers the use of non-opioid drugs in chronic musculoskeletal pain (CMP). CMP is a common occurrence in clinical practice[12]. The purpose of this consensus is to present the application of nonsteroidal anti-inflammatory drugs, noradrenaline reuptake inhibitor, serotonin and norepinephrine reuptake inhibitors, muscle relaxants and ion channel drugs in CMP. Drugs targeted to ion channels should be considered for CMP with neuropathic pain[13].

Expert consensus of CASP on the ion channel drugs for neuropathic pain[14]: The treatment of neuropathic pain is also an important clinical problem. According to this expert consensus, the indications, contraindications, usage and adverse reactions of sodium channel blockers (such as carbamazepine, oxcarbazepine, lidocaine and bupivacaine) and calcium channel regulators (such as gabapentin and pregabalin) were elaborated upon[15,16]. The inhibitory effect of a sodium channel drug, bulleyaconitine A, was fully explored because it has excellent clinical effects.

Expert consensus of CASP on pain treatment with a transdermal patch[17]: Transdermal patch is one percutaneous delivery method that can deliver drugs through the skin and capillaries at a certain rate to achieve a systemic or local therapeutic effect in the affected area. Nonsteroidal anti-inflammatory drug transdermal patch is effective in the treatment of chronic skeletal muscle pain with few side effects and is recommended as the first choice for the treatment of CMP. When the efficacy of transdermal nonsteroidal anti-inflammatory drugs alone is not enough, it can be combined with other analgesic drugs. Opioid transdermal patches are effective in the treatment of chronic pain, but they should not be used as the initial treatment for chronic pain because of the potential addiction and adverse reactions[18,19].

Interventional therapy

Generally speaking, medicine and analgesics can offer 60%-70% of pain relief in pain disease. If conventional medicine cannot provide enough relief, minimally invasive interventional therapy is needed. It requires detailed assessment of the patient's situation and the benefit-and-risk ratio. In the past 3 years, CASP has developed a number of expert consensus on diagnosis and treatment standards of special minimally invasive interventional therapy.

Expert consensus of CASP on the application of ozone therapy in pain medicine[20]: Ozone, a strong oxidant, can be used in the treatment of pain diseases. Due to a variety of biological effects in the body, it can provide significant effects[21]. The purpose of this consensus was to help the rational application of ozone in pain treatment thereby improving its efficacy and safety and to reduce and prevent the potential adverse reactions and complications.

Expert consensus of CASP on RF therapy technology in the department of pain[22]: Evidence suggests that RF is effective for pain treatment, including discogenic pain, postherpetic neuralgia, chronic lumbosacral radicular pain and phantom limb pain[23,24]. RF therapy can be divided into standard RF (thermocoagulation) mode and nondestructive pulsed RF mode. RF therapy has no thermal coagulation damage, so it has a wider range of use in the treatment of chronic pain.

Expert consensus of CASP on ultrasound-guided injections for the treatment of spinal pain in China (2020 edition)[25]: Ultrasound-guided injections for the treatment of spinal pain are increasingly being applied in clinical practice. This clinical expert consensus described the purpose, significance, implementation methods, indications, contraindications and technique tips of ultrasound-guided injections. This consensus offered references for physicians to successfully implement ultrasound-guided injections for chronic spinal pain.

CONCLUSION

To sum up, this special issue is a summary of different consensus made by the 7th CASP in the past 3 years. Many pain and orthopedic experts have worked hard for this. We wish this special issue can bring reference and help for doctors and the

disciplines in the diagnosis of chronic pain, drug treatment and application of minimally invasive interventional therapy. This will help provide standards and criteria in daily clinical work.

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GUIDELINES

Expert panel's guideline on cervicogenic headache: The Chinese Association for the Study of Pain recommendation

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Abstract

Cervicogenic headache (CEH) has been recognized as a unique category of headache that can be difficult to diagnose and treat. In China, CEH patients are managed by many different specialties, and the treatment plans remain controversial. Therefore, there is a great need for comprehensive evidence-based Chinese experts' recommendations for the management of CEH. The Chinese Association for the Study of Pain asked an expert panel to develop recommendations for a series of questions that are essential for daily clinical management of patients with CEH. A group of multidisciplinary Chinese Association for the Study of Pain experts identified the clinically relevant topics in CEH. A systematic review of the literature was performed, and evidence supporting the benefits and harms for the management of CEH was summarized. Twenty-four recommendations were finally developed through expert consensus voting for evidence quality and recommendation strength. We hope this guideline provides direction for clinicians and patients making treatment decisions for the management of CEH.

Key Words: Cervicogenic headache; Expert recommendation; Expert panel's guideline; Chinese Association for the Study of Pain; Chronic pain

Core Tip: Cervicogenic headache (CEH) was recognized as a unique category of headache. The treatments of CEH remain controversial among different disciplines. The Chinese Association for the Study of Pain asked a multidisciplinary expert group identified the clinically relevant topics in CEH. Twenty-four recommendations were finally developed through expert consensus voting for evidence quality and recommendation strength. This guideline provides direction for clinicians and patients making treatment decisions for the management of CEH.

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INTRODUCTION

Cervicogenic headache (CEH), characterized by pain starting in the neck or occipital area that can move to other areas of the head, is a relatively common clinical challenge[1,2]. However, controversies related to the management of CEH continue to exist between different disciplines[3]. In China and other developed countries, patients with CEH are typically managed by doctors of several different specialties, including general practitioners, neurologists and pain and rehabilitation physicians. Doctors from different disciplines are only rarely concentrated in highly specialized centers[4]. In addition, patients with CEH are likely to be treated with several different pharmacological and nonpharmacological interventions, often in combination. Therefore, the Chinese Association for the Study of Pain (CASP) has organized an expert group to develop guidelines for the management of CEH[4].

CEH DEFINITION AND DIAGNOSIS

The two conflicting viewpoints when defining CEH are as follows: (1) Relying on the clinical features, CEH is said to be characterized by unilateral head pain of fluctuating intensity that is increased by movement of the head, and the pain radiates from the occipital to the frontal regions; and (2) Relying on establishing the diagnosis involves demonstrating a cervical source of head pain and confirming the diagnosis by using anesthetic blocks that pinpoint the sources of pain in the upper cervical joints[5-7]. In accordance with the current International Headache Society criteria, the CASP expert group defines CEH as any headache caused by a disorder of the cervical spine or its components, such as bone, disc and/or soft tissue elements that is usually but not invariably accompanied by neck pain.

The diagnostic criteria recommended by the International Classification of Headache Disorders 3rd edition[8,9] are as follows: (1) Any headache fulfilling criterion (3); (2) 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; (3) Evidence of causation demonstrated by at least two of the following findings: (a) Headache developed in temporal relation to the onset of cervical disorder or appearance of the lesion; (b) Headache that significantly improved or resolved along with an improvement in or the resolution of cervical disorder or lesion; (c) The cervical range of motion is reduced, and the headache is significantly aggravated by provocative maneuvers; and (d) Headache disappears after diagnostic block to the suspected cervical spine structure or its supply nerve; and (4) Headache that is not better accounted for by another International Classification of Headache Disorders-3 diagnosis.

ANATOMY AND PATHOPHYSIOLOGY

The anatomic locus for CEH is the trigeminocervical nucleus in the upper cervical spinal cord, the convergence between the upper cervical nociceptive afferents and the trigeminal nociceptive afferents in the trigeminocervical complex[10]. This approach allows for pain arising from the upper cervical nerves to be referred to the regions of the head innervated by trigeminal afferents, such as the orbital, frontal and parietal regions[11,12].

CEH is believed to be caused by referred pain from the cervical nerves and upper cervical joints[13]. Pathological changes in the cervical zygapophyseal joints can generate pain in the areas innervated by the trigeminal nerve (*e.g.*, the frontal and periorbital regions) or the upper three cervical spinal nerves (*e.g.*, the occipital and auricular regions). Involvement of the C2-3 zygapophyseal joint and atlantoaxial joint is the most frequent source of CEH. Impairment of the C2-3 zygapophyseal joint reportedly caused CEH in 70% of all patients, of whom 27% could be diagnosed with third occipital neuropathic headache[14].

CLINICAL FEATURES AND EXAMINATION

CEH is a chronic unilateral head pain of fluctuating intensity that is increased by movement of the head and radiates from occipital to frontal regions[15]. The pain is

typically nonthrobbing, nonlancinating, of moderate to severe intensity and of variable duration. Patients with CEH may have restricted neck range of motion and may have ipsilateral neck, shoulder or arm pain. Most patients also show concomitant symptoms of nausea, tinnitus, dizziness, phonophobia, photophobia, blurred vision or disordered sleep[16].

A detailed history and examination should be the starting point for the clinicians. 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[6]. Additional maneuvers on physical examination should include movement tests of the cervical spine, such as passive flexion, extension and rotation and segmental palpation of the cervical facet joints. Imaging (through X-rays, computed tomography and magnetic resonance imaging) is considered useful to evaluate cervical disc degeneration, herniation and the degenerative changes in the atlantoaxial, zygapophyseal and uncovertebral joints. Although imaging can be employed to exclude certain diseases from probable diagnosis, it should not be considered a diagnostic modality for CEH[17].

MANAGEMENT

Despite the availability of several different treatment modalities, no proven effective treatment for CEH has yet been established. By using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methods[18], a group of 19 experts worked on questions that are considered essential for daily clinical management of patients with CEH and have developed recommendations accordingly.

Methods

This method consists of the identification of clinically relevant questions, followed by a systematic literature search and summary of the evidence with final recommendations being moderated by feedback from experts.

Multidisciplinary expert panel: The CASP organized an expert panel consisting of 19 professionals working in the field of pain medicine, neurology, neurosurgery and rehabilitation from China. Fourteen of them were pain physicians, two were neurologists, one was a rheumatologist, one was an orthopedist and one was a neuroscientist.

Organizers and experts' coordinators: Yan-Qing Liu, Hui Liu, Hong Xiao, Bao-Gan Peng.

Organizational committee: The CASP.

CASP experts: Hong Xiao, Bao-Gan Peng, Ke Ma, Dong Huang, Xian-Guo Liu, Yan Lu, Qing Liu, Li-Juan Lu, Jin-Feng Liu, Yi-Mei Li, Song Tao, Tao Wei, Wen Shen, Xiao-Qiu Yang, Lin Wang, Xiao-Mei Zhang, Zhi-Gang Zhuang, Hui Liu, Yan-Qing Liu.

Scope determination: A modified Delphi method was employed to establish the guideline related to the target topics in the management of CEH using the population, intervention, comparator and outcomes method[19]. The scope of these recommendations includes different treatments for CEH. The users are expected to be physicians (mainly pain physicians) and other healthcare professionals who care for patients with CEH. The core leadership team supervised and coordinated the project and established the following clinical questions: (1) What is the role of pharmacological therapy for CEH? Among nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, antiepileptic drugs and antidepressants, which of the drugs have shown efficacy in the long-term treatment of CEH? (2) Should nerve block, minimally invasive intervention and surgical procedures be considered if the medical treatment is not effective or tolerated? What are the outcomes of invasive operation under the guidance of imaging technologies such as ultrasound, X-ray and computed tomography? What are the indications, therapeutic effects, and complications of joint injections or nerve blocks such as atlantoaxial joint injection, C2-3 zygapophyseal joint injection, cervical spinal nerve root block, third occipital nerve block and occipital nerve block? What are the indications, therapeutic effects and complications of minimally invasive interventions or surgical techniques such as radiofrequency thermocoagulation and pulse radiofrequency, ozone injection and percutaneous laser disc decompression?; and (3) Can nonpharmacological and nonsurgical therapies, such

as physical therapy, traditional Chinese medicine, health education and psychological treatment, be considered as complementary management modalities for CEH?

Literature search: The literature review group members were assigned topics based on expertise, and 3-4 experts were responsible for 2-3 clinical questions. Papers published in peer-reviewed journals were identified using the PubMed/MEDLINE, Embase, Cochrane, China National Knowledge Infrastructure and WanFang Library. Systematic reviews, randomized and nonrandomized controlled trials, observational cohorts and case series limited to English or Chinese language publications were included. GRADE method was used to separately determine the quality of available evidence (rated as high, moderate, low or very low) based on the risk of bias, imprecision and inconsistency (Table 1). One or more recommendations were drafted for each topic.

Recommendation making: The expert panel assessed the feedback on the recommendations and evidence provided from the literature review group, and they rated the necessity for each item and selected recommendations in the first-round meeting. Recommendations due to poor-quality or conflicting evidence were eliminated, rephrased or combined. During the second round, according to the GRADE approach, the expert voting panel made recommendations (strong or weak/for or against) on the basis of the balance between desirable and undesirable effects, quality of evidence, values and preferences and costs (Table 2). To achieve consensus, an a priori decision was made to conduct up to three rounds of anonymous voting or until consensus was achieved (defined a priori as consensus agreement at ≥ 70% with a minimal response rate of 70%) for each draft recommendation, whichever came first[18]. Much of the evidence proved to be indirect, given that it did not specifically address the population, intervention, comparator and outcomes question as written and was of low-to-moderate quality.

Recommendations

After the synthesis of our experts' work and the implementation of the GRADE method, 24 recommendations were formalized by the organizational committee (Table 3).

Pharmacologic management: Pharmacologic treatment is recommended as the first-line therapy for CEH (Evidence quality: moderate; Recommendation strength: strong).

Pharmacologic treatments for CEH are largely based on case reports and a lack of convincing clinical evidence on effective medications for CEH. Despite that, pharmacotherapy remains among the best available treatments[6,20]. The medications used include NSAIDs, muscle relaxants, antiepileptic drugs and antidepressants[2,21]. Before using analgesic therapy for CEH, the patients require comprehensive education around safe limitations for medication use and prevent medication-induced headache.

NSAIDs are recommended for patients with CEH (Evidence quality: low; Recommendation strength: weak).

NSAIDs such as nonselective COX and selective COX-2 inhibitors can be effective treatment modalities for CEH[1]; however, owing to the low quality of evidence, the recommendation for NSAID administration is relatively weak. Clinical considerations aimed at risk mitigation for the safe use of NSAIDs include appropriate patient selection, regular monitoring for the development of potential adverse gastrointestinal, cardiovascular and renal side-effects and potential drug interactions.

Muscle relaxants are recommended for patients with CEH (Evidence quality: moderate; Recommendation strength: strong).

Muscle relaxants such as tizanidine, baclofen, and eperisone hydrochloride have central action mechanisms aimed at providing analgesic effects in the acute phase and for prevention[22,23]. Tizanidine can be combined with NSAIDs due to its gastro-protective effect and good safety profile.

Antiepileptic drugs are conditionally recommended for patients with CEH (Evidence quality: low; Recommendation strength: weak).

Common antiepileptic drugs include gabapentin and pregabalin, which can be used in patients with neuropathic pain[24].

Antidepressants are recommended for CEH patients with severe anxiety and depression. (Evidence quality: low; Recommendation strength: strong).

The evidence for these drugs is limited. However, considering its clinical efficacy in the treatment of headache, patients also presenting with severe anxiety and depression are recommended to use amitriptyline, venlafaxine or duloxetine[25]. When used alone or in combination with other drugs, the tolerability and side effects should be

Table 1 Grading of Recommendations, Assessment, Development and Evaluation system for rating quality of evidence

Quality of evidence	Definition
High quality	Further research is very unlikely to change confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is very uncertain

Table 2 Grading of Recommendations, Assessment, Development and Evaluation system for strength of recommendations

Recommendation strength	Definition
Strong	When the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Weak (''conditional'' or''discretionary'')	When the trade-offs are less certain either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

considered.

Anesthetic blockade: Anesthetic joint injections or nerve blocks are often used both diagnostically and therapeutically (Evidence quality: moderate; Recommendation strength: strong).

Anesthetic injections of the lateral atlantoaxial joint, the C2-3 zygapophyseal joint (and the overlying third occipital nerve) and/or the C3-4 zygapophyseal joint can temporarily reduce or relieve pain and may allow greater participation in physical treatments[26]. Patients with suboccipital or occipital pain aggravated by cervical rotation or pain due to inflammatory stimuli are expected to benefit from atlantoaxial joint injection (Evidence quality: low; Recommendation strength: weak). One study showed that injection to the atlantoaxial joint was effective in 81.2% of all cases[27]. C2-3 zygapophyseal joint 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 when the back is stretched (Evidence quality: low; Recommendation strength: weak). Selective nerve root injection reportedly showed 50% pain relief after 12 mo[28]; therefore, it can be used in patients with cervical spondylotic radiculopathy (Evidence quality: low; Recommendation strength: strong). The third occipital nerve block can be used to diagnose CEH and predict the efficacy of radiofrequency treatment (Evidence quality: low; Recommendation strength: strong). The occipital nerve injection is used to diagnose and treat occipital pain (Evidence quality: low; Recommendation strength: strong). In addition, imaging technologies (ultrasound[29], X-ray and computed tomography) are recommended for guiding invasive therapies (Evidence quality: high; Recommendation strength: strong).

Administration of glucocorticoid injections is recommended for CEH (Evidence quality: low; Recommendation strength: strong).

There are no controlled trials evaluating glucocorticoid injections for CEH. However, the results from small retrospective studies suggested that some patients may achieve pain relief through the administration of intra-articular glucocorticoid injections[30].

Minimally invasive interventional management: Radiofrequency intervention is conditionally recommended for patients with intractable CEH (Evidence quality: moderate; Recommendation strength: strong).

Percutaneous radiofrequency neurotomy can be considered for CEH arising from the C2-3 or C3-4 zygapophyseal joint if diagnostic anesthetic nerve blockade is temporarily successful in providing complete pain relief. However, the available evidence is limited and conflicting[31]. None of the supplied evidence indicates that radiofrequency ablation or pulsed radiofrequency therapy was effective for CEH. However, three small nonrandomized studies[32-34] on radiofrequency ablation and one study[35] on pulsed radiofrequency therapy suggested that these techniques were effective for CEH. Pulse radiofrequency is a type of neuromodulation therapy, and it has fewer complications than radiofrequency thermocoagulation[36]. Thus, pulse radiofrequency is preferred over ablation as a recommendation for patients with

Table 3 Chinese Association for the Study of Pain recommendations for the management of cervicogenic headache

Item	Recommendation	Quality	Strength
Pharmacologic management	Pharmacologic treatment is recommended as the first-line therapy for CEH	Moderate	Strong
	NSAIDs are recommended for patients with CEH	Low	Weak
	Muscle relaxants are recommended for patients with CEH	Moderate	Strong
	Antiepileptic drugs are conditionally recommended for patients with CEH	Low	Weak
	Antidepressants are recommended for CEH patients with serve anxiety and depression	Low	Strong
Anesthetic blockade	Anesthetic joint injection or nerve block are often used both diagnostically and therapeutically	Moderate	Strong
	Atlantoaxial joint injection for patients with suboccipital or occipital pain aggravated by cervical rotation or pain due to inflammatory stimuli	Low	Weak
	C2-C3 zygapophyseal joint 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	Low	Weak
	Selective nerve root injection could be used in patients with cervical spondylotic radiculopathy	Low	Strong
	Third occipital nerve block can be used to diagnose CEH and predict the efficacy of radiofrequency treatment	Low	Strong
	The occipital nerve injection is used to diagnose and treat occipital pain.	Low	Strong
	Imaging technology (ultrasound, X-ray and CT) are recommended for guidance of invasive therapies	High	Strong
	Glucocorticoid injection is recommended for CEH	Low	Strong
Minimally invasive interventional management	Radiofrequency intervention is conditionally recommended for patients with persistent CEH	Moderate	Strong
	Pulse radiofrequency is preferred over ablation for patients with persistent CEH	Low	Strong
	Ozone injection is recommended for CEH	Low	Weak
	PLDD is conditionally recommended for CEH	Low	Weak
Surgical procedures	Surgery is not recommended for CEH unless there is compelling evidence of a surgically amenable lesion causing the cervicogenic headache that is refractory to all reasonable nonsurgical treatments	Low	Strong
	Nonpharmacological and nonsurgical therapy is recommended as a complementary management for CEH	Low	Strong
Physical therapy	Physical therapy is the preferred initial treatment recommended for CEH	Moderate	Weak
	Cervical manipulation and mobilization are recommended for CEH	Moderate	Strong
TCM	TCM is conditionally recommended for CEH.	Low	Weak
Psychological therapy	Patients with refractory severe CHE need psychological assessment and intervention	Low	Strong
Health education	Health education is recommended for CEH	Low	Strong

CEH: Cervicogenic headache; CT: Computed tomography; NSAIDs: Nonsteroidal anti-inflammatory drugs; PLDD: Percutaneous laser disc decompression; TCM: Traditional Chinese medicine.

persistent CEH (Evidence quality: low; Recommendation strength: strong).

Ozone injection is recommended for CEH (Evidence quality: low; Recommendation strength: weak).

Ozone possesses strong anti-inflammatory and analgesic effects that can benefit patients in whom the use of glucocorticoid is contraindicated[37]. However, there is limited evidence showing that the ozone injection has potential benefits for CEH patients.

Percutaneous laser disc decompression is conditionally recommended for CEH (Evidence quality: low; Recommendation strength: weak).

Percutaneous laser disc decompression is effective in patients with cervical disc herniation, protrusion or disc degeneration along with neck and shoulder pain with nerve root symptoms[38].

Surgical procedures: Surgery is not recommended for CEH unless there is compelling evidence indicating the presence of a surgically amenable lesion causing CEH that is refractory to all reasonable nonsurgical treatments (Evidence quality: low;

Recommendation strength: strong).

Numerous surgical interventions have been performed for presumed cases of CEH. Available data are limited to small retrospective studies[39,40], but they suggest that surgery may be beneficial for the following three specific etiologies of CEH: (1) C2 spinal nerve compression by vascular/ligamentous structures; (2) osteoarthritis of the lateral atlantoaxial joint; and (3) upper cervical intervertebral disc pathology.

Nonpharmacological and nonsurgical therapies are recommended as a complementary management for CEH (Evidence quality: low; Recommendation strength: strong).

Physical therapy: Physical therapy is the preferred initial treatment recommended for CEH (Evidence quality: moderate; Recommendation strength: weak).

Physical therapy has been shown to provide the most long-term relief of CEH[41]. This may include cervical traction, massage and strengthening. A systematic review and meta-analysis revealed that physical therapy led to a statistically significant benefit for reduced pain, frequency and duration of CEH[42].

Cervical manipulation and mobilization are recommended for CEH (Evidence quality: moderate; Recommendation strength: strong).

In a large clinical trial[43], which evaluated 200 patients with CEH, patients assigned to 6 wk of active treatment with either manipulative therapy, low-load endurance exercise therapy or a combination of both therapies showed a significant reduction in headache frequency at 12 mo. The effect size was reported as moderate and clinically relevant[44].

Traditional Chinese medicine: Traditional Chinese medicine is conditionally recommended for CEH (Evidence quality: low; Recommendation strength: weak).

Traditional Chinese medicine treatments include acupuncture, silver needle, internal hot needle and other forms of Chinese medicine. However, the relevant research and the evidence are limited[45]. The overall quality of the evidence for traditional Chinese medicine in CEH management is generally low and occasionally moderate.

Psychological therapy: Patients with refractory severe CHE need psychological assessment and intervention (Evidence quality: low; Recommendation strength: strong).

Studies have indicated that the incidence of depression and generalized anxiety disorder is high in headache patients[46,47]. Patients with refractory severe CHE need psychological assessment, including past medical history, psychological status and the risk factors affecting prognosis. Past studies have indicated that the addition of psychological therapy on the basis of regular drug therapy can play a more significant therapeutic effect on headache. Psychotherapy includes listening, headache education, cognitive behavior therapy, biofeedback therapy and relaxation training[48].

Health education: Health education is recommended for CEH (Evidence quality: low; Recommendation strength: strong).

Neurophysiological pain education strategy addressing neurophysiology and neurobiology of pain can have a positive effect on pain[49]. Health education includes maintaining a good posture, keeping the neck and shoulder warm and appropriate neck exercises (such as neck flexion, neck rotation and Alexander's fitness)[41].

CONCLUSION

The CASP asked an expert panel to develop recommendations for a series of questions that are essential for daily clinical management of patients with CEH. A systematic review of the literature was performed, evidence supporting the benefits and harms for the management of CEH were summarized. Finally, 24 recommendations were developed through expert consensus voting for evidence quality and recommendation strength. We hope this guideline provides direction for clinicians and patients making treatment decisions for the management of CEH.

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EXPERT CONSENSUS

Expert consensus of Chinese Association for the Study of Pain on the application of ozone therapy in pain medicine

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Abstract

This consensus was compiled by first-line clinical experts in the field of pain medicine and was organized by the Chinese Association for the Study of Pain. To reach this consensus, we consulted a wide range of opinions and conducted in-depth discussions on the mechanism, indications, contraindications, operational specifications and adverse reactions of ozone iatrotechnique in the treatment of pain disorders. We also referred to related previous preclinical and clinical studies published in recent years worldwide. The purpose of this consensus is to standardize the rational application of ozone iatrotechnique in pain treatment, to improve its efficacy and safety and to reduce and prevent adverse reactions and complications in this process.

Key Words: Ozone iatrotechnique; Pain department; Expert consensus; Pain; Ozone; Guideline

Core Tip: We consulted a wide range of opinions and conducted in-depth discussions on the mechanism, indications, contraindications, operational specifications and adverse reactions of ozone iatrotechnique in the treatment of pain diseases. We also referred to the related previous preclinical and clinical studies published in recent years around the world. The purpose of this consensus is to standardize the rational application of ozone iatrotechnique in pain treatment, to improve its efficacy and safety and to reduce and prevent adverse reactions and complications in this process.

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INTRODUCTION

Ozone is a strong oxidant and can be used in the treatment of pain disorders due to a variety of significant biological effects in the body[1]. Since 2002 in the Pain Department of hospitals in China, ozone has been used in the therapy of some disorders, including degenerative spinal diseases, musculoskeletal disorders and diseases, rheumatic immune diseases, vascular diseases, metabolic diseases, neuropathic pain, *etc*[1-4]. There is a lack of uniform norms and guidelines in clinical practice due to the unreasonable application of ozone from time to time. Some adverse reactions and complications, such as injections into blood vessels or cerebrospinal fluid, have been observed. In order to standardize the rational application of ozone treatment technology in the pain clinic, improve the therapeutic effect and prevent and reduce the occurrence of adverse reactions, first-line clinical experts in the field of pain medicine in China were organized by the Chinese Association for the Study of Pain to assess and discuss the mechanism, indications, contraindications, operating norms and adverse reactions of

ozone in the therapy of pain disorders. The China Expert Consensus on the Application of Ozone Therapy in the Pain Department was reached by assessing the topics discussed below.

PHARMACOLOGICAL MECHANISMS

Under the appropriate ozone concentration, biochemical reactions similar to preadaptation are produced in the body's cells[5]. There are no ozone receptors in the human body. Therefore, the pharmacological mechanism of ozone is indirectly realized through other factors.

Ozone has a well-known analgesic effect. Subcutaneous injection of ozone at painful area quickly inactivates the inflammatory factors, reduces the stimulation of inflammatory factors to sensory nerve endings and inhibits peripheral sensitization thereby producing its analgesic effects[6]. In addition, direct stimulation to sensory nerve endings by ozone can induce the activation of endorphins in the nervous system thus inhibiting the transmission of peripheral injurious stimulation signals to the advanced center[7]. Ozone administered *via* the transforaminal route also stimulates inhibitory interneurons to release enkephalin and other substances thereby achieving central analgesia[8]. This type of analgesia occurs quickly after injection. This may be the molecular mechanism of rapid analgesia following ozone administration.

An endogenous antioxidant system can be initiated by ozone therapy (ozone autohemotherapy or tissue injection) by a variety of methods. The expression of heme oxygenase-1 in the local microenvironment is increased, and antioxidation is activated through heme oxygenase-1-mediated signaling to downstream targets[9]. The expression of superoxide dismutase is stimulated further decomposing excess peroxidation free radicals. Catalase is generated, and hydrogen peroxide is decomposed. The synthesis of glutathione peroxidase is increased, and organic peroxides are decomposed. Furthermore, the level of glucose-6-phosphate-dehydrogenase is increased in pentose phosphate bypass metabolism enhancing the antioxidant reduction ability of nicotinamide adenine dinucleotide phosphate[10]. Due to the effect of ozone, the body's active removal of free radicals and peroxides generated in the microenvironment as a result of physiological and pathological processes is accelerated.

Ozone has immunomodulatory and anti-inflammatory effects[8,11,12]. Peripheral sensitization caused by inflammation is the core factor in pain[13]. Ozone auto-hemotherapy or tissue injection have immune enhancement effects, such as enhancing phagocytic function of granulocytes and macrophages and improving the body's removal of pathogenic microorganisms or metabolic waste. On the one hand, it inhibits the synthesis of proinflammatory cytokines by inhibiting nuclear transcription factors, such as nuclear factor kappa-B[14]. On the other hand, it increases the synthesis and release of anti-inflammatory cytokines leading to the rapid elimination of inflammation[15]. Local tissue injection of ozone can increase oxygen supply, improve tissue hypoxia and act as a free radical scavenger. Ozone can be quickly reduced to oxygen after exposure to the surface of reductive cells creating an oxygen-rich environment in the local area. Stimulation of ozone affects vascular endothelial cells, which can release nitric oxide and other substances, dilate blood vessels to improve local microcirculation and thus stimulate tissue repair[16].

The effect of ozone on bidirectional regulation of immunity is also manifested in the induction of immune cells to produce massive amounts of cytokines. Ozone autohemotherapy can lead to a small release of interferon-γ, interferon-β, tumor necrosis factor α and granulocyte–monocyte colony stimulating factor in human blood[17-19]. These cytokines have multiple effects, such as immunostimulation or immunosuppression. The excessive use of ozone has a bidirectional regulation effect even on immunosuppression[20,21]. Therefore, different ozone concentrations and courses have different regulation methods and effects on the immunologic function of the body.

It should be noted that taken together, the functions of immunoregulation and antioxidation are achieved by triggering the body's endogenous protective mechanism. However, the buffering ability of the body's endogenous protection mechanism is limited. There are also great differences in the buffer capacity and repair capacity of different tissues and cell types. Ozone overdose within a short time may exceed the body's buffer capacity leading to reduced immune function, oxidative damage and adverse reactions. Therefore, it is necessary to strictly control the application of ozone concentration and total capacity. Indications and contra-

indications should be strictly observed.

INDICATIONS AND CONTRAINDICATIONS

Indications for ozone therapy are as follows: (1) Neuropathic pain: Herpes, postherpetic neuralgia and central pain[22], syringomyelia, diabetic peripheral neuropathy[23] and central and peripheral nerve injury pain[24]; (2) Vasogenic pain: diabetes and peripheral vascular disease[25], thrombotic ischemic pain[3,26,27], Raynaud's disease, erythromelalgia and vasculitis[28-30]; (3) Metabolic immune diseases: Ankylosing spondylitis, rheumatoid arthritis[31], allergic diseases and gout[32,33]; (4) Infectious diseases: Necrotizing ulcers, hard to heal wounds[34,35] and burns; (5) Physiological pain: Dysmenorrhea; (6) Tumor pain: Tumor pain during adjuvant therapy, radiotherapy and chemotherapy side effects, tumor consumption treatment and cancerous neuralgia[36]; and (7) Degenerative spinal diseases and joint and skeletal muscle diseases: Discogenic low back pain, lumbar disc herniation, cervical spondylosis, knee osteoarthritis, hip osteoarthritis and pain caused by chronic muscle, tendon, ligament, fascia and joint capsule strain[37].

Contraindications to ozone therapy are as follows[38]: (1) Ozone allergy; (2) Favism (glucose-6-phosphate-dehydrogenase deficiency); (3) Pregnant women; (4) Hyperthyroidism; (5) Sickle cell anemia; (6) Patients receiving kinase anticoagulant drugs; (7) Severe arrhythmia, hypertensive crisis and other cardiovascular diseases; (8) Hemochromatosis and patients receiving copper or iron therapy; and (9) Other relative contraindications (myocardial infarction, hypotension, hypocalcemia, hypoglycemia, internal hemorrhage, thrombocytopenia, coagulopathy, acute alcoholism and citrus allergy).

COMMONLY USED INJECTION CONCENTRATIONS, CAPACITY, TREATMENT AND OPERATION SPECIFICATIONS

Several forms of ozone are used in the treatment of pain. Ozone gas is easily decomposed at room temperature and pressure, is very unstable and can decompose into oxygen. It cannot be stored. On-site production is commonly used for immediate application. Ozone water is an ozone gas under a saturated state dissolved in a distilled water solution. Different to ozone gas, it is still a strong oxidation agent. In clinical medicine, ozone water is mainly used for local anti-inflammatory treatment, infection wound treatment and pelvic inflammatory disease treatment. Ozone oil is a mixture of ozone dissolved in a medical-grade greasy substance. Ozone in the oil is slowly released during use. Clinically, it is mainly used in the treatment of diseases of the mucous membranes, including diabetic foot, atopic dermatitis and chronic ulcer.

In clinical application, differences in the ozone concentration and capacity are significant over time relying mainly on the experience of physicians[39]. The ozone concentration is divided into the following three categories based on the method and mechanism of clinical application of ozone: High concentration (50-80 μg/mL); medium concentration (30-50 μg/mL); and low concentration (10-30 μg/mL). The oxidation capacity is increased with the rise in concentration[1]. The amount of ozone in the same area of different patients should be adjusted according to their tolerance, individual differences and other factors. Generally speaking, the concentration for intervertebral disc injection is 40 μg/mL, no greater than 30 μg/mL in other parts of the intervertebral disc and no greater than 45 μg/mL in autologous blood. In addition to air bath therapy, high-concentration therapy is not recommended.

The capacity of ozone injection is related to the therapeutic target, as described below: (1) Intra-articular injection[40]: It is recommended that intra-articular injection should be performed under X-ray/ultrasound positioning to ensure the injection of ozone into the joint cavity. According to the capacity, the joint cavity of the human body can be divided into large joints (shoulders, knees, hips), medium joints (skull) and small joints (elbows and wrists). The recommended standard for intra-articular injection of ozone is shown in Table 1; (2) Injection around the joint: Ozone is accurately injected into the pain points around lesions, the tendons and ligaments. The recommended ozone injection concentration is no greater than 30 μg/mL, and capacity is 1-5 mL/site. The total amount during a course of treatment is no greater than 30 mL with a frequency of 1-3 times/wk. The treatment course is 2-4 wk. Commonly used joint injection sites are around shoulder joints including coracoid sites, large and small

Table 1 Intra-articular injection and treatment

Target	Concentration, μg/mL	Capacity, mL	Frequency, times/wk	Course of treatment, wk
Large joint	< 30	10-20	1-2	2-4
Medium joint	< 30	5-10	1-2	2-4
Small joint	< 30	1-5	1-2	2-4

nodules of the humerus, intertubercular sulcus, sites below the acromion, the insertion point of the triangular muscle, the superior angle and inner corner of the scapula, the upper part of spinae scapulae and the lower part of spinae scapulae. Usually, 3-5 injection points are selected for each injection and include the lateral collateral ligament attachment sites, the suprapatellar bursa and infrapatellar bursa, fat pad sites, tubercles of the tibia and other painful areas; (3) Injection of soft tissue at pain points: The most obvious area of tenderness is selected for injection. It is recommended that the myofascial trigger points are located under the guidance of B-scan ultrasonography. The recommended ozone injection concentration is no greater than 30 μg/mL, capacity of 1-5 mL/site at a frequency of 1-3 times/wk and a treatment course of 2-4 wk. The total amount during treatment is no greater than 30 mL; (4) Injection around the nerve roots: Transforaminal injection, epidural steroid injection and interlaminar epidural injection are widely used to treat nerve root pain caused by diseases such as disc herniation. Bonetti *et al*[41] used 25 μg/mL ozone for transforaminal injection into the epidural space and achieved good results in the treatment of low back pain. In addition, other studies have confirmed the effectiveness of concentrations of 10 μg/mL and 20 μg/mL. Therefore, the recommended concentration for ozone injection of the epidural space is 10-30 μg/mL through various access points. The recommended volume is 3-5 mL for the cervical segment, 5-10 mL for the thoracic segment and 10-20 mL for the lumbar segment with a frequency of 1-3 times/wk. The course of treatment is 2-4 wk. It is recommended that this should be performed under the guidance of X-ray, nerve stimulator and ultrasound. If necessary, angiography can be performed to locate the puncture site. Local anesthetic testing should be performed to ensure the integrity of the dura mater before injection. The injection speed should be slow with the aim of obtaining a more precise curative effect and to ensure safety; and (5) Intradermal injection: This is mainly used for the treatment of herpes zoster and postherpetic neuralgia. The specific operation is as follows. An injection point on the skin in the painful area is selected. The ozone concentration for injection is 20 μg/mL. After injection, an orange peel-like ridge of less than 1 cm is formed at each point. The point-to-point distance is approximately 1 cm, forming a network arrangement. Injection is performed once every other day, 2-3 times a week.

Operation specifications are as follows. The injection should be implemented according to the relevant operation specifications shown in the Clinical Practices-Pain Science Volume published by the Chinese Medical Association. The injection should be performed under strict aseptic conditions. It is recommended that the accurate position should be achieved under imaging guidance. If necessary, angiography can be performed to locate the puncture position. Vital signs should be monitored to prevent the occurrence of adverse reactions.

OZONE INJECTION ABLATION FOR THE TREATMENT OF INTERVERTEBRAL DISC DISEASES

Ozone has been proven to cause dehydration of the nucleus pulposus[42,43]. Therefore, the injection of ozone into the intervertebral disc can reduce the lesion volume of the intervertebral disc and help alleviate the compression on nerve roots[44,45]. More importantly, ozone has a good anti-inflammatory effect, which is conducive to reducing inflammation of the intervertebral disc, nerve roots, ganglia and surrounding tissues.

Indications include patients with disc herniation who have similar clinical symptoms, signs and imaging findings. Contraindications include issues with ozone application and in patients receiving lumbar puncture.

Ozone ablation in the treatment of herniated lumbar intervertebral disc should be performed in a sterile environment and monitored by imaging. Patients should be

informed of all the potential risks and benefits of treatment and have signed an informed consent before treatment.

The concentration for ozone ablation in the treatment of herniated lumbar intervertebral disc is usually 40 μg/mL[46,47]. The capacity of each lumbar spine disc is 4-5 mL[46], and the capacity of each cervical spine disc is 2-3 mL. The injection rate should be slow, and the patient's response should be observed throughout. Although intervertebral disc ablation is effective after only one treatment, it can be repeated several weeks or months later.

PREVENTION AND TREATMENT OF ADVERSE REACTIONS AND COMPLICATIONS

Allergic reaction is a common side effect. If patients suffer diffuse erythema, rash and itching, it is usually considered an allergic reaction. No further risks and complications have been noted.

OZONE AUTOLOGOUS BLOOD THERAPY

Ozone autologous blood transfusion therapy (hereafter referred to as "autologous blood"), also known as ozone immunotherapy, involves an appropriate concentration and volume of ozone used to treat a certain amount of blood extracted from the patient's body. Then the blood is reinfused into the patient's body in an effort to obtain clinical efficacy. It includes large autologous blood therapy and small autologous blood therapy[1]. In large autologous blood therapy, a total of 100-150 mL of blood is obtained each time. It is then reinfused into venous blood vessels after treatment with an appropriate volume of ozone. In small autologous blood therapy, only 5-10 mL blood is obtained. After ozone treatment, intramuscular injection is performed, generally into the gluteus muscle[48,49]. Large autologous blood therapy is mostly used during surgery.

Mechanism of the action of large autologous blood therapy

The mechanism of the action of large autologous blood therapy is unclear at present. Some studies have shown that ozone binding to blood effects the following aspects: (1) Activates erythrocyte metabolism, increases the oxygen saturation of hemoglobin and enhances the application of oxygen and adenosine triphosphate in tissues. It improves oxygen supply, promotes blood circulation, enhances cell vitality and repairs tissue cells; (2) Regulates the body's immune system. It enhances the phagocytic function of granulocytes and macrophages, improves the body's ability to remove metabolic waste and accelerates the removal of germs, viruses, *etc*.; and (3) Activates the antioxidant enzyme system, removes lipids from the blood and metabolic waste, enhances the activity of antioxidant enzymes in the body and reduces the damage caused by free radicals in the body[14]. It improves blood viscosity, reduces blood glucose, uric acid, bilirubin, lactic acid and pyruvate, strengthens the decomposition of cholesterol and triglycerides, improves the status of vascular walls and prevents systemic atherosclerosis and neurological lesions[50].

Equipment and large autologous blood therapy procedure

The large autologous blood treatment room should be a well-ventilated, air-disinfected independent treatment space with an average area greater than 20 square meters *per* treatment bed.

Preparation before treatment

The windows (doors) of the treatment room are opened for ventilation. The power supply, oxygen cylinder and interface connection are checked. The oxygen cylinder switch is opened. The oxygen pressure is checked to make sure there is no air leakage. The power switch of the ozone generator is turned on. The supplies are checked: Special package for basic autologous blood therapy, a bottle of 150 mL saline and treatment vehicle (tourniquet, disinfection cotton swab and disinfectant).

Treatment

The patient is placed in the supine position. The middle vein of the patient's elbow is

selected for blood collection. The blood collected should be shaken slowly and evenly clockwise during blood collection, thereby blood and anticoagulants are fully mixed. A volume of 100-150 mL is often used for blood collection. The maximum volume is 200 mL. After the completion of blood collection, a certain concentration of ozone gas at the same volume is injected under aseptic collections. At the same time as ozone injection, the blood collected is slowly and evenly shaken clockwise, so that ozone and blood are fully mixed. The mixing time is approximately 3-4 min from the time of ozone injection, and then the blood is reinfused into the patient's body. Attention is paid to monitoring the patient at the time of reinfusion.

Courses and concentrations of large autologous blood therapy

In large autologous blood therapy, the course of treatment is generally 10-15 times. The treatment can be performed once a day or every other day. A course interval of more than 6 mo is recommended.

The concentration of ozone during large autologous blood treatment is usually increased from a low dose. The initial concentration is 20-30 μg/mL with an increment of 5 μg/mL. The concentration can be increased between the first and second therapy. The maximum concentration is no more than 45 μg/mL. The patient's treatment outcome and side effects need to be assessed before each increase in concentration to ensure safety.

Precautions

The whole process should be carried out under sterile conditions. Every operator should have a set of consumables (blood collector, blood harvesting and infusion tubes, ozone collectors, normal saline). The patient's condition should be closely observed during the operation process. If there is a problem, then it should be solved immediately. The amount of blood collected, ozone injection and ozone concentration should not be increased without authorization. Blood reinfusion should be slow. It is usually completed within 10-15 min. During the first treatment, it should be slowed down further to prevent complications, especially in elderly patients.

Side effects of large autologous blood therapy

There are few side effects of large autologous blood therapy. Patients may have a rash or other allergic reactions, which can be easily resolved. If necessary, symptomatic treatment can be performed. Some patients faint during venous puncture due to emotional stress. Anticoagulant allergy is manifested as a mild numbness of the lip and tip of the tongue, which can be relieved spontaneously. In addition, it can be solved by changing the anticoagulant. Some patients feel nauseous, and flatulence or mouth odor can occur. These symptoms can be relieved spontaneously.

In addition to the general introduction of ozone treatment indications, large autologous blood therapy is widely used in other treatments, including respiratory, digestive, neurological, endocrine and metabolic systemic diseases[51-54].

EXPERT CONSENSUS STATEMENT

Ozone is a gaseous molecule with strong oxidation characteristics, which is widely used in the treatment of pain and related diseases.

The effects of ozone include analgesia, anti-inflammation, oxygen supply increase and bidirectional regulation of immunologic function.

Local ozone injection can be used in intradermal sites, skeletal muscle pain points, sites around the joint cavity, nerve roots, *etc*. The local injection concentration is no greater than 30 μg/mL. The total amount during each treatment is no greater than 30 mL. The course of treatment is determined according to the location.

Ozone injection can be used for the treatment of intervertebral disc diseases. For ozone injection ablation for the treatment of intervertebral disc diseases, 40 μg/mL is considered the commonly used concentration. The capacity of each lumbar spine disc is 4-5 mL, and the capacity of each cervical spine disc is 2-3 mL.

Indications, contraindications and operating norms should be strictly observed in ozone autologous blood therapy. Generally, 100-150 mL of blood is extracted, up to a maximum of 200 mL. The maximum ozone concentration is 45 μg/mL.

Ozone can also be used for adjuvant treatment of pain-related diseases.

Operators should comply with the consensus on ozone application indications, contraindications and use norms to ensure the safe application of ozone treatment technology.

CONCLUSION

The purpose of this consensus is to standardize the rational application of ozone iatrotechnique in pain treatment, to improve its efficacy and safety and to reduce and prevent adverse reactions and complications due to this process.

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EXPERT CONSENSUS

Chinese Association for the Study of Pain: Experts consensus on ultrasound-guided injections for the treatment of spinal pain in China (2020 edition)

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Author contributions: Wang XR and Cheng ZX communicated with others to co-ordinate the preparation and completion of work assignments; Wang Y drafted the English manuscript; Cheng ZX, Zhao DQ, and Fang HW provided a general overview of ultrasound-guided spinal pain injections; Wu BS, Zheng YJ, Wang AZ, Liu H, Xu H, Wang Y, Fang HW, and Zhang JY were involved in the ultrasound-guided injection techniques for cervical, thoracic, lumbar, and sacral spinal pain in detail; All authors contributed to this expert consensus through each of the following: (1) Framework and conception design; (2) Revising it critically for important intellectual content; and (3) Giving final approval for the version to be published.

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Abstract

Spinal pain (SP) is a common condition that has a major negative impact on a patient's quality of life. Recent developments in ultrasound-guided injections for the treatment of SP are increasingly being used in clinical practice. This clinical

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expert consensus describes the purpose, significance, implementation methods, indications, contraindications, and techniques of ultrasound-guided injections. This consensus offers a practical reference point for physicians to implement successfully ultrasound-guided injections in the treatment of chronic SP.

Key Words: Spinal pain; Ultrasound-guided injections; Facet joints; Spinal nerve roots; Posterior spinal nerve; Experts consensus

Core Tip: Recent developments in ultrasound-guided injections for the treatment of spinal pain are increasingly being used in clinical practice. This consensus offers a practical reference point for physicians to implement successfully ultrasound-guided injections in the treatment of chronic spinal pain.

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INTRODUCTION

Spinal pain (SP) is a common condition that has a major negative impact on patient's quality of life[1]. Targeted injections in the spine guided by imaging devices are advantageous over conventional injection techniques as they can be delivered with improved accuracy and reduce the risk of complications[2,3]. The recent development of portable ultrasound systems has led to the increased clinical implementation of ultrasound-guided spine injections[4]. These techniques can significantly reduce the requirements for radiation-guided treatments and avoid unnecessary radiation exposure[5]. However, the standard clinical practice of ultrasound-guided injections in the spine has yet to be clearly defined in terms of the application process, indications, and technical operations[6]. To establish clinical standards for ultrasound-guided SP injections, this expert consensus was proposed by domestic experts working on ultrasound-guided pain treatments to guide clinicians and medical experts on the correct use of ultrasound-guided injections for SP.

PURPOSE AND SIGNIFICANCE OF ULTRASOUND-GUIDED SP INJECTIONS

SP is a frequently occurring condition that manifests clinically with pain in the head and neck, the extremities, the chest wall, and the back, requiring pain management[7,8]. The curative treatment of SP remains challenging, often resulting in patients experiencing chronic pain with severe impact on their quality of life. Ultrasound can be used to provide real-time information during SP targeted injections. Ultrasound-guided SP injections can be used to eliminate inflammation and to treat pain through direct injection of drugs into areas of pain origin, such as the facet joints, spinal nerve roots, or the medial branch of the posterior spinal nerve[2].

BASIC REQUIREMENTS OF MEDICAL INSTITUTIONS

Medical institutions delivering SP injection techniques should be matched with their respective functions and clinical expertise.

Secondary and tertiary hospitals should have pain-relating services approved and registered by health administrative departments such as surgery, pain management,

and anesthesiology departments. Also, hospitals should have all of the required devices and facilities necessary to deliver SP injections.

The basic requirements of facilities at medical institutions using SP injections are as follows: (1) Basic facilities for clinical SP injections including a preparation, operation, and postoperative observation rooms or wards; (2) Basic devices for SP injections including a nerve stimulator, ultrasound machine, and a C-arm X-ray machine (as some procedures may need to be performed using both ultrasound and the C-arm X-ray machines). The operation room for SP injections should be equipped with the following devices: A tracheal intubation device, a multi-functional anesthesia machine, a monitor device, and a defibrillator; (3) Basic drugs for SP injections and emergency drugs that may be required during accidents or complications; and (4) Sterilization devices, adequate infection control, and management measures should exist within the hospital.

Doctors delivering ultrasound-guided SP injections should be specialist clinicians who work on pain management and have received ultrasound training.

IMPLEMENTATION CONDITIONS FOR ULTRASOUND-GUIDED SP INJECTIONS

Common parameter settings of the ultrasound device

The following common parameter settings should be applied during ultrasound-guided SP injections[9,10]: (1) Regulation of imaging depth: Proper depth refers to the target structure placed in the center of the ultrasound image or at 1 cm deeper than the target structure; (2) Gain regulation (gain of time/distance compensation): Ultrasound signals attenuate as they pass through tissues. Gain regulation and compensation for attenuation can allow structural echoes in different tissues to be distinguished; (3) Focus regulation: A suitable focus number should be chosen and depth adjusted to ensure the focus depth is in line with the depth of the target structure; and (4) Proper use of Doppler function: The Doppler effect should be utilized to identify vessels and the direction of drug diffusion.

Patient preparation

Patients undergoing SP injections are not required to fast, except when intravenous anesthesia is required[11]. In these circumstances, patients should fast for 8 h before treatment. Generally, an access to the peripheral venous is established before puncture and injection. The monitoring of basic vital signs (non-invasive blood pressure, electrocardiogram, and oxygen saturation) is required during operation. Before puncture, midazolam can be injected intravenously at a dosage of 0.02-0.06 mg/kg. For pediatric patients, ketamine can be delivered by intramuscular injection at a dose of 0.5-1 mg/kg[12]. For patients with breathing difficulties, a nasal catheter or oxygen mask should be used.

Rescue facilities

Ultrasound-guided SP injections should be performed in an operation or treatment room that has the necessary conditions for treatments. The onset time of injection is dependent on the target nerve, patient-specific characteristics, and the use of local anesthetics. Doctors performing the injections should have sufficient time and space to undertake the injection and also for post-operative follow-up. Rooms used for the injection procedure should be equipped with monitoring facilities, an oxygen supply, rescue drugs, and all other relevant materials.

Aseptic principles

Proper sterile practices and draping are recommended before puncture. The transducer and cable should be covered with a sterile plastic sleeve to ensure the injection is performed under sterile operating conditions to prevent infection in the puncture area and to avoid damage to the ultrasound probe by disinfectant.

Probe selection

The probe is a device that conveys and receives ultrasound waves. It is divided into linear (high frequency) and convex array (low frequency) probes. The linear array probe has high resolution but poor penetration ability, whilst the convex array probe has low resolution but good penetrating ability. If the target structure to be injected is located at the deeper area, the convex array probe should be selected, otherwise, the

linear array probe should be used for ultrasound guidance[13].

Scanning techniques[14]

Probe pressurization: The distance between the target and probe should be minimized to improve imaging quality. Sliding the probe along the skin surface should be performed to track certain structures.

Probe rotation: The probe should be rotated to obtain an image of the target structure and switched between its cross-section and vertical sections.

Probe tilt: The incident angle between the probe and the skin should be adjusted to enable the ultrasound beam to be fully reflected by the target structure. This allows the probe to receive the clearest possible images.

Method of needle insertion

Needle insertion methods can be divided into in- and out-of-plane according to the position of the needle puncture within the scanning range of the ultrasound probe[15]. The in-plane puncture method results in the needle tip and shaft being observed in the ultrasound images. The out-of-plane puncture method shows a high echo bright spot in the ultrasound image, however, this method cannot distinguish the needle tip and shaft. As a result, the in-plane puncture method should be preferentially used for injection into the spinal nerve root to avoid complications[16].

INDICATIONS AND CONTRAINDICATIONS FOR ULTRASOUND-GUIDED SP INJECTIONS

Indications

Ultrasound-guided SP injections can be used to treat tumors and multilevel intervertebral disc disorders in which surgical treatment is unsuitable[6]. These include lumbar disc herniation, cervicogenic headaches, occipital neuralgia, articular process disorders, medial branch pain of the posterior spinal nerve, herpes zoster and post-herpetic neuralgia, reflective sympathetic dystrophy, thoracic outlet syndrome, intercostal neuralgia, post-operative recurrent radicular pain, and radicular pain. Other indications include scenarios requiring immediate alleviation of radicular pain and in patients with a positive neurological examination, but insignificant vital signs[17-21]. For more detailed indications for spine-related pain or diseases, please refer to Table 1.

Contraindications

Absolute contraindications for ultrasound-guided SP injections include uncooperative patients (including mental patients), patients with whole-body infection or infection in the puncture area, patients with bleeding tendencies, patients allergic to local anesthetics, patients with severe hypovolemia, patients with unclear diagnosis, and patients adversely affected by illness due to injections[22,23].

Relative contraindications include patients with severe heart disease, patients with severe systemic conditions, patients with other diseases that can be adversely affected due to injections, and patients with severe hypertension, diabetes, or active ulcers.

COMMON TECHNIQUES OF ULTRASOUND-GUIDED SP INJECTIONS

Cervical spine

The cervicogenic pain refers to pain caused by disorders of the cervical structures. Specifically, these include: The cervical sympathetic nerve, the cervical dorsal root ganglion, the cervical nerve root, the cervical dorsal rami nerve, the medial branch of the cervical dorsal rami nerve, the cervical zygapophyseal joints, the cervical atlantoaxial joints, and the cervical intervertebral disc. Ultrasound-guided injection techniques for cervical SP include stellate ganglion block, selective cervical nerve root block, medial branch block of the posterior cervical nerve, cervical zygapophyseal joint block, block of the atlantoaxial joint block, C2 dorsal root ganglion block, block of the nerve root and posterior nerve branch, the greater occipital nerve block, and the third occipital nerve block[24-27]. All of the techniques mentioned above can be performed under real-time ultrasound guidance.

Table 1 Contents of Spinal Pain[52] can be used as a reference for the selection of clinical indications for clinical ultrasound-guided injections

Chapter	Contents
Chapter 1	Preface
Chapter 2	Spine anatomy
Chapter 3	Cervicogenic Pain
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Part 2	Cervical spinal nerve and dorsal rami syndrome
Part 3	Cervical facet joint pain
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Part 6	Ossification of the posterior longitudinal ligament
Part 7	Cervicogenic headache
Chapter 4	Thoracic spinal pain
Part 1	Thoracic disc thoracalgia
Part 2	Thoracic stenosis
Part 3	Thoracic radicular neuralgia
Part 4	Thoracic spinal dorsal rami nerve syndrome
Part 5	Thoracic facet joint pain
Part 6	Back thoracic myofascitis
Part 7	Thoracic interspinal and supraspinal ligamentitis
Chapter 5	Lumbar spinal pain
Part 1	Lumbar intervertebral disc herniation
Part 2	Stenosis of lumbar spinal canal
Part 3	Lumbar spine instability
Part 4	Lumbar spinal dorsal rami nerve syndrome
Part 5	Lumbar facet joint pain
Part 6	Lower back myofascitis
Part 7	Lumbar interspinal and supraspinal ligamentitis
Part 8	Lumbar discogenic pain
Part 9	Lumbar spondylolisthesis
Part 10	Third lumbar transverse process syndrome
Chapter 6	Sacrococcygeal spinal pain
Part 1	Sacrococcygeal spinal dorsal rami nerve syndrome
Part 2	Coccyalgia
Part 3	Sacral cyst
Part 4	Cauda equina injury syndrome
Part 5	Perineum Pain
Chapter 7	Other spinal pains
Part 1	Ankylosing spondylitis
Part 2	Osteoporotic compression fracture of spine
Part 3	Pain syndrome after failed back surgery
Part 4	Spine tumors

Part 5	Osteoporotic spinal pain
Part 6	Spinal tuberculosis
Part 7	Spinal vertebral epiphysitis
Part 8	Brucellar spondylitis
Part 9	Scoliosis
Part 10	Spinal-derived abdominal pain
Chapter 8	Expert consensus of spinal pain

Patients are required to lie on their lateral sides with the upper limbs placed parallel to the body. After skin disinfection and covering with surgical drapes, the ultrasound scanning is performed from the junction of the posterior part of the neck and the occipital bone. The probe is placed perpendicular to the long axis of the cervical vertebrae and slowly moved from the head side to the tail side. When an "arc" acoustic shadow is detected, this indicates the location of the C1 vertebral laminae. The probe is then gradually moved to the tail side. It indicates the C2 spinous process when an acoustic shadow with a bifurcation is seen. Other spinous processes can be located in this way. The probe can also be placed at the level of the inferior margin of the lateral cricoid cartilage to observe the anterior and posterior tubercle of cervical transverse process. The arm-shaped acoustic shadow can be seen at the level of C7 transverse process since the anterior tubercle is absent in C7 transverse process. Following identification, the probe should be moved to the head side to locate the relevant transverse process of the cervical vertebrae. These two methods should be carried out to confirm the relevant spine segments before injection.

Stellate ganglion block, see Table 2 for more details.

Recommendations: The stellate ganglion may be located in the front of C6, C7, and T1 vertebrae due to anatomic variations[28]. In these cases, injection into the surface of the *longus colli* should be used to achieve a blocking effect with local anesthetics diffusing through the prevertebral fascia[29]. At the C6 section, attention should be paid to the obstacle from the anterior tubercle of the C6 transverse process during the stellate ganglion block. The vagus nerve can be easily blocked if the direction of puncture is to the inner side (flat angle). The needle tip may be located in the muscle of *longus colli* if the puncture is too deep. Puncture at the C7 section should avoid accidental injuries to the vertebral artery, vertebral vein, cupula pleurae, and phrenic nerve[30-32].

Cervical nerve root block, see Table 2 for more details.

Recommendations: Avoidance of injuries in the vertebral vessel, the radicular artery, the ascending cervical artery, and the deep cervical artery[33]. The drug dosage should be controlled to prevent diffusion into the spinal canal, which results in neuraxial anesthesia or total spinal anesthesia[34].

The cervical zygapophysial joint block, see Table 2 for more details.

Recommendations: The drug dose should be controlled to prevent diffusion into the spinal canal, which would result in neuraxial anesthesia[35-37]. In clinical practice, treatments should not be limited to particular injured zygapophyseal joints. Improved efficacy can be achieved by blocking in the injured zygapophyseal joint, the posterior branch of the inferior nerve root, and the posterior branch superior to the nerve root[38].

The medial branch block of the posterior rami of cervical spinal nerve, see Table 2 for more details.

Recommendations: The puncture plane should be correctly selected. It is important to avoid the injuries to the vertebral artery during the puncture procedure.

Block of the atlantoaxial joint, the medial branch of C2 nerve root and dorsal root ganglion, and the third occipital nerve, see Table 2 for more details.

Recommendations: This procedure should be performed using ultrasound-guided in-plane technique. The probe should be shifted, tilted, and rotated to ensure the puncture needle and target are in the same plane and to ensure the tip and shaft of the puncture needle is completely visible in ultrasound image.

Thoracic spine

The thoracic SP refers to pain that may be caused by many disorders. Specifically, these include disorders of the following: The thoracic nerve root, the thoracic dorsal rami nerve, the intercostal nerve, the lateral branch of the intercostal anterior rami nerve, the anterior cutaneous branch of the intercostal anterior rami nerve, the facet

Table 2 Contents of the Ultrasound-guided Injection for Spinal Pain Technical Guide

Chapter	Contents
Part 1	Stellate ganglion block
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Part 5	Block of the atlantoaxial joint, the 2nd cervical nerve root, the ganglion, and the posterior rami
Part 6	Thoracic nerve root block
Part 7	Thoracic paravertebral block
Part 8	Thoracic erector spinae muscle plane block
Part 9	Intercostal nerve block
Part 10	Serratus anterior muscle plane block (The lateral branch of the intercostal anterior rami nerve)
Part 11	Thoracic transverse muscle plane block (anterior cutaneous branch of intercostal anterior rami nerve)
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Part 13	Thoracic retrolaminar block (Medial branch of spinal posterior rami nerve)
Part 14	Costotransverse joint injection
Part 15	Ultrasound-guided lumbar epidural block
Part 16	Ultrasound-guided block of sacral epidural block
Part 17	Ultrasound-guided selective lumbar nerve block
Part 18	Ultrasound-guided lumbar zygapophysial joint block and the medial branch block of the posterior lumbar nerve
Part 19	Ultrasound-guided lumbar sympathetic ganglion block

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joint of the thoracic spine, and the costotransverse joint. Morbidity associated with pain in the thoracic vertebra is lower (around 15%) than pain associated with the cervical and lumbar vertebra. Several techniques may be used for ultrasound-guided injection of thoracic SP including nerve root block and neurolysis, paravertebral nerve root block, block of the posterior branch of thoracic nerve and neurolysis, intercostal nerve block and neurolysis, block of the lateral branch of the intercostal anterior rami nerve, intercostal anterior rami nerve block, and neurolysis[39,40]. In addition, thoracic facet joint injection and costotransverse joint injection can also be included[41,42]. All of the techniques listed above can be performed using real-time ultrasound guidance.

Thoracic nerve root block, see Table 2 for more details.

Recommendations: Withdrawal the syringe before injection to avoid intravascular injection.

Paravertebral nerve root block, see Table 2 for more details.

Recommendations: The drug dose should be controlled to avoid excess drug entering the epidural space that may block or damage the adjacent nerves[43].

Thoracic erector spinae plane block, see Table 2 for more details.

Recommendations: Needle insertion should be performed in- or out-of-plane, and 20 mL of the drug should be injected when the needle tip reaches the target[44].

Intercostal nerve block, see Table 2 for more details.

Recommendations: The intercostal nerve runs along the inferior margin of the target costal. The position of intercostal vessels should be observed using the Doppler effect before puncture. Injury to the pleura needs to be avoided during the needle insertion. In-plane needle insertion should be adopted, with the puncture needle being advanced from the caudal side of the probe. The needle tip may puncture the muscles of the back and the internal and external intercostal muscles located to the inferior margin of the target costal and the shallow surface of the innermost intercostal muscle. No blood present during the syringe withdrawal should be confirmed before injection.

Serratus anterior muscle plane block (lateral branch of intercostal anterior rami nerve), see Table 2 for more details.

Recommendations: The blocking effect is determined by the diffusion of the local

anesthetic into the correct layers. The serratus anterior muscle should be identified and the injection should be performed by inserting the puncture needle into the shallow or deep surface of the serratus anterior muscle[45].

Thoracic transverse muscle plane block (anterior cutaneous branch of intercostal anterior rami nerve), see Table 2 for more details.

Recommendations: A striped, high-echo acoustic shadow can be seen in the shallow surface of the internal thoracic artery that is the transverse muscle and the intercostal muscle. The local anesthetic should be injected between these two muscles in order to block the anterior cutaneous branch of the intercostal nerve.

Thoracic zygapophyseal joint block, see Table 2 for more details.

Recommendations: No wide or deep acoustic windows are present between the thoracic zygapophyseal joints. The needle should be inserted in-plane from the caudal side to the cranial side. The drug should be injected after penetrating the articular capsule.

Thoracic retrolaminar block (medial branch of spinal posterior rami nerve), see Table 2 for more details.

Recommendations: The accident injection into the spinal canal through the interlaminar space should be avoided to prevent the neuraxial anesthesia[46].

Costotransverse joint injection, see Table 2 for more details

Recommendations: The in-plane technique is recommended to avoid pneumothorax[42].

Lumbar and sacral spine

The lumbosacral SP refers to pain caused by disorders of relevant structures around the lumbosacral spine. The ultrasound-guided interventional treatments for lumbosacral SP include lumbar and sacral epidural space injection, selective lumbar nerve root block, lumbar zygapophysial joint injection, block of the medial branch of the posterior lumbar nerve, and lumbar sympathetic ganglion block[47-50].

Ultrasound-guided lumbar epidural block, see Table 2 for more details.

Recommendations: Lumbar epidural space injection is a common technique used in clinical pain management. The success rate of difficult epidural access can be improved under ultrasound guidance. The paramedian sagittal oblique scanning and paramedian transverse scanning are often used for the ultrasound-guided epidural access. The ultrasound probe in the paramedian sagittal scanning technique is located 1-2 cm adjacent to the spine, with the scanning direction in line with the sagittal axis of the spine, and tilted towards the central line of the spine. The inferior margin of the ultrasound probe in the paramedian transverse scanning technique is located 3-4 cm adjacent to the spine midline, with the scanning direction vertical to the sagittal axis of the spine, and tilted towards the central line of the spine. The in-plane technique is suggested to avoid puncturing the dura mater[47,51].

Ultrasound-guided sacral epidural block, see Table 2 for more details

Recommendations: The sacral epidural block is widely used in sacral SP treatments. Since there are many variations of the sacral hiatus in adults that have associated difficulties during puncture, ultrasound guidance can improve the success rate of the sacral epidural block. The block can be performed with the short-axis out-of-plane technique or with the long-axis in-plane technique. The location of ultrasound probe in the short axis technique is perpendicular to the long axis of the spine; whilst in the long-axis technique, it is in the same direction of the long axis of the spine.

Ultrasound-guided selective lumbar nerve block, see Table 2 for more details.

Recommendations: Selective lumbar nerve block can be used for both diagnosis and treatment purposes. Compared to X-ray and computed tomography guided techniques, ultrasound-guided selective lumbar nerve block has a success rate of more than 90% and the advantage of reducing radiation exposure. Paramedian transverse scanning should be adopted in the selective L1-L4 nerve root block. The ultrasound probe should be placed perpendicular to the sagittal axis of the spine, 3-4 cm from the midline of the spine. Selective L5 nerve root block adopts paramedian transverse scanning in the triangle area of the lumbar, sacrum, ilium triangle.

Ultrasound-guided block of the lumbar zygapophysial joint and medial branch of the posterior lumbar nerve, see Table 2 for more details.

Recommendations: Lower back pain caused by degeneration of the lumbar facet joint and inflammatory stimulation of the facet joint capsule is termed lumbar facet joint syndrome. Treatments of this syndrome include lumbar facet joint injection, medial branch block of the posterior lumbar nerve, and radiofrequency ablation of the medial branch of the posterior lumbar nerve. Medial branch block of the posterior lumbar nerve can be used for both diagnosis and treatment, which can relieve lower back pain in the long term through multiple blocks. Disorders of one lumbar facet joint

should be treated with a block or radiofrequency ablation in the same segment, as well as the superior segment of the medial branch of the posterior lumbar nerve[50].

Ultrasound-guided lumbar sympathetic ganglion block, see Table 2 for more details.

Recommendations: Lumbar sympathetic ganglion block is used to treat sympathetic nerve pain of the lower limbs and vasospastic disease. The block is usually performed under X-ray or computed tomography image guidance. Ultrasound-guided lumbar sympathetic ganglion block can be applied to slim patients, with puncture making full use of the Doppler effect. This avoids injury of the vessels around the vertebrae. Dual guidance of X-ray and ultrasound are often applied in clinical practice.

CONCLUSION

This expert consensus was proposed by domestic experts working on ultrasound-guided pain treatments to guide clinicians and medical experts on the correct use of ultrasound-guided injections for SP.

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EXPERT CONSENSUS

Chinese Association for the Study of Pain: Expert consensus on diagnosis and treatment for lumbar disc herniation

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Abstract

Lumbar disc herniation is a common disease in the clinical context and does great harm to either the physical or mental health of patients suffering from this disease. Many guidelines and consensus for the diagnosis and treatment of lumbar disc herniation have been published domestically and internationally. According to the expert consensus, clinicians could adopt tailored and personalized diagnosis and treatment management strategies for lumbar disc herniation patients.

Key Words: Lumbar disc herniation; Diagnosis and treatment; Disc degeneration; Radiofrequency thermocoagulation; Percutaneous disc ablation; Expert consensus

Core Tip: Lumbar disc herniation is a common disease in the clinical context and does great harm to either the physical or mental health of patients suffering from this disease. Therefore, a team containing experts in relevant fields was organized by the Spinal Pain Research Group of the Chinese Association for the Study Pain and compiled the Chinese pain expert consensus on the diagnosis and treatment for lumbar disc herniation through reviewing literature, soliciting opinion and engaging in

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INTRODUCTION

Lumbar disc herniation (LDH) is a common disease in the clinical context and does great harm to either the physical or mental health of patients suffering from this disease. Many guidelines and consensus for the diagnosis and treatment of LDH have been published domestically and internationally[1-4], but the one that makes a general summary for these publications in clinical practice has not yet been written. Therefore, a team containing experts in relevant fields was organized by the Spinal Pain Research Group of the Chinese Association for the Study Pain and compiled the Chinese pain expert consensus on diagnosis and treatment for LDH through reviewing literature, soliciting opinion and engaging in discussion repeatedly. According to the expert consensus, clinicians could adopt tailored and personalized diagnosis and treatment management strategies for LDH patients.

The databases used for building the consensus included PubMed, Web of Science, Embase, China National Knowledge Internet, Wanfang Data, The Cochrane Library and Up To Date. Medical terms including "lumbar disc herniation" and "lumbosacral radiculopathy" were used as the main keywords, and "low back pain" and "sciatica" were set as the secondary keywords for searching. Only randomized controlled trial research papers, cohort research papers and meta-analyses were included while papers describing non-disc-related causes of pain (such as spinal stenosis, inflammation, tumors, *etc.*) were excluded from the search result. The classification and evaluation of the research evidence in this consensus was based on the Oxford Centre for Evidence Based Medicine's Levels of Evidence.

DEFINITION

As the lumbar disc experiences degenerative changes, the annulus fibrosus is partially or completely ruptured. Then the nucleus pulposus alone or together with the annulus fibrosus and cartilage endplate protrudes outwards, and these structures stimulate or compress the sinus spinal nerves and nerve roots. LDH manifestations like low back pain, which is caused by the forgoing pathological process, is the major symptom.

EPIDEMIOLOGY

LDH is a frequent and common disease that majorly affected adults in the clinical context. At least 95% of LDH occurs in L_{4-5} and L_5-S_1[5,6]. Relevant foreign studies indicate that the incidence of LDH is around 2%-3%, while the incidence in men over 35 is about 4.8% and that in women is about 2.5%[7].

CAUSE OF DISEASE

Disc degeneration

Lumbar disc degeneration is the fundamental factor suggesting the pathogenic basis for LDH. The pathophysiological alternation of degeneration includes the reduction of water content or moisture content in the fibrous annulus and nucleus pulposus, loss of the nucleus pulposus elasticity and occurrence of concentric annulus fissures.

Injuries

Cumulative trauma injuries caused by physical repetition and labor, sedentary lifestyle, squatting, driving and sports are important factors in the initiation of LDH.

Congenital lumbosacral anomalies

Congenital anomalies such as lumbar sacralization, sacral lumbarization, hemivertebra deformities, facet joint deformities and asymmetry of the articular process would change the stress borne on the lower lumbar spine. Then this leads to increased intervertebral disc pressure, making the individual susceptibility to degeneration and injury.

Genetic factors

The incidence of LDH in populations of color is low. Factors including encoding structural proteins, matrix metalloproteinases, apoptosis factors, growth factors and vitamin D receptors are associated with the increased risk of LDH[8-10].

Others

Pregnancy, obesity, diabetes, hyperlipidemia, smoking, infection, *etc*. are also risk factors for LDH.

PATHOGENESIS

Intervertebral disc degeneration

The intervertebral disc is mainly composed of the nucleus pulposus, annulus fibrosus and cartilage plate. Type II collagen decreases while type I collagen increases as the disc degenerates owing to factors such as aging. The alteration in the container of the disc results in the loss of disc elasticity and thus reduces its buffer function in the confront of external forces and finally makes the body more vulnerable to trauma and injury. Once the disc is denatured or damaged, it is difficult for this structure to realize self-repair as its congenital feature characterizes insufficient blood supply[11,12].

Mechanical stress injury

When the spine is under excessive load due to prolonged sedentary conditions, squatting, long-term bending or physical labor, the pressure inside increases. Degenerative changes in the disc are accelerated by cell apoptosis or immune response and eventually develop into LDH.

Immune inflammation

A herniated disc could cause a variety of inflammatory immune responses leading to changes of itself and thus aggravates herniation with corresponding clinical symptoms. The nucleus pulposus can act as an autoantigen to induce an autoimmune reaction and promote the occurrence and development of LDH.

Imbalance of extracellular matrix metabolism

In normal intervertebral discs, the expression of matrix metalloproteinase and metalloproteinase tissue inhibitors maintain a dynamic equilibrium. When the balance is disrupted, the process of extracellular matrix degradation is affected, and the result is reduced disc elasticity and accelerated disc degeneration.

In short, the pathogenesis and mechanism of LDH are considerably complicated, and each stage of the disease may be the result of merely a single factor or the joint action of several factors. Of note, different factors may also deteriorate in different stages and as a result would aggravate LDH.

CLINICAL MANIFESTATIONS

Symptoms

Low back pain: Low back pain is often the initial symptom of LDH. The pain is generally in the lumbosacral region, mostly soreness and pain, which can radiate to the buttocks with repeated episode occurrence. The symptoms are aggravated by sedentary conditions, squatting or exertion after labor, and relieved after rest.

Lower limb pain: Radiation pain may occur in the lower extremities, and symptoms worsen after standing, walking, sneezing or coughing and are relieved during bed rest. Patients with severe disorders may even feel paresthesia or numbness in the corresponding nerve distribution area. Most LDH occurs in L_{4-5} and L_5-S_1, which can lead to sciatica and radiation pain in the posterolateral lower extremities. A small number of LDH cases involving the high level of spine often affects the L_{2-4} nerve roots causing femoral neuralgia and pain in the groin area or anteromedial part of the lower limbs. Radiating pain usually affects only one side, and only a few patients may show symptoms of both lower limbs (Table 1)[13].

Cauda equina nerve symptoms: Large central disc herniation, prolapse or free intervertebral disc tissue can compress the cauda equina nerve causing pain in the lower extremities and perineum, hypoesthesia or numbness and even dysfunction of urine and bowel.

Signs

General signs: Lumbar scoliosis and lameness may occur. Lumbar movement, mainly forward bending, is limited. Tenderness near the vertebrae is often discovered on the affected side of the intervertebral disc, and pressing the point will result in distal radiological discomfort when compressed.

Special signs: (1) The straight leg raise test (SLRT) or Lasegue's sign and its strengthening test: L_{4-5} and L_5-S_1 herniated discs compress the sciatic nerve, and the SLRT is often positive. A positive result for the SLRT and its enhancement test can usually further rule out causes outside the spine. If SLRT is positive on the healthy side, this usually indicates a serious manifestation of spinal canal herniation; and (2) Femoral nerve traction test: When femoral nerve traction test is positive, it often indicates that L_{2-4} nerves are involved.

Nervous system performance: (1) Sensory impairment: The affected spinal nerve roots will have paresthesia in the corresponding innervated areas. The original syndrome has hyperesthesia in the early stage followed by numbness, tingling and sensory loss; (2) Decreased muscle strength: The muscles innervated by the affected nerve roots may have varying degrees of muscle weakness, and muscle atrophy may occur in the patients suffering long duration of disease. When the L_5 spinal nerve roots are involved, the ankle and toe dorsiflexion will decrease. When the S_1 spinal nerve roots are involved, toe and plantar flexion will decrease; and (3) Abnormal reflexes: Reflexes of the affected tendon are weakened or disappear. Abnormal knee tendon reflex abnormalities are more common in L_4 spinal nerve root compression, and weakness or missing of Achilles tendon reflex is commonly associated with S_1 spinal nerve root compression. Impaired cremaster and anal reflexes and weakened anal sphincter tone are widely seen in cauda equina involvement.

Imaging

X-ray: When the physiological curvatures of the lumbar spine are broken, lateral radiograph shows that the intervertebral space narrows or narrows in anterior and widens in the posterior. Orthotopic radiograph can show scoliosis, and the height of the affected side of the intervertebral space is often lower than that of the healthy side.

Computed tomography: When intervertebral disc tissues protrude into the spinal canal, they will compress the nerve root or dural sac. Based on this point, the diagnosis of local calcification or osteogenesis using computed tomography (CT) scan can be better than the result from magnetic resonance imaging (MRI).

MRI: Sagittal, coronal and transverse positions can visually display the shape, location and size of the protrusion and the relationship with nerve root compression, which show great value in the initial diagnosis and differential diagnosis of lesions[14]. CT and MRI show no significant differences in the diagnosis of LDH in terms of sensitivity and specificity, but MRI is better than CT for soft tissue imaging. The level of intervertebral disc signal can reflect the degree of degeneration. Therefore, it is recommended to give priority to MRI examination for patients with LDH. If patients were not able to take MRI, CT examination could be also taken into consideration[15] (recommendation grade B, evidence level 2a).

Table 1 Clinical manifestations of different lumbar disc herniation segments[13] (recommendation level B, evidence level 2a)

Protruding segment	Affected nerve	Pain area	Superficial hypoesthesia	Muscle strength decline	Hyporeflexia
L_{1-4}, L_{4-5} lateral	L_4	Lower waist, buttocks, anterolateral thighs, medial calves	Anterolateral thigh, knee joint, medial leg	Quadriceps dorsal extensor	Knee jerk
L_{4-5}, L_5-S_1 lateral	L_5	Sacroiliac, buttocks, lateral thighs, lateral calves, dorsal feet	Lateral leg, dorsal foot, great toe (hallux)	First toe back extension, foot back extension	No
L_5-S_1	S_1	Sacroiliac, waist, buttocks, posterolateral thigh, posterolateral calf, posterolateral foot	Back of calf, lateral ankle, outside of foot	First toe plantar flexion, toe flexion	Ankle reflex

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnosis

The final diagnosis of LDH must be combined with clinical symptoms, signs and imaging results to make a comprehensive judgment. The symptoms and signs of the affected segmental nerves should be consistent with the area of the nerve innervated by the protrusions on MRI or CT.

Criteria: (1) Radiation pain in the lower extremities, the location of pain associated with the corresponding innervation area involved; (2) Paresthesia in the lower limbs and reduced superficial sensation in the affected innervated area; (3) SLRT, strengthened SLRT, healthy side SLRT or femoral nerve pull tests positive; (4) Tendon reflexes weaker than the healthy side; (5) Reduction of muscle strength; (6) Selective nerve root block can attenuate pain or paresthesia in the lower limbs; and (7) Lumbar MRI or CT shows disc herniation, and nerve compression is consistent with the symptoms and signs caused by the affected nerve. If three of the first six criteria are met, combined with the seventh, the patients should be diagnosed as LDH[13-15] (recommended level A, level of evidence 1a).

Attention: (1) Low back pain is not a necessary condition for the diagnosis of LDH, but patients often have a history of low back pain; (2) Diagnostic imaging such as MRI or CT alone should not be used as the basis for diagnosing LDH (recommended level A, level of evidence 1a); (3) Myelography is invasive and not recommended for routine practice[15] (recommended level B, level of evidence 2a); (4) Neuro-electrophysiological examination and infrared thermography examination are not recommended for routine practice due to limited diagnostic value for LDH[16,17] (recommended level B, level of evidence 2a); and (5) Discography and selective nerve root block surgery should be used to figure out the responsible segment in cases of multisegmented LDH that is difficult to clarify the main responsible segments.

Differential diagnosis

LDH should be differentiated from diseases including piriformis syndrome, lumbar spinal stenosis syndrome, lumbar tumor, spinal infections, cauda equina neuroma, spondylolisthesis, ankylosing spondylitis and herpes zoster.

TREATMENT

Most patients with LDH will relieve their symptoms over time. Therefore, an individualized treatment regimen should be taken according to the course, clinical manifestations, the location of the disc herniation and the severity of the corresponding nerve root compression. The routine strategies used for LDH treatment include general treatment, drug treatment, minimally invasive treatment, surgery and rehabilitation.

Nonsurgical treatment should be taken as the first-line treatment for most patients with LDH (recommended level A). Generally, conservative treatment should last for at least 4-6 wk (recommended level A), including rest, physical therapy, traction, acupuncture and medication. Although most patients with LDH benefit from conservative treatment, evidence suggests that patients receiving minimally invasive interventional therapy at the early stage can achieve superior outcomes compared with those who undergo long-term conservative treatment in pain relief and functional recovery[18,19] (recommended level B, level of evidence 2b).

General treatment

Bed rest is required during the acute episode, but long-term bed rest is not recommended. Patients should be encouraged to carry out appropriate and regular daily activities and to wear a back support belt during activities. General treatments such as traction and massage may be suggested according to the condition. In addition, proper health education can help in preventing recurrence and relieving symptoms.

Drug treatment

Acetaminophen, nonsteroidal anti-inflammatory drugs (ibuprofen, celecoxib, etoricoxib, *etc.*, recommended level A, level of evidence 1b), ion channel modulators (gabapentin, pregabalin, *etc.*), tramadol, opioids (oxycodone, fentanyl, buprenorphine, *etc.*[2,20-22] recommended level B, level of evidence 2), dehydration drugs (mannitol), glucocorticoids, central muscle relaxants (eperisone, chlorzoxazone, *etc.*), neurotrophic agents, microcirculation improvement and traditional Chinese medicines all have an effect on LDH to a certain degree and should be used according to the clinical situation.

Minimally invasive surgery and treatment

Soft tissue lysis surgery: The needle-knife can loosen adhesive tissues, improve the blood supply of the soft tissue and reduce nerve compression. Internal heat needle and silver needle can improve LDH symptoms to varying degrees and should be performed clinically if appropriate[23,24].

Injection treatment: Including epidural injection, selective nerve root injection, sacral canal injection, lumbar sympathetic ganglion injection, *etc.* (1) Epidural injection: Drugs can be administrated around the root of the affected nerve by approaches like anatomic localization or image-guided operations *via* foramina, an interlaminar approach (including lateral recess approach) or sacral hiatus puncture. Epidural steroid injection, which can relieve the symptoms of low back pain in patients with sciatica in the short term, should be taken into consideration[25,26] (recommendation level A, evidence level 1b). During epidural steroid injection treatment, glucocorticoids should be administrated in small doses at the beginning. A higher dose is not equal to a better clinical efficacy, and epidural steroid injection is associated with serious complications, especially spinal cord injury and cerebral infarction caused by granular glucocorticoids. The incidence of complications in the waist region is lower than that of the neck area[27] (recommended level B, level of evidence 2b). Local injections of hyaluronic acid and cytokine inhibitors in patients with LDH and radicular pain require more high-quality randomized controlled trial research evidence; (2) Selective nerve root injection: LDH patients receive selective root injection of glucocorticoids that can reduce the inflammation of compressed nerve roots and surrounding tissues and attenuate pain on most clinical occasions. Long-term pain control can be achieved in some patients, providing support that this method should be considered as the preferred treatment[28] (recommended level A, evidence level 1a); (3) Sacral canal injection: Sacral injection (which can also be performed under ultrasound guidance) can help to relieve the pain of lumbosacral root compression in patients with LDH; (4) Lumbar sympathetic ganglia injection: Lumbar sympathetic nerve injections are usually L_2 and L_3 sympathetic nerve injections, which can treat sympathetic nerve-related pain in the lower limbs caused by LDH[29] (recommended level B, evidence level 2a); and (5) Injection of the posterior branch of the lumbar spinal nerve: When lumbar and sacral areas are affected by LDH, chronic strain, edema of the intervertebral foramina or spinal canal tissue, narrowing of the intervertebral aperture, inflammation of the tendon and ligament and facet joint disorder can cause the stimulation of the posterior branch of the spinal nerve in the corresponding segment. It causes symptoms such as soreness, stiffness, pain and limitation of activity in the local or adjacent tissues. Injection of the posterior branch of the spinal nerve is an effective treatment method, and it should be performed under the guidance of images such as ultrasound.

Radiofrequency thermocoagulation: Radiofrequency thermocoagulation can be safely and effectively used in the treatment of LDH. Clinical applications should strictly adhere to the indications.

Percutaneous disc trioxide ablation: Percutaneous intervertebral disc trioxygen injection is an effective and safe method with a complication rate of around 0.1%. A cumulative effect induced by ganglion and epidural injections of glucocorticoids/local

anesthetics may improve the overall treatment effect[20] (recommended level C, level of evidence 4).

Percutaneous disc ablation: As a safe and effective LDH treatment technique, low-temperature plasma percutaneous discectomy should be taken into consideration[30] (recommended level A, level of evidence 1a. It can significantly relieve pain and improve mobility. Clinical applications must strictly follow the indications. Low-temperature plasma radiofrequency can also be used in combination with ozone to treat LDH[31] (recommended level B, level of evidence 2c).

Percutaneous low-energy laser disc repair: Percutaneous low-energy laser disc repair is an upgrading version of technology based on percutaneous laser disc decompression. A semiconductor laser with a wavelength of 970 nm is used to inject a small amount of isotonic or hypertonic saline into the disc during treatment[32].

Percutaneous disc collagenase chemical lysis: For patients whose diagnosis is accurate and conservative treatment is ineffective, collagenase injection treatment can be considered. It is easy to administer and has a remarkable effect[33] (recommended level B, level of evidence 2b). Methods of collagenase injection can be divided into the intra-disc, extra-disc and combined method. Collagenase injection should avoid entering the subarachnoid space.

Percutaneous discectomy: Percutaneous discectomy is effective and can be used as a treatment for LDH with radiculopathy[34-36] (recommended level B, level of evidence 2b), but the application is strictly limited to the indications[37].

Percutaneous spinal endoscopic lumbar discectomy: Compared with open surgery, percutaneous endoscopic lumbar discectomy has a shorter length of stay and shows better results in terms of pain relief and functional recovery[38-41] (recommendation level B, level of evidence 2b). Percutaneous endoscopic lumbar discectomy contains two types of techniques: Percutaneous endoscopic transforaminal discectomy and percutaneous endoscopic interlaminar discectomy. Generally, percutaneous endoscopic transforaminal discectomy is suitable for scapular, central and recurrent LDH, whereas percutaneous endoscopic interlaminar discectomy is preferred for axillary and displaced intervertebral discs (recommended level A). Compared with open discectomy, percutaneous endoscopic lumbar discectomy has less bleeding and shorter in-hospital stays[40] (recommended level A, level of evidence 1a).

Surgical treatment

Surgical treatment should be considered if conservative treatment following a rigorous and strict protocol fails to achieve clinical efficacy. The aim of minimally invasive surgery is to relieve pain and/or symptoms of nerve damage instead of a curative effect on disc degeneration and reversing disc herniation.

Rehabilitation treatment

Traction therapy: Lumbar traction is one of the commonly used conservative treatments for patients with LDH that can release intervertebral disc pressure, loosen adhesion tissues, relax ligaments, relieve muscle spasm, improve local blood circulation and address facet joint disorders.

Extracorporeal shock wave: Extracorporeal shock wave treatment can effectively reduce pain in patients with low back pain and improve their functional status and quality of life[42-44].

Medium- and low-frequency electrotherapy: Commonly used in clinical settings, low-frequency electrotherapy causes percutaneous nerve electrical stimulation (transcutaneous electrical nerve stimulation) and can interfere with electrotherapy. Transcutaneous electrical nerve stimulation can relieve pain, improve dysfunction, and uplift the grade of muscle activation in LDH patients[45]. Of note, its curative effect has not been recognized[45,46].

High-intensity laser therapy: High-intensity laser therapy with anti-inflammatory, antitumor and analgesic effects can be used to reach lesions where low-power laser stimulation cannot, such as the deep areas of large and/or small joints[47,48].

PREVENTION

The prevention of LDH can be carried out with reference to the three-level prevention system for chronic diseases, including steps following the order of the prevention of the initial of LDH, the prevention of the recurrence of LDH radiculopathy symptoms and the prevention of the recurrence after LDH surgery.

Prevention of LDH

Enhancement of self-awareness of professional protection, correct weight-bearing postures at the waist and proper back muscle function training may have a certain preventive effect on acute LDH[49,50] (recommended level C, level of evidence 4).

Prevention of recurrence of LDH radiculopathy

Weight control, regular back muscle function exercise and correction of poor posture may help to prevent recurrence[51,52] (recommended level C, level of evidence 4).

Prevention of symptomatic recurrence after LDH

Postoperative recurrence can be prevented by wearing a back support belt and performing exercises to strengthen back muscle function.

CONCLUSION

According to the expert consensus, clinicians should adopt tailored and personalized diagnosis and treatment management strategies for LDH patients.

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EXPERT CONSENSUS

Expert consensus of Chinese Association for the Study of Pain on the non-opioid analgesics for chronic musculoskeletal pain

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Abstract

Chronic musculoskeletal pain (CMP) is a common occurrence in clinical practice

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and there are a variety of options for the treatment of it. However, the pharmacological therapy is still considered to be a primary treatment. The recent years have witnessed the emergence of opioid crisis, yet there are no relevant guidelines on how to treat CMP with non-opioid analgesics properly. The Chinese Medical Association for the Study of Pain convened a panel meeting to develop clinical practice consensus for the treatment of CMP with non-opioid analgesics. The purpose of this consensus is to present the application of nonsteroidal anti-inflammatory drugs, serotonin norepinephrine reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, muscle relaxants, ion channel drugs and topical drugs in CMP.

Key Words: Chronic musculoskeletal pain; Non-opioid analgesics; Nonsteroidal anti-inflammatory drugs; Noradrenaline reuptake inhibitor; Nociceptor; Cyclooxygenase

Core Tip: Chronic musculoskeletal pain (CMP) is a common disease seen in pain clinics. There are a variety of treatment options available for CMP, among which pharmacological treatment is considered to be a simple and effective basic treatment. The opioid crisis caused by excessive dependence on opioids for CMP treatment has drawn much attention and causes high vigilance to opioid safety in China and other countries. Therefore, the Chinese Association for the Study of Pain, a branch of Chinese Medical Association, convenes a panel meeting to provide guidance to the treatment of CMP with non-opioid analgesics.

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INTRODUCTION

Chronic musculoskeletal pain (CMP), characterized by persistent or recurrent pain in muscles, tendons, bones and related soft tissues, is a common disease seen in pain clinics. CMP involves a wide range of tissues and causes a lot of comorbidities. Sometimes the severe and persistent pain may lead to psychological disorders. CMP seriously affects patients' quality of life, and results in excessive medical cost and heavy social burden. In recent years, with population aging and social pressure caused by the modern lifestyle, along with other factors, the incidence of CMP has been increasing drastically, which highlights the significance of the treatment for CMP. There are a variety of treatment options available for CMP, among which pharmacological treatment is considered to be a simple and effective basic treatment. It is important to use the pharmacological treatment in a safe and effective way, which can be a challenge in many aspects. For example, the improper use of nonsteroidal anti-inflammatory drugs (NSAIDs) for CMP is very common in China. The knowledge on alternative drug is insufficient when NSAIDs fail to effectively relieving pain or result in intolerable side effects. In Western countries, the opioid crisis caused by excessive dependence on opioids for CMP treatment has drawn much attention and causes high vigilance to opioid safety in China and other countries. In this context, how to use non-opioid analgesics to treat CMP is of great social significance. Therefore, the Chinese Association for the Study of Pain, a branch of Chinese Medical Association, convenes a panel meeting to develop this expert consensus to provide guidance to the treatment of CMP with non-opioid analgesics.

PATHOGENESIS

CMP involves more than 150 diseases of the human locomotor system with complex pathogenesis and numerous etiology, which can be generally divided into three major categories: neuropathic, mechanical, and inflammatory[1,2]. Nerve injury or entrapment due to various causes, muscle mechanical instability due to degenerative changes in muscles, and increased release of local inflammatory factors can, in most cases, directly stimulate nociceptors and sensitize them. Regardless of which category the CMP is, its pathological changes include local histopathological changes and systemic pathological changes, resulting in neurological dysfunction or structural changes[3].

Similar to other types of chronic pain, peripheral sensitization and central sensitization represent the basic pathogenesis of CMP. Overexpression of the proinflammatory factors, IL-1β, TNF-α, IL-6, and IL-8[4], and down-regulation of the anti-inflammatory factors IL-4 and IL-10 play an important role in CMP[5] . Persistent inflammatory reactions also cause an imbalance in the osteogenic-osteoclastic process, leading to osteophyte formation and osteoporosis[6] as well as muscle fibrosis and/or calcification which further cause pain.

Protracted chronic pain leads to local structural changes such as sclerosis and/or softening of bones, muscle spasms, joint contractures, *etc*. which will further result in functional impairment, including motor limitation, cognitive and affective disorders such as memory loss, and anxiety/depressive symptoms[7]. Cognitive and affective disorders cause decline in social skills and deterioration of decision-making systems. It is now clear that structural and functional abnormalities in high centers such as the anterior cingulate cortex and insular cortex may mediate cognitive and affective disorders in chronic pain, and in addition, they may cause and maintain central sensitization through descending facilitation pathways[8]. This Synaptic plasticity makes CMP a type of chronic intractable pain disorder with affective disorders or dysfunction.

NSAIDS

NSAIDs are a class of non-steroidal drugs with antipyretic and analgesic effects. The main mechanism of action of NSAIDs is to inhibit the activity of cyclooxygenase (COX) and further reduce the synthesis of prostaglandins[9]. There are many types of NSAIDs, which can be divided into non-selective COX inhibitors and selective COX-2 inhibitors according to their selectivity for cyclooxygenase subtypes. According to their different chemical structures, they can be divided into salicylic acids, indoles, anilines, pyrroles, enolic acids, arylacetic acids, and ibufenac, and commonly used drugs include indomethacin, ibuprofen, diclofenac, meloxicam, celecoxib, and etoricoxib. NSAIDs have good analgesic effects on mild to moderate CMP caused by inflammation.

A ceiling effect has been confirmed for NSAIDs. Dose escalation should be avoided, as well as the combination of two NSAIDs drugs. The adverse effects of NSAIDs are of increasing concern, with non-selective COX inhibitors predisposing to the risk of gastrointestinal bleeding and selective COX-2 inhibitors predisposing to cardiovascular and adverse renal effects[10]. Therefore, in clinical practice, it is important to prescribe NSAIDs according to the approved labels and use these drugs in consideration with the general condition of the patient. NSAIDs should be used with caution or avoided in patients with previous history of upper gastrointestinal ulcer bleeding, ischemic heart disease or kidney disease.

SEROTONIN-NORADRENALINE REUPTAKE INHIBITOR

Serotonin-noradrenaline reuptake inhibitors (SNRIs) are a class of commonly used antidepressant medications with representative products of duloxetine and venlafaxine, which act as analgesic and antidepressant in CMP management. Their analgesic mechanism is to enhance the role of the descending inhibitory system of pain and reduce the uploading of nociceptive stimulation signals through the spinal cord.

A number of international studies and guidelines have shown that SNRIs have considerable therapeutic effects on various chronic musculoskeletal pains[11,12]. The first guidance that includes duloxetine as recommended treatment option is the 2014 Guidelines for the Treatment of Knee Osteoarthritis by the Osteoarthritis Research Society International (OARSI). Duloxetine has demonstrated a better therapeutic effect

when used in combination with NSAIDs, with additional benefit in depressive symptoms[13-15]. In a double-blind, randomized controlled study of 407 Chinese patients in 2017, the BPI pain score in the treatment group was significantly lower than that in the placebo group. The secondary efficacy endpoints such as Patient Global Impression, Western Ontario and McMaster Osteoarthritis Index (osteoarthritis index score), and CGI were also significantly improved. The treatment of pain with duloxetine was achieved by a direct analgesic effect, rather than its antidepressant effect[16]. Forty-three to sixty-seven percent of patients achieved pain relief (≥ 30% or ≥ 50% reduction in pain score, improvement in physical function, and subjective improvement) after 13 wks treatment with duloxetine (60-120 mg, qd); however, it is not recommended to continue the treatment if there is no improvement after more than 4 wks of continuous treatment.

Three randomized controlled trials investigating duloxetine for the treatment of chronic low back pain (CLBP) have concluded consistently that the study group had significantly lower pain scores and improvements in other secondary outcomes when compared with placebo groups[17-19]. Another study showed that duloxetine was effective in reducing opioid consumption compared to other treatments[20]. In the 2017 American College of Physicians guideline, duloxetine was listed as a treatment option for CLBP, with a moderate grade of recommendation[21]. At present, there are few clinical studies on SNRIs for the treatment of CLBP in China that can provide clinical evidence to support their role in CLBP management.

Fibromyalgia causes extensive pain in the muscles and soft tissues in the whole body, and the cause of the disease remains unknown. Duloxetine has been shown to significantly reduce pain score in patients with fibromyalgia, with many patients achieving significant improvement during the first week of treatment, regardless of concomitant depression status at the dose of 60 mg/day[22].

MPS is a local pain syndrome caused by aseptic inflammation of skeletal muscle. Patients are often accompanied by anxiety, depression and insomnia. SNRIs can be used as an adjuvant therapy, but there is no clear clinical evidence to support their efficacy.

Dry mouth and nausea are common among the adverse reactions of SNRIs. Other adverse reactions include dizziness, drowsiness, constipation and loss of appetite. SNRIs have a favorable safety profile when compared with NSAIDs in terms of gastrointestinal and cardiovascular adverse reactions; and when compared with other antidepressants in terms of cardiovascular risks. The incidence of adverse effects is lower when duloxetine is administered at a starting dose of 30 mg/day. The incidence of dose-related adverse effects of duloxetine at 120 mg/day is significantly higher than that at 60 mg/day dose.

MUSCLE RELAXANT

Muscle relaxants can be divided into two categories: skeletal muscle relaxant and central relaxant.

Skeletal muscle relaxants: Baclofen and dantrolene

Baclofen, which mainly acts on presynaptic GABA receptors by reducing synaptic conduction[23]. Indication: Multiple sclerosis, muscle spasms caused by spinal cord disease, and brain-derived muscle spasms[24]. Adverse reactions include drowsiness, sedation, nausea and hypotension. Dosage should be gradually reduced during long-term treatment[25].

Dantrolene produces muscle relaxation effects mainly by inhibiting the release of calcium ions[26] and can be used to treat spasms caused by upper nervous system diseases[27], and is currently mainly used to treat malignant hyperthermia.

Central relaxant: benzodiazepines, non-benzodiazepines and tizanidine

The representative drugs of benzodiazepines in clinical practice are diazepam, oxazepam, estazolam, lorazepam, midazolam, alprazolam and clonazepam. They act mainly by elevating the inhibitory neurotransmitter GABA[23], producing hyperpolarization effects. It has sedative, hypnotic, anxiolytic, and myorelaxant effects. A common adverse effect is excessive sedation.

The representative drug of non-benzodiazepines in clinical practice is eperisone, which acts on spinal motor neurons and skeletal muscle, relaxes muscle spasm, improves local microcirculation of blood, blocks the vicious cycle of "pain-muscle tension-local blood circulation disorder", thus improving CMP, especially in chronic

low back pain as the first-line treatment option. The most common adverse reactions are mild adverse reactions such as nausea and anorexia.

Tizanidine is an α2 receptor agonist that acts through presynaptic inhibition of motor neurons[23]. Indications: Neck, shoulder and low back pain, multiple sclerosis, cerebrovascular events and other types of myotonia. It has been reported in the literature that it is not recommended as a first-line drug for the treatment of chronic musculoskeletal pain. Tizanidine is known to have sedative and antihypertensive effects, and should be administered at a low dose when initiating the treatment[28].

ION CHANNEL DRUGS

The ion channel drugs used in clinical practice include three categories: Calcium ion channel modulators (gabapentin, pregabalin), sodium channel blockers (carbamazepine, oxcarbazepine, lidocaine, *etc*.) and potassium channel openers (flupirtine), among which calcium ion channel modulators are most widely used in chronic musculoskeletal pain. Calcium ion channels play an important role in many physiological processes of the nervous system, such as the regulation of neuronal excitability, the release of transmitters at synaptic sites, synaptic plasticity, and gene transcription, all of which are achieved through the regulation of calcium influx by calcium ion channels. Calcium ion channel blockers relieve pain by inhibiting calcium influx and reducing the release of neurotransmitters, thereby reducing the abnormal excitation of pain conduction pathways[29]. Among them, potassium channel openers have been withdrawn from market because of their hepatotoxicity[30].

Common ion channel drugs

Gabapentin: Gabapentin was first used to control seizures and was subsequently found to have a role in the treatment of neuropathic pain as well[31]. Its structure is similar to that of GABA, but it does not target GABA receptors and does not affect the synthesis and uptake of GABA. The α2δ-1 subunit of the voltage-gated calcium ion channel is the target site of gabapentin, and the specific binding can block the transport of α1 units of calcium ion channels from the cytoplasm to the cell membrane in dorsal root ganglia and spinal dorsal horn neurons. In addition, the axoplasmic transport of α2δ-1 subunits from the dorsal root ganglia to the spinal dorsal horn can also be blocked by gabapentin. Gabapentin can also inhibit pain *via* other targets, such as transient receptor voltage channels, NMDA receptors, protein kinases, and inflammatory factors[32].

The clinical role of gabapentin in chronic musculoskeletal pain is mainly for some "tunnel" syndromes such as carpal tunnel syndrome, cubital tunnel syndrome and other musculoskeletal pain caused by corresponding nerve entrapment as well as fibromyalgia, chronic nerve or traumatic body pain[33]. Common adverse effects include vertigo, drowsiness, ataxia, and peripheral edema[34].

Pregabalin: Like gabapentin, Pregabalin blocks the influx of extracellular calcium, thereby reducing the release of excitatory amino acids.

The clinical role of pregabalin in chronic musculoskeletal pain is also similar to that of gabapentin. The adverse reactions of pregabalin include peripheral edema, PR interval prolongation, dizziness, drowsiness, ataxia, headache, language disorder, tremor, etc. The adverse reactions of metabolic/endocrine system are weight gain, with an incidence of 4%-12%; elevated creatine kinase level and myoclonus are observed in the musculoskeletal system, and rhabdomyolysis has been reported in individual cases; mild and transient elevation of liver enzyme level, lack of saliva, constipation, visible thrombocytopenia, blurred vision, diplopia, amblyopia, *etc*. are infrequently reported with pregabalin.

Carbamazepine: Carbamazepine is a commonly used antiepileptic drug with membrane stabilizing potential, which can inhibit sodium ion channels in the cell membrane, reduce neurotransmitter release and neural cell excitability. It is commonly used in antiepileptic therapy and treatment for trigeminal neuralgia and glossopharyngeal neuralgia. It is not commonly used for chronic musculoskeletal pain[35].

Oxcarbazepine: Oxcarbazepine, known as a 10-ketone derivative of carbamazepine, is a brand-new antiepileptic prodrug of its active metabolite 10-hydroxycarbamazepine (MHD)[36]. Oxcarbazepine acts similarly to carbamazepine by blocking voltage-dependent sodium ion channels, stabilizing neuronal cell membranes, inhibiting neuronal repetitive firing and reducing synaptic impulse firing. Its clinical use is

similar to that of carbamazepine and less commonly used for chronic musculoskeletal pain.

TOPICAL DRUGS

Topical non-opioid analgesics for the treatment of CMP include NSAIDs, local anesthetics, capsaicin, and traditional Chinese medicines (TCMs). The common dosage forms are cream/emulsion, solution, spray, gel, and patch. Topical drugs penetrate through the skin directly to the affected tissue to exert analgesic effects, with the advantages of rapid onset, high local concentration, less systemic exposure and less systemic adverse effects, which make them more appropriate for long-term CMP management than oral formulations[33,37,38].

NSAID preparations

Several CMP-related guidelines and expert consensus have pointed out[33,37-44] that topical NSAIDs have a confirmed analgesic effect and are the most clinically well-documented and prescribed topical analgesics, which can be used as first-line treatment for mild to moderate CMP, either for local short-term treatment or as initial treatment before oral NSAIDs in combination with oral preparations for patients with moderate and severe pain. Topical NSAIDs include ketoprofen, ibuprofen, flurbiprofen, diclofenac, and indomethacin. Different dosage forms have different efficacies, which mainly depend on the skin permeation characteristics (permeability coefficient), water content, and whether it contributes to the dissolution and migration of active drugs. Generally gels are superior to other dosage forms[45]. Some experts suggest that topical NSAIDs gel is often used in ultrasonic drug penetration therapy, during which it helps local penetration and absorption and improves the efficacy[37]. Topical NSAIDs are well tolerated and safe to patients, and common adverse reactions are mild or transient skin irritation reactions (erythema, itching, *etc.*) at the application site.

Lidocaine preparations

Lidocaine exerts its analgesic effect by blocking peripheral nerve pain receptor-gated sodium channels and can be used to relieves mild to moderate CMP, and concomitant neuropathic pain (especially those with cutaneous hyperalgesia)[33]. 5% gel plaster and compound ointment are commonly used, and the main adverse reaction is mild to moderate local skin irritation[46].

Capsaicin preparations

Topical capsaicin acts on peripheral nerve axons, reducing the synthesis and release of substance P to produce analgesic and antipruritic effects. It is capable of effectively relieving neuropathic and OA pain[47]. Patches and ointments are commonly used.

TCMs

Yunnan Baiyao (ointment, aerosol), Qingpeng ointment, Qizheng Xiaotong plaster and other topical Chinese patent medicines commonly used in clinical practice have certain effects of improving microcirculation and analgesia, but high-quality evidence are needed to support the mechanism of action and long-term efficacy.

OTHERS

Other medications used to treat CMP include: (1) Anti-osteoporosis drugs bisphosphonates[48]; (2) Biologics such as TNF-α antagonists, IL-1 antagonists, CD20 monoclonal antibodies, and cytotoxic T cell activation antigen-4 antibodies can be used for CMP treatment caused by rheumatoid arthritis and ankylosing spondylitis[49]; (3) Recent studies have shown that nerve growth factor may benefit CMP patients[50]; and (4) TCM (drug and therapy) for CMP is also widely used in clinical practice.

CONCLUSION

CMP refers to persistent or recurrent pain in muscles, tendons, bones, and related soft tissues. The pathogenesis of CMP is complex, and its development involves a variety of factors, including tissue degeneration, traumatic, immune, metabolic, neurological, psychiatric and affective factors.

Pharmacological treatments are the basic treatment component for CMP, and the commonly used non-opioid pharmacological treatments are NSAIDs and muscle relaxants. Recently, the indication for the treatment of CMP has been approved for the antidepressant drug duloxetine, which is considered to be a new option for CMP management. Drugs targeted on ion channels should be considered for CMP with neuropathic pain.

In the clinical management of CMP with non-opioid drugs, the approved label indications and adverse reactions should be carefully considered before prescription. The goal is to balance the effectiveness and risk of the drugs, maximize the therapeutic effect while avoiding the adverse reactions. The pharmacological combination treatment should be designed with prudence to increase the clinical effects, and reduce the dose of individual drugs as well as potential adverse reactions.

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EXPERT CONSENSUS

Expert consensus on the diagnosis and treatment of myofascial pain syndrome

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Abstract

Myofascial pain syndrome (MPS) is characterized by myofascial trigger points and fascial constrictions. At present, domestic and foreign scholars have not reached a consensus on the etiology and pathogenesis of MPS. Due to the lack of specific laboratory indicators and imaging evidence, there is no unified diagnostic criteria for MPS, making it easy to confuse with other diseases. The Chinese Association for the Study of Pain organized domestic experts to formulate this Chinese Pain Specialist Consensus on the diagnosis and treatment of MPS. This article reviews relevant domestic and foreign literature on the definition, epidemiology, pathogenesis, clinical manifestation, diagnostic criteria and treatments of MPS. The consensus is intended to normalize the diagnosis and treatment of MPS and be used by first-line doctors, including pain physicians to manage patients with MPS.

Key Words: Myofascial pain syndrome; Myofascial trigger points; Diagnosis; Treatment; Consensus; Pathogenesis

Core Tip: Myofascial pain syndrome (MPS) refers to a type of chronic pain syndrome that recurs in muscles, fascia or related soft tissues and can be accompanied by obvious emotional disorders or dysfunctions. At present, domestic and foreign scholars have not reached a consensus on the etiology and pathogenesis of MPS. Due to the lack of specific laboratory indicators and imaging evidence, there is no unified diagnostic criteria for MPS, making it easy to confuse with other diseases. The consensus is intended to normalize the diagnosis and treatment of MPS and be used by first-line doctors to manage patients with MPS.

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INTRODUCTION

Myofascial pain syndrome (MPS) refers to a type of chronic pain syndrome that recurs in muscles, fascia or related soft tissues and can be accompanied by obvious emotional disorders or dysfunctions[1]. MPS is characterized by myofascial trigger points (MTrPs) and fascial constrictions. The trigger points are sensitive to stimuli, causing localized pain and referred pain. MPS can occur alone or in combination with other diseases[2]. The term "myofascial pain" was first proposed by an American scholar called Dr. Travell in 1952[3]. After that, MPS, also called myofascitis, myofascial fibrositis, myositis, fibromyositis, muscle strain and myofascial syndrome, has attracted more and more attention from clinicians[4]. At present, domestic and foreign scholars have not reached a consensus on the etiology and pathogenesis of MPS. Due to the lack of specific laboratory indicators and imaging evidence, there is no unified diagnostic

criteria for MPS, making it easy to confuse with other diseases[5]. Therefore, the Chinese Association for the Study of Pain organized domestic experts to formulate this consensus in order to normalize the diagnosis and treatment of MPS.

ETIOLOGY

The etiology of MPS is not completely understood. Muscles and fascia suffering from aseptic inflammation may result in adhesion. It is currently hypothesized that the pain of MPS is due to the stimulation of sensory nerves by an algogenic substance in the inflammatory environment and the compression of inflammatory edema tissues. MPS generally occurs among those performing sustained low-level static exertions, such as office workers, musicians, dentists and other occupational groups[6,7]. The residual tension produced by the persistent static force of long-term awkward working posture causes a blood circulation disorder of the skin. Accordingly, metabolites accumulate to stimulate the peripheral nerve endings, causing sensory nerve dysfunction including diffusion of referred pain, hyperalgesia and allodynia[8-10]. At the same time, the sympathetic nervous system stimulation causes vasoconstriction of skin blood vessels and decreases the blood flow, forming a vicious cycle.

The causes of the development of MTrP can be divided into two categories: Predisposing factors and risk factors[11]. Predisposing factors include: (1) Acute muscle injury or continual muscle stress; (2) Mental stress, overfatigue or insufficient sleep; and (3) Intense cooling of muscles. Risk factors include: (1) Hormonal changes and metabolic defects, such as hypothyroidism and menopause; (2) Nutrient deficiency: Vitamin B and iron deficiency; (3) Chronic infection; (4) Local chronic instability of biomechanics; and (5) Immune diseases. Traditional Chinese medicine believes that this disease is mostly caused by muscle strain, wind-cold dampness, obstruction of meridian and obstruction of Qi and blood.

EPIDEMIOLOGY

There are no accepted diagnostic criteria for MPS, resulting in a variable range of estimates from epidemiological studies. Most of the available data shows that MPS is usually related to musculoskeletal pain. MPS is a common disease that can be seen at any age, though mostly in elderly adults, athletes, hard physical laborers and sedentary workers. About 30.0% to 93.0% of patients with musculoskeletal pain suffer from MPS. About 46.1% of the patients reveal active MTrP in the physical examinations[2,12]. Clinical studies have shown that at least 40.0% of skeletal muscle pain syndrome is mainly because of the activated trigger points in painful muscles[13]. The predilection sites of MPS are the neck, shoulders and back. At present, the prevalence rate of chronic pain induced by trigger points is increasing annually. The patients suffering from MPS present as persistent pain, and the range of physical motion always decreases with the age increase.

PATHOGENESIS

The mechanisms underlying myofascial pain and formation of MTrPs are still unclear. Mense *et al*[14] proposed that the MTrPs might be initiated by an abnormal increase of acetylcholine at the motor endplate, leading to a consistent muscle contraction, which may be enhanced in traumatic/microtraumatic conditions produced by a local acute or chronic overload. The consistent muscle contraction in turn increases local energy consumption and local ischemia. The changes may induce pain or pain hypersensitivity by enhancing the local release of nociceptive substances, including substance P, calcitonin gene-related peptide and proinflammatory cytokines[15,16]. The substances can sometimes spread to adjacent spinal cord segments and cause referred pain characterized by MTrPs[17]. The central pain sensitization can increase the excitability of neurons and the expansion of the neuronal receptive fields causing refractory referred pain[18]. Alternatively, Stecco *et al*[19] suggested that muscular fascia, a form of connective tissue, may undergo pathological change under overload and damage leading to the biomechanical change of muscles and eventually to the reduction of contraction force and flexibility of muscles[20]. The inflammatory changes mentioned above may exacerbate the pathological change, leading to pain or

enhancing pain. The pathological change of muscular fascia may be related to the abnormal changes in myofibrils, fibroblasts and extracellular matrix[21].

CLINICAL MANIFESTSTIONS

MPS is often secondary to a variety of diseases or comorbidities. It is often unidentified and misdiagnosed, resulting in wrong treatment. Therefore, we should increase our understanding of the disease. Different parts of MPS have different clinical manifestations. The following are common characteristics[22-26].

Symptoms

(1) Pain: It is characterized by regional pain, which is mostly acid distension pain, with a few associated with burning pain, jumping pain, numbness and sensory abnormality. It can manifest as persistent pain, and a few can be paroxysmal. Cold, fatigue and muscle overload can induce aggravating pain, which can be alleviated by mild activity and heat; (2) Stiffness and limited range of motion: It manifests as stiffness, weakness, decreased endurance of the affected muscles and loss of related muscle coordination. The test muscles contract randomly, and the patient suddenly stops pushing prematurely; (3) Dysautonomia: Corresponding segmental sweating, chilling, pallor, slight edema and vertical hair activity, *etc.*; (4) Proprioceptive disorder: Dizziness, tinnitus, imbalance feeling and weight perception disorder when lifting objects. It is common in head and neck MPS; (5) Depression: Long-term MPS leads to repeated visits for patients and suspected diseases, which may lead to depression. It is common in patients with mental stress. Conversely, depression can reduce the pain threshold and strengthen the pain, thereby forming a vicious cycle; and (6) Dyssomnia: Poor sleep quality is often caused by night pain and morning pain.

Signs

(1) Restricted movement: muscles with trigger points can be restricted from stretching due to pain during examination. No muscular atrophy; (2) Taut bands: Consisting of a group of tense muscle fibers, it is sensitive and persistently stiff at palpation. Taut band can be confirmed by palpation through pressing or pinching the muscles; (3) Painful nodules or ropes: Muscle spasm is a kind of involuntary muscle contraction. Unlike the muscle tension band that is limited to local muscle fibers, tenderness and hard texture spread to the entire muscle; (4) MTrP: It is a small and sensitive tenderness area that presents in the accessible taut bands and can cause pain in remote areas spontaneously during compression or acupuncture. Each trigger point has a specific area of referred pain; (5) Tenderness: Compression locally induces local pain rather than referred pain; and (6) Local twitch response: It is a temporary contraction of the muscle fibers on the taut bands associated with the MTrPs. When appropriate plucking palpation or acupuncture is given at the point of irritation, the muscle fibers of the trigger bands usually present a local twitch response.

Examination

Currently there are no routine laboratory and specific imaging studies to confirm MPS. The following examinations such as electromyography, infrared thermography and ultrasound elastography can assist the diagnosis.

DIAGNOSIS

With pathogenic factors or past suffering history

Clinical manifestations: (1) Symptom: Pain, stiffness and body movement limitation (the pain might be induced/enhanced or released by changing posture or body movement); with or without any other symptom(s); and (2) Sign: Restricted movement (might be induced/enhanced or released by changing posture or body movement), MTrPs and/or tenderness (or sore to touch). Accompanied with (or without) any other sign(s).

Pathological targets can be accurate through physical examination of body movement and/or biomechanical force evaluations.

Auxiliary examinations

(1) Imaging examinations (such as X ray, computed tomography, ultrasound imagination or magnetic resonance imaging) can help to recognize the musculature and myofascial locations, shapes, sizes, depths, elasticity, nodes and calcifications. Among them, more studies have been done on ultrasound imaging and magnetic resonance imaging; (2) Infrared thermal imaging helps with the evaluation of tissue blood flow, tissue metabolism and temperature changes; (3) Local myofascial elasticity can also be measured by means of some special tools; and (4) There is no accepted and definite laboratory basis that can be referred to.

For the diagnosis of MPS

The above 1 and 2 conditions must be compulsory[22], while conditions 3 and 4 should be auxiliary.

DIFFERENTIAL DIAGNOSIS

MPS is easy to confuse with many diseases with similar clinical symptoms, and it should be distinguished from the following diseases.

Fibromyalgia

Fibromyalgia (FM) is a group of clinical syndromes characterized by general pain and obvious physical discomfort with unknown etiology, often accompanied by fatigue, sleep disorders, morning stiffness, depression, anxiety and other mental symptoms. In 2016, the American College of Radiology updated FM diagnostic standards[27] that the diagnosis of fibromyalgia was independent of other diagnosis. The pain symptom between FM syndrome (FMS) and MPS is similar. The differences between them include the location of pain in MPS is relatively local, and there are obvious MTrPs in MPS, which are quite painful with referred pain on palpation. The differentiating features of MPS from FMS are listed in Table 1.

Polymyalgia rheumatica

Polymyalgia rheumatica (PMR), a group of clinical syndromes, is characterized by symmetrical myalgia and stiffness in the neck, scapula and pelvis. The patients always show signs of mild tenderness. Most people who develop PMR are older than 50. The increase of erythrocyte sedimentation rate and C-reactive protein is one of the important diagnostic indexes of PMR in the acute phase[28]. Patients with PMR usually respond well to low dose glucocorticoid treatment, which can be used as a diagnostic treatment.

Chronic fatigue syndrome

The diagnostic criteria for chronic fatigue syndrome (CFS) proposed by the Centers for Disease Control and Prevention in the United States include: (1) Main symptoms: An unexplained feeling of fatigue, which is severe enough to decrease a person's activity level by 50% or more; (2) Secondary symptoms: Low fever, pharyngeal pain, lymphadenopathy, myasthenia, myalgia, arthralgia, sleep disorders, neuropsychic symptoms and post exertional malaise lasting more than 24 h; and (3) Signs: Low fever, pharyngitis and palpable lymph nodes. CFS can be diagnosed by the main symptom, at least six of the secondary symptoms and two of the positive signs. The main symptom with at least eight of the secondary symptoms can also be the diagnostic criteria for CFS. At present, the diagnosis of CFS is based on the Centers for Disease Control and Prevention 1994 criteria[29].

Polymyositis

Polymyositis (PM) is one of the idiopathic inflammatory myopathies. If patients are accompanied with skin lesions, then it can be called as dermatomyositis. The clinical symptoms manifest as symmetrical muscle weakness and pain, especially in the shoulder girdle, pelvic girdle and cervical muscles. Slow progressive atrophy can also be seen in the affected muscles. The diagnostic criteria proposed by the Chinese Medical Association Rheumatology Branch[30] are as follows: (1) Symmetric proximal muscle weakness; (2) Elevation of serum levels of skeletal muscle enzymes; (3) Myopathic changes in electromyography; (4) Typical rash of dermatomyositis; and (5) Characteristic muscle biopsy abnormalities. A definite diagnosis of PM requires four criteria. Clinical diagnosis comprises three criteria, and possible diagnosis requires two

Table 1 Differentiating features of myofascial pain syndrome and fibromyalgia syndrome

Features	FMS	MPS
Female:Male	10:1	2:1
Pain range	Generalized	Relatively limited
Pain point distribution	Generalized	Relatively localized
Referred pain	No	Yes
Induration or stripe sensation	No	Yes
Injecting local anesthetics to MTrPs	No relief	Complete relief
Anatomical site of the MTrPs	Tendon attachment	Muscle belly
Myotonic rigidity	Generalized	Local
Fatigue	Yes	No
Sleep disorders	Yes	No
Prognosis	Difficult to cure	Good

FMS: Fibromyalgia syndrome; MPS: Myofascial pain syndrome; MTrPs: Myofascial trigger points.

criteria. PM mainly affects the proximal muscles. It can manifest as limb pain and weakness and trouble lifting the arms, which is similar to PMR. The difference is that perifascicular atrophy can be seen in PM. Moreover, PM always associates with high serum creatinine kinase levels and abnormal waveform in electromyography. Pathological examination of the muscle usually reveals perifascicular atrophy and lymphocyte infiltration in PM.

THERAPEUTIC PRINCIPLES AND METHODS

MPS is a relapsing disease. The foremost thing is that the etiological and inducing factors should be removed as much as possible, otherwise the curative effect may not be realized. Because there are many different treatment options available for MPS, treatment plans should meet the lesion site, course of disease and individual situation. Patients of short disease course and slight symptoms can select rehabilitation training and physical therapy. If a patient has a long course of disease, wide range of symptoms and unsatisfactory curative effects after accepting various therapeutic methods, then silver needle acupuncture therapy and percutaneous radiofrequency (RF) ablation accompanied with psychological therapy can be selected.

Physical rehabilitation therapy

The purpose of physical rehabilitation therapy for MPS is to restore the function of myofascial and to reduce the pain.

Extracorporeal shock wave therapy: Extracorporeal shock wave transmits the mechanical energy to the body through a certain medium and acts on the MTrPs and spasmodic muscle tissue without damaging the surrounding tissues. In the process of treatment, the trigger point of pain is located through the communication between physicians and patients, the so-called "biofeedback method", so that the trigger-point of myofascial pain can be found. Combined with the divergent shock wave, it is used to relax the tense muscles, relieve the smooth muscles, locate and treat the superficial MTrPs and treat the large and/activated area of connective tissue. Focused shock wave is used to eliminate the lesion of tendon attachment point, decompose calcification deposition, locate the trigger-point and pain point, induce the "referred pain" and treat the trigger point in a superficial and deep way.

Hyperthermia, phototherapy and magnetic therapy: (1) Low frequency electrotherapy: Use pulse current with frequency less than 1000 Hz to treat; (2) Medium frequency electrotherapy: Use sinusoidal alternating current with frequency between 1000-100000 Hz to treat; (3) High frequency electrotherapy: The oscillatory current with frequency above 100 kHz and the electromagnetic field are used for treatment,

which has no exciting effect on nerve and muscle; (4) Phototherapy: Use all kinds of light radiation to treat; and (5) Magnetic therapy: It is a kind of physical therapy that uses the magnetic field on the human body to treat diseases with the effect of analgesia, detumescence and pain relief.

Manipulation, stretching and kinesiology tape: Manipulation and stretching refers to the method by which muscles are forced to move. The patient can complete the process in a relaxed state with no force and no muscle contraction. It can dilate vessels, accelerate lymph circulation and promote the absorption and excretion of inflammatory mediators to eliminate inflammation and edema of muscles. Kinesiology tape is an elastic ultrathin permeable tape with varying widths and elasticity. It can be cut into different shapes according to the needs and pasted on the muscles requiring treatment. It has the therapeutic effect of relieving spasms, relaxing muscles, improving incorrect movements, stabilizing joints, improving circulation, alleviating edema and relieving pain.

Drug therapy

In the current situation of limited etiology treatment, symptomatic treatment based on symptom relief is important to improve the quality of life of patients with MPS. We should prescribe oral medication at the lowest dose and the shortest course of treatment as possible, paying attention to factors including the patient's general condition, dosage, course of treatment and drug interaction in order to reduce drug-related adverse reactions and ensure the safety of drug use[31].

Nonsteroidal anti-inflammatory drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs) mainly have antipyretic, analgesic, anti-inflammatory and antirheumatic effects (such as ibuprofen injection, loxoprofen sodium cataplasms, *etc.*), which can effectively relieve pain. It is the most commonly used medicine to cure chronic pain diseases. Nonselective NSAIDs have strong anti-inflammatory and analgesic effects but also have obvious gastrointestinal side effects. The selective COX-2 inhibitors (such as celecoxib, etocoxib, *etc.*) can significantly reduce the occurrence of gastrointestinal adverse reactions. Factors that may increase the risk of NSAID related upper gastrointestinal adverse events (gastrointestinal ulcer, bleeding, perforation) old age, history of severe upper gastrointestinal ulcer or hemorrhagic disease, concurrent use of warfarin or other anticoagulants, use of oral corticosteroids or high dose NSAIDs, *etc*. Therefore, it is recommended to prescribe such drugs at the lowest effective dosage and shortest course of treatment as possible. It is forbidden for patients to take two NSAIDs at the same time[32,33].

Anti-anxiety and depression drugs: In the treatment of chronic pain, 5-hydroxytryptamine and norepinephrine reuptake inhibitors (duloxetine, *etc.*) and tricyclic antidepressants (amitriptyline, *etc.*) are commonly used. Patients with chronic myofascial pain are commonly accompanied by anxiety and depression. Such drugs can relieve pain by alleviating the patients' psychological problems. The side effects of such drugs include dry mouth, constipation, blurred vision, *etc*[34]. It is generally recommended to start taking such drugs from a low dose and gradually increase to an effective dose.

Ion channel regulators: Sodium channel blockers (such as bulleyaconitine) and calcium channel blockers (such as gabapentin and pregabalin) are commonly used ion channel regulators and are used as the first-line drugs for neuropathic pain and for the treatment of MPS. The common side effects include drowsiness, dizziness and edema. Such drugs should be given at lower doses and increased slowly[35].

Central muscle relaxant: Such drugs are mainly used to cure spasm or musculoskeletal related diseases by blocking the vicious cycle of skeletal muscle tension, *i.e.* hyperactivity of muscle tension, circulatory disorder, muscle pain and hyperactivity of muscle. Such drugs include tizanidine, chlorzoxazone, eperisone, baclofen, *etc*. It is recommended to treat patients with myofascial pain when NSAIDs are not effective alone or with muscle spasm[36].

Opioids: Opioids including codeine, tramadol, morphine and oxycodone are mainly applicable for patients with moderate and severe pain on the condition that NSAIDs do not acquire efficacy. Such drugs are not used as the first-line drugs[37].

Needle punching

Acupuncture and moxibustion: Acupuncture and moxibustion therapy are based on the theory of human meridians. The acupuncture needle is inserted into acupoints by twisting and lifting, and the moxibustion is another kind of therapy, which is burning the wormwood or moxibustion herbs to fumigate the acupoints on the body surface to stimulate specific parts of the human body. Acupuncture and moxibustion therapy have been widely accepted in the treatment of pain[38]. In recent years, the research on acupuncture and moxibustion for MPS focuses on new therapies, new acupuncture instruments and multimode acupuncture. In addition, under the guidance of MTrP theory, dry needle therapy is gradually increasing in China[39]. With respect to these methods, the total effective rate is good. The short-term effect of pain relief is satisfactory. However, the long-term cure rate remains uncertain[40].

Silver needle puncture: The treatment of silver needle combined with heat conduction is an effective method for the treatment of intractable MPS. The diameter of soft silver needle body is 1.1 mm, and the tip is blunt, which increases the difficulty of scratching blood vessels and nerves making the treatment relatively safe. The operator inserts the silver needle into the tenderness point (area), then a small range of thrusting, lysis, separation and heat conduction are performed. The aseptic inflammation at the attachment of soft tissue was eliminated due to the deep heat effect in the myofascial membrane of the diseased tissue and periosteum. The silver needle acupuncture has been widely applied and popularized in the clinic for the high safety, simple operation, wide range of indication and excellent long-term effectiveness. The newly developed thin silver needle (0.6 mm in diameter) in the treatment of the small joints of the limbs and maxillofacial region gains some advantages, but the clinical report of long-term outcomes is lacking.

Acupotomy: Acupotomy is a blade shaped like a silver needle with a thick needle body and a needle tip of 0.8 cm wide, which can incise or peel off adhesion and small nodules of local soft tissues. For MPS, the mechanical stimulation and separation of acupotomy could enhance the activity of local tissues and accelerate the lymphatic circulation. The incision of scar tissue leads to the reduction of local pressure and pain. Because of its accessibility and convenience, it is widely used in China. However, the acupotomy should be utilized with caution or prohibited in some areas containing major nerves, vessels or organs due to the invisible operation with a sharp needle tip.

Internal heated needle: The internal heated needle, which is exerted by operators according to the theory of fasciology, is prodded into the fascia. Thereafter, it can produce accurate temperature from the tip of the needle to the treatment part of the needle body after it is connected to the temperature instrument. The internal heating could activate the body repair mechanism to achieve treatment effectiveness. Due to its short term application, there is no high-quality literature to support its definite long-term effect.

Injection techniques

Injection techniques are currently prescribed as one of the most comprehensive and important treatments in pain medicine. Injections, considered to function effectively for MPS, can be applied individually or combined with drugs and physical rehabilitation[33].

The major complication of MPS injection is infection. Accidental puncture into a blood vessel or spinal canal can cause nerve injury to occur. A transient fever or pain can occur following this injection technique, and the patient should be warned of this possibility prior to the procedure. The process of injection should be entirely aseptic, and the vital signs of the patient should be monitored[41].

Injection of local trigger points: Palpation with finger pressure prior to the procedure may find points inducing cord sensation and radiating pain. Injection would function better at the points where muscle twitching is induced during puncture[42]. Then treating the scheduled area by means of typical MTrPs with careful palpation rather than on the basis of soft-tissue anatomy will result in a positive effect[40].

In recent years, ultrasound-guided therapies for MTrPs have been widely used. Ultrasound guidance can improve the therapeutic success of injections in MPS-related cervical headache, shoulder pain, chest wall pain, back pain, *etc*[43]. Ultrasound assists to identify deep MTrPs that cannot be observed by the naked eye. Observing local convulsive responses under the help of ultrasound supports positioning accuracy and improving efficiency[44]. Puncture in this area with an in-plane or out-of-plane approach under ultrasound guidance to elicit a local convulsive response can locate

the trigger point to perform precise ultrasound-guided injection. Furthermore, injury to normal tissues can be avoided by the visibly real-time punctures, which eventually reduces incidents of complications[45].

Neural blockade: Neural blockade is aimed at the myofascial areas of important nerve distribution. By inhibiting aseptic inflammation of peripheral nerves and separating and loosening local soft tissues, a therapeutic effect is produced. The procedure must be performed under ultrasound or X-ray guidance[46].

Conventional medications: The medications for MPS injections include local anesthetic, corticosteroids and botulinum toxin[47].

In combination with acupuncture and stretch therapy, a total of 0.1 mL to 0.5 mL of local anesthetic is drawn up as long as the puncture induces intolerable soreness or twitching in the patient. The stretch therapy should also be followed gradually and slowly as the puncture is completed. The most common dose of local anesthetics is 0.5% to 1% of lidocaine or 0.1% to 0.5% of ropivacaine. An additional small dose of corticosteroid may be needed in severe cases[48].

The most common formulation of botulinum toxin applied for MPS is type A and B. Type A is conventionally prescribed, while type B is only prescribed for cases with type A failure[49,50]. The suggested dose for a single trigger point or an individual "tight bandage" in muscles is 5 U, with a total dose of 15 U to 35 U in a 2-wk interval[51]. The stretching exercise is also comprehensively required during injection therapies to consolidate the effects of the botulinum toxin with affected muscles.

Oxygen-ozone injection: Oxygen-ozone injection induces muscle twitching in the same way as stimulating MTrPs by a tiny needle producing a therapeutic effect similar to dry-needle treatment. Compared to corticosteroid injection, ozone can be metabolized and transformed into oxygen with the final absorption into the tissue, avoiding the side effect of local adhesion and the systematic response of a corticosteroid[52]. The concentration of ozone injected should be no more than 30 μg/mL, with the dose of 1 mL to 5 mL for a single trigger point and a maximum of 30 mL at a time. Furthermore, the injection of ozone is recommended to be prescribed for one to three times in a week, with a course of treatment of 2 wk to 4 wk[53].

RF treatment

RF technology has developed rapidly in recent years. It is one of the main treatment methods in pain medicine and an effective treatment method for MPS[54]. The RF treatment for MPS can be divided into thermal coagulation RF and pulsed RF according to different RF energy output modes.

RF thermal coagulation treatment: RF thermal coagulation of myofascial pain is applied to the muscle fascia without important nerves around, such as the trapezius, supraspinatus, gastrocnemius, *etc*. The main targets of treatment are the MTrP and the fascia. The MTrP is determined physically upon palpitation. After that, the skin over the MTrP is marked and sterilized, a sterile surgical towel is placed, and a local anesthetic is administered with 0.5% lidocaine. Then, the RF cannula is inserted into the fascia under the guidance of ultrasound. The output temperature is set to be 75 °C and duration of 15-30 s. Thermal coagulation RF therapy can be performed at the same time for different MTrPs, while the same point can only be treated once a week.

Pulsed RF treatment: The energy output mode of pulsed RF is intermittent and of high intensity, which produces high voltage with low temperature. Therefore, it can avoid the damage of nerves around the needle tip. Pulsed RF of myofascial pain is applied to the muscle fascia with important nerves around, such as the scalenus, piriformis, gluteus medius, *etc*. During the procedure of local anesthesia, we should avoid injecting local anesthetics into the muscle layer near the treatment points. When the needle reaches the target fascia under the guidance of ultrasound, the parameters should be set to 42 °C for 120 s. Similarly, pulsed RF therapy can be performed at the same time for different points of myofascial.

The mechanism of RF therapy is to produce a therapeutic effect by damaging the abnormal peripheral nerve of local hyperplasia, separating and releasing the contracture of soft tissue and improving microcirculation[55]. Several studies have shown that RF treatment of trapezius pain, psoas pain, heel pain and other MPS has a significant effect[56-58]. The complications of RF treatment of MPS include the injury caused by puncture operation. Therefore, it is necessary to be familiar with the anatomical structure of the puncture site, pay attention to the direction and depth of puncture and carry out the procedure under the guidance of ultrasound or X-ray. In

addition, thermal coagulation RF may cause heat damage to local nerves, resulting in local skin numbness and other abnormal feelings. Therefore, before RF thermal coagulation, a stimulation test should be done to avoid damaging important nerves.

Psychotherapy and pain medicine health education

In chronic cases, patients are prone to anxiety, depression or somatization due to the recurrence of the disease and long-term torture of pain as well as economic, social and personal problems. For such patients, in addition to conventional treatment, health education and psychological treatment, such as the biofeedback, hypnotic analgesia and cognitive-behavioral therapy, should also be performed.

Existing studies and meta-analysis suggest that cognitive behavioral therapy can enhance the efficacy of MPS[59,60]. Secondly, through exercise, stretching the muscles where the trigger points are located can help eliminate the trigger points and the pain they cause[2,61]. Pain medicine education is conducive to the recovery of patients with MPS[62].

CONCLUSION

Patients should be educated about the causes, treatment and prognosis of this type of pain. Patients should be encouraged to actively treat MPD, eliminate the fear of the disease, actively cooperate with medical care and eliminate the trigger points of pain through the above comprehensive treatment as soon as possible. In short, early treatment, good living habits and scientific and standardized exercise are the keys to early recovery of MPS.

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EXPERT CONSENSUS

Chinese Association for the Study of Pain: Expert consensus on chronic postsurgical pain

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Abstract

Chronic postsurgical pain is a common surgical complication that severely reduces a patient's quality of life. Many perioperative interventions and management strategies have been developed for reducing and managing chronic postsurgical pain. Under the leadership of the Chinese Association for the Study of Pain, an editorial committee was formed for chronic postsurgical pain diagnosis and treatment by experts in relevant fields. The editorial committee composed the main content and framework of this consensus and established a working group. The working group conducted literature review (1989-2020) using key words such as "surgery", "post-surgical", "post-operative", "pain", "chronic", and "persistent" in different databases including MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews. Only publications in the English language were included. The types of literature included systematic reviews, randomized controlled studies, cohort studies and case reports. This consensus was written based on clinical practice combined with literature evidence. The first draft of the consensus was rigorously reviewed and edited by all the editorial committee experts before being finalized. The level of evidence was assessed by methodological experts based on the Oxford Centre for Evidence-Based Medicine Levels of Evidence. The strength of recommendation was evaluated by all editorial committee experts, and the opinions of most experts were adopted as the final decision. The recommendation level "strong" generally refers to recommendations based on high-level evidence and consistency between clinical behavior and expected results. The recommendation level "weak" generally refers to the uncertainty between clinical behavior and expected results based on low-level evidence.

Key Words: Chronic postsurgical pain; Treatment; Interventional; Prevention

Core Tip: Chronic post-surgical pain (CPSP) is a common surgical complication. An editorial committee of experts in relevant fields was organized by the Chinese Association for the Study of Pain to draft this expert consensus. This expert consensus includes the definition, risk factors, pathogenesis, clinical manifestations, treatment and prevention of CPSP. It describes various treatments of CPSP with their associated recommendation levels, based on the clinical practice and literature references. This consensus also proposes the responsibilities and collaboration for surgeons, anesthesiologists and pain physicians in the management of CPSP, which will have significance in guiding the clinical practice.

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INTRODUCTION

Chronic post-surgical pain (CPSP) is one of the most common surgical-related complications despite continuous improvements in surgical procedures, more aggressive acute pain interventions and the use of multiple preventive measures. CPSP is defined as the presence of surgical-related pain for more than 3 mo post-surgery, not including pain caused by explicit reasons (such as chronic infection, recurrence of malignant tumor, *etc.*)[1]. Some propose that pain lasting more than 2 mo after surgery be called persistent post-surgical pain. The incidence of CPSP varies with the type of operation: Thoracotomy (approximately 50%)[2], mastectomy (20%-50%)[3] and amputation (30%-80%)[4]. Investigations have found that CPSP is common in major

surgeries as well as certain minor surgeries such as herniorrhaphy and cesarean section[5,6]. Due to the lack of comprehensive understanding of its mechanisms and treatments, the negative effects of CPSP on a patient's postoperative quality of life are increasingly prominent. Surgical trauma like CPSP is a planned injury that should be minimized as much as possible, which requires more research in this area.

RISK FACTORS

The risk factors of CPSP include three broad aspects: preoperative factors, surgical factors and postoperative factors (Table 1)[7-14]. Understanding and identifying these risk factors can help in the screening of high-risk patients, which would enable physicians to formulate a more specific perioperative pain management program. This, in turn, can help improve the postoperative analgesia and reduce the occurrence of CPSP.

PATHOGENESIS

The occurrence of CPSP is a complex process, including physiological, psychological, social and environmental factors. However, the pathogenesis of CPSP has not been fully understood. The general view is that surgically related tissue damage and its persistent inflammatory response eventually lead to sensitization of the peripheral and central nervous system, which facilitates the development of CPSP.

Peripheral sensitization

After tissue damage, sustained local stimulation causes a decrease in peripheral nociceptor threshold. Inflammatory factors, such as bradykinin, prostaglandin and substance P, are produced at the injury site. These inflammatory factors cause upregulation of the transient receptor potential vanillin subtype 1 receptor[15], voltage-dependent sodium channels[16] and voltage-dependent calcium channels[17].

Central sensitization

Persistent signals from the peripheral nervous system cause central nervous system sensitization. Excitatory neurotransmitters (*e.g.*, substance P, glutamate) cause increased excitability in secondary neurons of the spinal dorsal horn. GABAergic interneurons reduce their inhibition of the endogenous analgesic descending inhibitory system[18]. The inhibitory effect of the descending 5-hydroxytryptamine pathway on nociceptive signals in spinal cord processing becomes significantly reduced[19]. Increased excitability of the gray matter region-medullary medulla ventral medial nucleus axis also takes place[20].

MANIFESTATIONS AND DIAGNOSIS

CPSP is manifested as neuropathic pain, such as spontaneous pain, hyperalgesia and allodynia. However, its specific characteristics vary by surgery. CPSP after thoracotomy is manifested as pins and needles, burning or electric-like sensation in the surgical wound and corresponding area innervated by the intercostal nerve. It is also frequently accompanied by numbness, formication, feeling cold or hot and foreign body sensation. CPSP after mastectomy is characterized by persistent burning, pins and needles and electric-like sensation or bursting pain in the surgical area, lateral chest, armpit and anterior medial upper arm. It may be accompanied by numbness and hypoesthesia. After joint replacement, CPSP is typically characterized by joint soreness and faint pain. However, some patients may have dragging pain and joint stiffness, while a few patients may have the characteristics of neuropathic pain and sensory disturbances. Chronic pain after amputation can be categorized as stump pain and phantom limb pain. Stump pain usually occurs at the amputation site after the wound has been healed for a period time, and it has a major neuropathic component. Phantom limb pain is ongoing pain felt in parts of the body that have been amputated. It mostly occurs at the distal end of the limb. Sensations caused by phantom limb pain include electrical shock, cutting, bursting or burning.

CPSP can cause psychiatric dysfunctions, such as anxiety, depression and pain, catastrophizing in some patients. The existence of sleep disorders is also very

Table 1 Risk factors for chronic postsurgical pain[7-14]

Risk factors for CPSP[7-14]	
Preoperative factors	Preoperative chronic pain; psychological factors (depression, anxiety, pain catastrophizing and fear of surgery); smoking; younger age; female gender; genetic susceptibility
Surgical factors	Type and site of surgery (amputation, breast cancer, thoracotomy, hysterectomy, inguinal hernia repair, cesarean section); surgical technique (open surgery > laparoscopy and thoracoscopy, traditional hernia repair > tension-free hernia repair); extensive use of electric knife; long operation time; infection on incision site; nerve damage or compression
Postoperative factors	Severe acute postoperative pain; opioid use (high doses of opioids can cause hyperalgesia and may be related to NMDA receptor activation); neuropathic pain (early postoperative neuropathic pain is prone to chronic); complication (cardiovascular, respiratory, renal/gastrointestinal, wound, thrombotic or neural)

CPSP: Chronic post-surgical pain; NMDA: N methyl D aspartate.

common, including difficulty falling asleep, waking up early, poor sleep quality and nightmares. Patients with severe symptoms also experience reduced work and social capacity.

The diagnosis of CPSP requires the following five criteria: (1) Appearance after surgical trauma; (2) Lasting for at least 3 mo; (3) Continuation of immediate or delayed acute pain after surgery; (4) Located on, but not limited to, the surgical area and/or the innervated area of the affected nerve; and (5) Exclusion of other causes, such as chronic infection, malignant tumor recurrence, *etc*. Neuroelectrophysiological examination can determine the location and extent of nerve injury and predict the prognosis early and accurately. Infrared thermography helps to evaluate pain severity and treatment outcomes.

TREATMENT

Medication

Most CPSP symptoms have neuropathic pain properties; therefore, pharmacotherapy for neuropathic pain is currently recommended. Common drugs included in its management are anticonvulsants, antidepressants and analgesics (Table 2)[21].

Interventional therapy

Nerve block: Depending on the location of the pain, a nerve block in the corresponding innervation area may be possible. A mixture of local anesthetics and glucocorticoids is commonly used. Nerve block can stop the transmission of pain signals, inhibit neuroinflammation and promote neural function recovery.

Thoracic epidural block, thoracic paravertebral nerve block, erector spinae plane block, anterior serratus plane block, intercostal nerve block and local infiltration can relieve chronic pain after thoracotomy and breast surgery [Level (LE): 5; strength of recommendation (SR): Strong] (Table 3). Lumbar epidural block, lumbar paravertebral nerve block and posterior medial branch of spinal nerve block can relieve chronic pain after spinal surgery (LE: 5; SR: Strong). Transversus abdominis plane block can relieve chronic abdominal pain after open abdominal surgery and laparoscopic surgery[22] (LE: 4; SR: Strong). Ilioinguinal/iliohypogastric nerve block can relieve chronic post-herniorrhaphy groin pain[23] (LE: 3b; SR: Strong).

Nerve modulation: Nerve modulation promotes neural function recovery by regulating the central, peripheral or autonomic nervous system.

(1) Pulsed radiofrequency (PRF): PRF is one of the most commonly used neuromodulation methods. A pulse current is transmitted to the peripheral nerve, which regulates the excitability of the affected neuron by changing the electromagnetic field. Parameters such as pulse frequency, pulse duration, voltage, tissue temperature and duration should be adjusted in the operation to achieve the best therapeutic effect.

PRF of stellate ganglion can alleviate chronic pain after breast surgery[24] (LE: 1b; SR: Strong). PRF of the dorsal root ganglion of T2 and T3 can alleviate chronic pain after breast surgery[25] (LE: 4; SR: Strong). PRF of thoracic dorsal root ganglion can alleviate chronic pain after thoracotomy[26] (LE: 3b; SR: Strong). PRF of lumbar dorsal root ganglion can alleviate chronic post-amputation phantom pain and stump pain[27,28] (LE: 4; SR: Strong). PRF of the ilioinguinal nerve and genital branch of the genitofemoral nerve can alleviate chronic post-surgical orchialgia caused by groin surgery[29] (LE: 1b;

Table 2 Algorithm for pharmacotherapy of chronic post-surgical pain

Algorithm for pharmacotherapy of CPSP	
First-line therapy	Gabapentin; pregabalin; duloxetine; venlafaxine; tricyclic antidepressants
Second-line therapy	Capsaicin cream/patch; lidocaine cream/patch; tramadol; paracetamol dihydrocodeine
Third-line therapy	Strong opioids; botulinum toxin type A

CPSP: Chronic post-surgical pain.

Table 3 Oxford Centre for Evidence-Based Medicine levels of evidence

Level	Therapy/prevention, etiology/harm
1a	Systematic review of RCTs
1b	RCT
1c	"All-or-none"
2a	Systematic review of cohort studies
2b	Cohort study or poor RCT
2c	"Outcomes" research; ecological studies
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion without critical appraisal, or based on physiology, bench research or "first principles"

RCT: Randomized controlled trial.

SR: Strong).

(2) Spinal cord stimulation (SCS): SCS can regulate pain-related signaling pathways and neurotransmitter balance and inflammation and pain-related neuropeptide levels. It can be considered for patients who have failed to respond to conventional drugs and physical, psychological and nerve block therapies.

SCS can be used to treat intractable chronic pain after lumbar surgery. High-frequency spinal cord stimulation is superior to traditional low-frequency stimulation. However, it is necessary to fully understand the indications and contraindications[30] (LE: 1a; SR: Strong). For intractable chronic post-surgical abdominal wall pain, chronic post-amputation phantom pain or stump pain and chronic pain after limb fracture surgery, *etc.*, SCS can be considered if a temporary stimulation test is effective (LE: 5; SR: Weak).

(3) Intrathecal drug delivery systems: Continuous subarachnoid infusion of opioids, local anesthetics or clonidine has a definitive therapeutic effect on nociceptive pain as well as a good analgesic effect on intractable neuropathic pain. After full evaluation and comprehensive consideration, it can be used to treat intractable chronic pain after abdominal and limb surgery (LE: 5; SR: Weak).

(4) Others: Transcutaneous electrical nerve stimulation, repeated transcranial magnetic stimulation and transcranial direct current stimulation can improve pain to some extent. They can be used as adjuvant therapy for chronic pain after thoracotomy, breast surgery, joint replacement and limb surgery. For example, transcutaneous electrical nerve stimulation can relieve phantom limb pain for a short time[31] (LE: 2b; SR: Weak).

Neurolysis: Neurolysis can be considered for intractable CPSP with clear nerve location and no pain relief after routine treatment. Common techniques include physical methods (radiofrequency thermocoagulation), chemical methods (alcohol, phenol) and surgical resection. However, nerve damage from neurolysis can lead to paresthesia or loss of the corresponding innervation area. At the same time, there is a risk of recurrence of CPSP and appearance of new pain after the procedure. Therefore, a cautious decision must be made after carefully weighing the advantages and

disadvantages.

Radiofrequency thermocoagulation of stellate ganglia can relieve chronic pain after breast surgery[24] (LE: 1b; SR: Weak). Surgical intercostal neurolysis can relieve chronic pain after thoracotomy[32] (LE: 4; SR: Weak).

Physical therapy/cognitive behavioral therapy

Physical therapy (manual therapy, rehabilitation exercise, myofascial trigger point therapy, extracorporeal shock wave therapy, ultrasound therapy, laser therapy, *etc.*) can reduce muscle spasms, improve blood circulation, regulate peripheral nerve activity and promote the restoration of mechanical balance. Cognitive behavioral therapy is the use of cognitive and behavioral techniques to change the patient's poor cognition and break the vicious cycle of psychological factors in order to significantly reduce pain and improve pain-related physical and emotional disorders[33].

Cognitive behavioral-based physical therapy can promote the recovery of chronic pain after lumbar spine surgery[34] (LE: 1b; SR: Strong). Myofascial trigger point therapy combined with rehabilitation exercise can relieve chronic pain after total knee arthroplasty[35] (LE: 4; SR: Strong). Considering the universality of physical therapy and cognitive behavioral therapy, they can be used for the treatment of chronic pain after various surgeries when necessary (LE: 5; SR: Strong).

Traditional Chinese medicine

Acupuncture is a treasure in traditional Chinese medicine. It acts on the corresponding acupoints of the human body to regulate Yin and Yang, dredge the meridians and collaterals, promote blood circulation and remove blood stasis. Acupuncture can alleviate postoperative pain, reduce the use of opioids and promote a patient's functional recovery[36]. Acupuncture can be used to treat chronic pain after thoracotomy, breast surgery, abdominal surgery, spinal surgery, arthroplasty and limb surgery (LE: 1a; SR: Strong).

PREVENTION

The high prevalence and long course of CPSP severely affect the postoperative quality of life for patients with this condition. Identifying high-risk patients for CPSP, conducting relevant psychological interventions and instituting effective preventative measures can lead to significant social and economic benefits. First, a comprehensive analysis of the patient's condition must be made to develop the optimum surgical plan and minimize neural tissue damage. Next, an individualized multimodal analgesic program, given the complexity of the pathogenesis of chronic pain, can be provided. If CPSP does occur, treatment from pain specialists should be performed as soon as possible.

Optimized surgical procedure

The surgeon should evaluate for an optimized surgical plan based on the benefits and risks for the patients and minimize intraoperative tissue and nerve damage. Compared with open surgery, laparoscopic surgery can reduce the occurrence of CPSP in inguinal hernia repair, and patients recover more quickly after surgery[37] (LE: 1a; SR: Strong). Compared with open lobectomy, thoracoscopic lobectomy can significantly reduce the incidence of CPSP[38] (LE: 4; SR: Strong).

Multimodal analgesia

Multimodal analgesia refers to the use of pharmacology and other forms of intervention that target the peripheral and central nervous systems to alleviate acute postoperative pain and reduce the use of opioids and related side effects. The concept of multimodal analgesia has been widely accepted, and most medical centers have developed their own plans for different surgeries.

Regional anesthesia can significantly reduce the incidence of CPSP: Thoracic epidural block can be used to prevent chronic pain after thoracotomy[39] (LE: 1a; SR: Strong). Thoracic paravertebral nerve block does little to prevent chronic pain after breast surgery[40]. It can be used as an effective analgesic measure during and after surgery, but it is inadequate as a preventive measure to reduce CPSP (LE: 1b; SR: Strong). Transversus abdominis plane block or quadratus lumborum block does little to prevent chronic pain after caesarean section[41]. It can be used as an effective

analgesic measure during and after surgery, but it is inadequate as a preventive measure to reduce CPSP (LE: 3b; SR: Strong).

Preventive analgesia: The main drugs used are lidocaine, antidepressants and anticonvulsants, but conclusions appear heterogeneous. Intravenous infusion of lidocaine can be used to prevent chronic pain after breast surgery to some extent[42]. Recommended dosage is 1.5 mg/kg bolus followed by 2 mg/kg/h (LE: 1a; SR: Strong). Venlafaxine (antidepressant) can be used to prevent chronic pain after breast surgery[43]. Recommended dosage is 37.5 mg/d for 10 d starting the night before surgery (LE: 1b; SR: Weak). Increasing evidence suggests that prophylactic gabapentin and pregabalin (anticonvulsants) have little effect on CPSP prevention[44,45]. Routine preventive use is not recommended, except in high-risk patients (LE: 1a; SR: Strong).

Psychological intervention

It is important to fully communicate with the patient about the surgical plan and expected results before surgery. For major operations, such as orthopedic surgery, thoracotomy and abdominal surgery, patients with psychological difficulties should be identified in time and provided with perioperative cognitive behavioral therapy and relaxation therapy to reduce the incidence of CPSP[46] (LE: 1a; SR: Strong).

Rehabilitation

It is recommended to develop a customized postoperative rehabilitation training plan based on different surgical procedures. Active rehabilitation training after surgery can reduce swelling in the surgical area and surrounding tissues, reduce tissue adhesion, accelerate organ function recovery, improve joint mobility and thereby reduce the incidence of CPSP (LE: 5; SR: Strong).

DIVISION AND COOPERATION

The specialists who are closely involved in CPSP include surgeons, anesthesiologists and pain physicians. Cooperation between them can maximize the benefit to the patient. Because CPSP is a common complication associated with surgery, the surgeon is obliged to try to reduce its incidence by screening patients, optimizing the surgical plan and completing the operation carefully. However, most surgeons focus their clinical work on the management of the primary disease. Anesthesiologists and pain physicians are primarily responsible for managing pain, with the former providing perioperative analgesia and the latter providing postoperative chronic pain management. Postoperative acute pain chronicization is a continuous patho-physiological process, which requires continuous clinical attention and management. In practice, anesthesiologists and pain physicians perform their respective responsibilities, leaving a middle period unattended, which makes it impossible to effectively control CPSP in time. In order to seamlessly connect the work of surgeons, anesthesiologists and pain physicians to ensure the continuity of postoperative pain management, the division of labor and cooperation between these specialties needs to be clarified (Table 4).

CONCLUSION

Due to the complex nature of CPSP, preventive measures are not well established, though it is now known that CPSP cannot be prevented by a singular measure. The occurrence of CPSP can be reduced by actively managing postoperative acute pain through multimodal analgesia, targeted at peripheral and central mechanism accompanied by psychological intervention. When CPSP occurs, pain management should be performed at the earliest possible time. The close cooperation of anesthesiologists and pain physicians will likewise help reduce the incidence of CPSP. The key to effective management of CPSP is early detection coupled by early diagnosis and early treatment.

Table 4 Division and cooperation between surgeons, anesthesiologists and pain physicians

Division and cooperation between surgeons, anesthesiologists and pain physicians	
Surgeon	(1) Optimize surgical methods based on the principle of minimizing tissue trauma; (2) Communicate with the anesthesiologist before surgery to negotiate the best anesthesia plan; and (3) Provide preventive medication and necessary psychological intervention for patients at high risk of CPSP
Anesthesiologist	(1) Carefully evaluate the patient's medical history, including chronic pain, opioid use, drug abuse and mental illness. Screen for patients at high risk of CPSP; (2) Educate patients and their families. Inform them about the possible challenges of perioperative analgesia and the risks of CPSP; (3) Communicate with the surgeon before the operation to understand the surgical method and discuss the best anesthesia plan; (4) Establish perioperative pain management files; (5) Based on a comprehensive assessment of the patient's condition, an individualized multimodal analgesic plan is formulated; (6) Carefully evaluate and record the analgesic effect on the patient; (7) If the patient does not have good postoperative analgesia and uses high-dose opioids, the pain management file should be transferred to the pain physician 1 wk after the operation; and (8) Based on the follow-up results and the latest progress on research, continue to summarize and optimize the analgesia schemes for different surgical operations
Pain physician	(1) Review the perioperative pain management files after taking over the patient; (2) Carefully analyze the nature and source of pain and develop a corresponding treatment plan; (3) Establish a follow-up mechanism; (4) If CPSP occurs, provide pain management in time; and (5) Regularly discuss difficult cases of CPSP with surgeons and anesthesiologists. Summarize risk factors and feedback treatment effect. Discuss further optimization of perioperative analgesia plan and preventive measures

CPSP: Chronic post-surgical pain.

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EXPERT CONSENSUS

Expert consensus of the Chinese Association for the Study of Pain on ion channel drugs for neuropathic pain

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Abstract

Neuropathic pain (NPP) is a kind of pain caused by disease or damage impacting the somatosensory system. Ion channel drugs are the main treatment for NPP; however, their irregular usage leads to unsatisfactory pain relief. To regulate the treatment of NPP with ion channel drugs in clinical practice, the Chinese Association for the Study of Pain organized first-line pain management experts from China to write an expert consensus as the reference for the use of ion channels drugs . Here, we reviewed the mechanism and characteristics of sodium and calcium channel drugs, and developed recommendations for the therapeutic principles and clinical practice for carbamazepine, oxcarbazepine, lidocaine, bulleyaconitine A, pregabalin, and gabapentin. We hope this guideline provides guidance to clinicians and patients on the use of ion channel drugs for the management of NPP.

Key Words: Ion channel drug; Neuropathic pain; Expert consensus; Guideline; Gabapentin; Carbamazepine; Oxcarbazepine; Lidocaine; Bulleyaconitine A; Pregabalin

Core Tip: Ion channel drugs are the treatment of choice for neuropathic pain; however, non-adherence to these drugs makes pain relief unsatisfactory. The Chinese Association for the Study of Pain organized first-line pain management experts from across China to write an expert consensus on the guidelines for usage of ion channel drugs. Here, we reviewed the mechanism and characteristics of sodium and calcium channel drugs, and developed recommendations for the therapeutic principles and clinical practice for carbamazepine, oxcarbazepine, lidocaine, bulleyaconitine A (BLA), pregabalin, and gabapentin.

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INTRODUCTION

Objective and significance

Neuropathic pain (NPP) is a kind of pain caused by disease or damage impacting the somatosensory system[1]; it has a complex pathogenesis. The prevalence of NPP in the general population is as high as 8.0%[2]. Based on these data, there are about 90 million NPP patients in China, and the incidence of NPP is increasing gradually.

Currently, the main treatment for NPP is clinical drug therapy, of which the most common drugs include anticonvulsants, antidepressants, opioid analgesics, and N-methyl-D-aspartate (NMDA) antagonists. Most are ion channel drugs, but the response rate is only about 46.3%[3]. Due to the complexity of NPP etiology/pathogenesis, diverse nature of pain, duration of disease and pain ranging, a reasonable combination therapy of different ion channel drugs is an effective way to improve the clinical efficacy currently. To regulate treatment of NPP with ion channel drugs in clinical practice, the Chinese Association for the Study of Pain (CASP) organized first-line pain management experts from China to write an expert consensus as a reference for the use of ion channel drugs.

Abnormal expression of ion channels and NPP

The clinical manifestation of NPP includes decreased pain threshold, increased pain response and spontaneous pain, which are mainly related to peripheral and central sensitization. Peripheral sensitization refers to the abnormal expression of voltage-dependent ion channels in primary afferent neurons, leading to increased excitability and increased pain signals. The central one refers to the continuous enhancement of synaptic transmission efficiency on the pain pathway, then amplify the pain signals. The abnormal expression of ion channels induces NPP. There are currently two types of ion channel drugs in clinical use: sodium channel blockers and calcium channel modulators. Sodium channel blockers are represented by carbamazepine, lidocaine, and BLA. They block different types of voltage-dependent sodium channels and inhibit overexcited sensory neurons. Calcium channel adjusting section comprises gabapentin and pregabalin, which selectively inhibit synaptic transmission of pain, to alleviate NPP without directly blocking effects on the calcium channel. The $\alpha_2\delta1$ subunit located in the presynaptic calcium channel of the spinal dorsal horn is upregulated during NPP, resulting in increased release of neurotransmitters and enhanced synaptic transmission of pain. Gabapentin and pregabalin bind to this subunit, downregulating it and exerting analgesic effects. In short, by inhibiting the peripheral sensitization and central sensitization, ion channel drugs affect NPP. Sodium channel blockers and calcium channel modulators have anticonvulsant effects as well.

Treatment principle of ion channel drugs

(1) Individualized therapy: It is necessary to pay attention to the wide dose difference to achieve the effective analgesia of the patient. When a drug is not effective, the resistance occurs or effective duration shortened after long-term treatment, it is not advisable to change the drug easily. It is advised to increase the dose to obtain satisfactory results without serious side effects, but care should be taken to avoid exceeding the toxic threshold; (2) Timely administration: Take drugs with proper interval based on their onset time, to maximize analgesia effect; (3) Oral administration: Choose oral, non-invasive approach medicine as possible; (4) Closely observe the medication's onset time, effective duration, degree of analgesic effect, and side effects to ensure an adequate course of treatment; and (5) Adjust the dosage of drugs according to the state of illness: Combination therapy should be considered when the effect of the single drug is not effective.

CLASSIFICATION AND INTRODUCTION OF ION CHANNEL DRUGS

Sodium channel antagonist agent

Mechanism and characteristics of sodium channel drugs: The sodium ion channel is a transmembrane glycoprotein on the cell membrane, which selectively allows sodium to pass through the membrane. Sodium channel antagonist agents can eliminate or alleviate acute pain, inflammatory pain, and NPP and effectively improve the symptoms of hyperalgesia of NPP[4].

Typical drugs of sodium channel antagonists: Representative drugs for sodium ion channel antagonists include carbamazepine, oxcarbazepine, lidocaine, and BLA. Carbamazepine works by inhibiting cell membrane sodium ion channels, reducing neurotransmitter release, and reducing nerve cell excitability. In addition, it also acts on gamma-aminobutyric acid (GABA) receptors, interferes with glutamate functions through NMDA receptors, and regulates central sensitization. The mechanism of oxcarbazepine is by blocking voltage-dependent sodium channels in the brain, stabilizing the neuronal cell membrane, inhibiting repetitive firing of neurons, reducing the release of synaptic impulses, and reducing high voltage-activated calcium currents in the striatum and cortical neurons, thereby reducing the glutamate-induced transmission of cortical striatum synapses[5]. Both mechanisms may be involved in the treatment of neuralgia by oxcarbazepine. Some studies have also suggested that oxcarbazepine may play a role by inhibiting substance-P mediated pain transmission[6].

Lidocaine is a typical sodium channel antagonist; it inhibits sodium ion channels and blocks the action of increased excitability of central neuron, thereby impacting peripheral and central endings and having analgesic effects[7].

BLA can state dependently inhibit voltage-gated sodium channels. Second, BLA may have anti-inflammatory and analgesic effects through many methods including

lowering serum prostaglandin E2 levels, regulating serotonin (5-hydroxytryptamine) levels in the brain and stimulating the expression of dynorphin A in spinal microglia, relieving beta- endorphin inhibition which raises pain thresholds.

Pharmacokinetics, pharmacodynamics, and physicochemical properties of sodium ion channel antagonists: Carbamazepine is commonly used as anticonvulsant drugs. Its gastrointestinal absorption is slow and irregular. Due to dose-dependent induction by itself or other enzymes as well as age, comorbidities, combination therapy, *etc.*, it appears to have high variance of individual pharmacokinetics (PKs)[8]. The formulation and food intake do not affect the rate and speed of absorption. After taking a single dose of carbamazepine, peak plasma concentration reached within 12 h, peak concentration reached 4-5 h (0.5-25 μg/mL) after oral administration of 400 mg, and steady-state plasma concentration was reached within 1-2 wk. It has been recommended that the carbamazepine plasma concentration of 4-12 μg/mL is "effective" in adults[9]. Carbamazepine is metabolized by the liver. Epoxidization is its major metabolic pathways, and it is metabolized by cytochrome P450 3A4 to pharmacologically active 10, 11- epoxy carbamazepine. Protein binding rates of these two substances are 76% and 48%-53%. They can pass through the placental barrier and be secreted with lactating. Carbamazepine's $t_{1/2}$ is related to the duration of treatment, 25-65 h for a single administration, and 12-17 h for long-term administration[10]. Its half-life of children is significantly shortened, and there is no change in the PKs in elderly patients. PK data in patients with liver or renal disease are still insufficient (Table 1).

Oxcarbazepine is a new type of anticonvulsant drug. It is a 10-keto derivative of carbamazepine. It mainly works through its active metabolite, 10- hydroxycarbamazepine (MHD). After taking a single dose of oxcarbazepine, the absorption time is 1 to 3 h, the peak serum concentration of its metabolite MHD is 4 h to 12 h, the protein binding rate of oxcarbazepine and MHD is 60% and 40%, and the $t_{1/2}$ respectively is 1 to 5 h and 9 to 11 h[11]. Oxcarbazepine can be directly converted into the active metabolite MHD without P450 enzyme; therefore, the adverse effects of drugs and the drug interactions when combined are less. Oxcarbazepine and carbamazepine have different metabolic pathways in the liver *via* cytochrome P450 oxidase. Oxcarbazepine is reduced to MHD in the cytoplasm by reductase. MHD is not metabolized by the liver but excreted by the kidney. MHD's steady-state levels can be reached within 2-3 d. Without liver drug enzyme induction and self-induction phenomenon and the blood drug concentration is nearly linear, making it easier to control the dose (Table 1).

The PKs of intravenous administration and transdermal lidocaine patch are very similar. About 70% of lidocaine binds to plasma proteins, mainly to α-1-acid glycoprotein. Lidocaine binds to plasma proteins in a concentration-dependent manner. It may pass through the placenta and the blood-brain barrier through passive diffusion. Lidocaine can be rapidly metabolized into a variety of metabolites in the liver with a bioavailability of about 35%. Metabolites include monomethyl glycerol dimethylaniline and glycine dimethylaniline. Their pharmacological effects are similar with lidocaine, but their activity is lower than lidocaine. Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted as its original form. When administered intravenously, lidocaine plasma clearance half-life is 81-149 min. Systemic clearance rate is 0.33-0.90 L/min (Table 1).

BLA classification is a diterpene diester, is a state-dependent sodium channel antagonist, no resistance and addiction, less adverse effects, is a potent analgesic and anti-inflammation agent. There are no studies of human PKs. After intravenous injection in rats and the blood drug-time curve appears to be an open three-compartment model. Its three-phase half-lives are: the fast-distribution phase half-life ($t_{1/2}$ fast-distribution) = 2.87 min, distribution phase half-life ($t_{1/2}$ distribution) = 11.6 min, elimination phase half-life ($t_{1/2}$ elimination) = 5 h. In tissues, the concentrations in the liver and adrenal glands are highest, followed by the kidney, lung, spleen, and heart. The concentration in brain is lower, while in the brainstem is higher than in the cortex. After 4 h later of administration, the concentration in each organ was reduced by 50%. Within 6 d after administration, the amount of urine excretion accounted for 46% of the one intake, most of which is excreted within 21 h which is 82.3% of the total urine excretion. Exclusion from feces within 6 d accounted for 21.9% of one intake, and excretion from feces within 48 h accounted for 86.2% of total excretion from feces (Table 1).

Calcium channel modulators

Mechanisms of calcium channel modulators: Calcium ion channels play an important

Table 1 Pharmacodynamics of ion channel drugs

	Sodium channel blockers				Calcium channel modulators	
	Carbamazepine	Oxcarbazepine	Lidocaine, by iv	BLA	Pregabalin	Gabapentin
T max	Within 12 h	4.5 h	5 min		1 h	3 h
C max	0.5-25 μg/mL	31.5 μmol/L	2-5 mg/lanalgesic use		3.83-9.46 μg/mL	2.7-2.99 mg/L
$t_{1/2}$	25-65 h (single dose); 12-17 h (long-term oral)	2 h; 9 h (MHD)	10 min (single dose); 1.5-2 h (continuous infusion)	4 h	5-6.5 h	6.5 h
Bioavailability	58%-85%	> 95%	100%		90%	47%-60%
Effect-onset time	8-72 h	1-3 h	5 min (onset); 1 h (maintain)		Within 30 min (acute toothache); 5 h (maintain); 1 wk (diabetic neuropathy)	24-28 h (repeated administration); no capping effect
Metabolism	Liver	Liver	Liver (mainly)		Liver (less)	No metabolism in the body
Excretion	Kidney (72%); Feces (28%)	Kidney (> 95%)		Kidney (mainly)	Kidney (92-99%) excreted as drug prototype	Kidney (mainly) excreted as drug prototype

BLA: Bulleyaconitine A; C max: Maximum concentration; iv: Intravenous; MHD: Monohydroxycarbazepine; $t_{1/2}$: Half life time; T max: Peak time.

role in many physiological processes of the nervous system such as the regulation of excitability of neurons, the release of transmitters at synapse, synaptic plasticity, and gene transcription. These processes are achieved by regulating of calcium ion influx. Calcium channel modulators reduce the excitement of pain conduction pathways by inhibiting the influx of calcium ions and reducing the release of neurotransmitters, thereby achieving the purpose of pain relief[12].

Typical calcium channel modulators: Typical drugs of calcium channel modulators include gabapentin and pregabalin. Gabapentin was first used to control seizures and then was also used to treat NPP. Its structure is similar to that of GABA, but it does not work by binding with GABA receptors nor does it affect GABA synthesis and uptake. The voltage-gated calcium channel α2δ-1 subunit is the site of action of gabapentin. Specific binding can block the transport of α1 units of calcium channels from the cytoplasm to the cell membrane in dorsal root ganglia and spinal dorsal horn neurons. At the same time, the axoplasmic transport of the α2δ-1 subunit from the dorsal root ganglia to the spinal dorsal horn can also be blocked by gabapentin. Gabapentin can also inhibit the occurrence of pain through other sites such as transient receptor voltage channels, NMDA receptors, protein kinases, and inflammatory factors[13]. Similar to gabapentin, pregabalin blocks extracellular calcium ion influx in order to reduce the release of excitatory amino acids.

PKs, pharmacodynamic, and physicochemical characteristics of calcium channel antagonists: Gabapentin is mainly absorbed through the active transportation of amino acid transport systems in the intestine, and a ceiling effect occurs when saturated dose is reached. Oral gabapentin has high and dose-dependent bioavailability. Oral administration 300 mg need approximate 3 h to reach peak plasma at 2.7-2.99 mg/L. It can penetrate the blood-brain barrier, and the concentration of the drug in the cerebrospinal fluid can reach 9% to 14%[14] of the dosage after oral administration. Gabapentin has a distribution volume of about 0.6 to 0.8 L/kg and a half-life of about 6.5 h. The drug does not bind to plasma proteins, is not metabolized in the body, and is excreted from the kidneys as a prototype. Its clearance is consistent with creatinine clearance rate (CCR) (Table 1).

Pregabalin is an artificial synthetics compound by amino acid and natural neurotransmitter analogue, is water- and fat-soluble as well, easily cross the blood-brain barrier, and no GABA-like biological activity. Pregabalin is widely absorbed by the intestine after oral administration. It works within 30 min for acute toothache and sustains for 5 h. For diabetic neuropathy, onset time is about 1 wk after administration. The peak time of plasma concentration is about 1 h, and its absorption is fast and its therapeutic dose is non-linearly related to the plasma concentration. The bioavailability of pregabalin is 90%. Pregabalin is less metabolized in the liver; 92% to 99% of pregabalin is excreted by the kidney as a prototype and less than 0.1% of the

oral amount is excreted with feces. The half-life is 5 to 6.5 h (Table 1).

CLINICAL APPLICATION OF ION CHANNEL DRUGS

Sodium channel antagonists

Clinical indication: Carbamazepine and oxcarbazepine are the first choice for the treatment of glossopharyngeal neuralgia and trigeminal neuralgia (TN). The International Association for the Study of Pain, Neuropathic Pain Special Interest Group and other association's guidelines and consensus have recommended carbamazepine and oxcarbazepine as first-line treatments for primary TN. Carbamazepine has also been recommended as the first-line treatment for glossopharyngeal neuralgia[15-19]. In addition to TN, it can also be used as a second-line medication for other NPPs such as diabetic peripheral neuropathy and postherpetic neuralgia (PHN)[20] (Table 2).

Lidocaine is commonly used formulation is 2% injection and 5% cream/patch. Two percent lidocaine injection is mainly used for regional nerve block treatment. It was shown that intravenous infusion of low dose lidocaine has good analgesic effect for PHN, TN, complex regional pain syndrome (CRPS), diabetic peripheral neuropathy, tumor patients with radiotherapy and chemotherapy, peripheral neuralgia, cancer pain, fibromyalgia and other NPP[21,22].

Five percent lidocaine cream or patch is used to treat acute herpes zoster neuralgia and PHN, diabetic peripheral NPP, post-traumatic NPP, sunburn, or hyperalgesia caused by capsaicin. Topical lidocaine can be used as first-line treatment for herpes zoster-related neuralgia, and the commonly used formulation is lidocaine cream and patches. The U.S. Food and Drug Administration authorized 5% lidocaine patches may be used for zoster-related NPP. For persistent pain and allodynia caused by NPP not related to herpes, it is also effective, especially for later ones[23]. It is often recommended for peripheral NPP rather than central NPP. For secondary pain caused by central nervous system damage, intravenous lidocaine (5 mg/kg) is effective for specific pain and hyperalgesia.

BLA has good anti-inflammatory, analgesic and immunomodulatory effects. Currently, tablets and capsules are commonly used. Combined with opioids, it can reduce the dose of opioids and the incidence of adverse effects. It is widely used for the treatment of rheumatic immune disease, osteoarthritis, cancer pain, and other chronic pain diseases[24].

Administration and dosage: The recommended initial dose of carbamazepine for analgesia is 100 mg, twice per day. The maintenance dose is 400-800 mg/d, several times per day. The maximum dose is 1200 mg/d. The recommended initial dose of oxcarbazepine is 150 mg, twice per day, with a maintenance dose of 300-600 mg/d and a maximum dose of 1800 mg/d. Five percent lidocaine patch/cream is used for non-damaged skin, and its patch should cover the most painful areas. Five percent lidocaine patch can be used up to three patches at one time according to the prescribed amount, and the cumulative patch time within 24 h should not exceed 12 h. Five percent lidocaine cream is applied at 1.5-2.0 g/10 cm^2. Most literature recommends intravenous lidocaine at 5 mg/kg, and the infusion time should not be less than 90 min[25]. The dosage of BLA is 0.4 mg capsules or tablets, one tablet (capsule), twice to three times per day.

Side effects and precautions: (1) Carbamazepine: It has a narrow treatment window and is prone to inducing adverse effects on many systems. Common side effects are blurred vision, dizziness, fatigue, nausea, and vomiting, which mostly occur after 1-2 wk of treatment. Rash, urticaria, liver dysfunction, and hypothyroidism are seldom. Granulocytopenia and bone marrow suppression, arrhythmia, liver, and kidney failure are rare. Guidance from the Clinical Pharmacogenetics Implementation Consortium[26] states that serious diseases such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis caused by carbamazepine are highly correlated with patients' variant alleles human leukocyte antigen-B (HLA-B)*15:02 and HLA-A*31:01. Precaution: Carbamazepine treatment should be strictly evaluated by risk/benefit assessment, follow-up of patients with hematuria, liver and kidney function, and monitoring of plasma-concentration if possible. Attention should be paid to drug interactions with acetaminophen, digitalis, phenobarbital, erythromycin and so forth, and adverse effects should be treated in a timely manner. Attention should also be paid to hyperalgesia caused by carbamazepine withdrawal. At the same time, patients should be informed of the risk of SJS and toxic epidermal necrolysis before

Table 2 Guidelines/expert consensus recommendations for ion channel drugs

Ref.	Year	Institution	Recommendations	
			Sodium channel blockers	Calcium channel modulators
Finnerup *et al*[15]	2016	IASP	Topical use of lidocaine for PHN (first-line medication); Carbamazepine and oxcarbazepine for TN (first-line medication)	Gabapentin and pregabalin for NPP (first-line medication)
Attal *et al*[16]	2010	EFNS	Same with IASP (2010)	Gabapentin and pregabalin for diabetic neuralgia, PHN, central pain (first-line medication); Gabapentin not recommended for HIV neuralgia, post-traumatic neuralgia
CASP neuropathic pain treatment expert group[17]	2013	CASP	Same with IASP (2010); Bulleyaconitine A and lidocaine infusion is effective for NPP; Local anesthetics recommended for nerve block and intrathecal drug infusion	Same with IASP (2010)
Moulin *et al*[18]	2014	CPS	Topical use of lidocaine (second-line medication)	Same with IASP (2010)
Sumitani *et al*[19]	2018	JSPC	Carbamazepine for TN (first-line medication); Oxcarbazepine is not approved in Japan	Same with IASP (2010)

CASP: Chinese Association for the Study of Pain; CPS: Canadian Pain Society; EFNS: European Federation of Neurological Societies; HIV: Human immunodeficiency virus; IASP: International Association for the Study of Pain; JSPC: Japanese Society of Pain Clinicians; NPP: Neuropathic pain; PHN: Postherpetic neuralgia; TN: Trigeminal neuralgia.

administration. HLA-B and HLA-A genotypes can be checked when conditions are warranted. HLA-B and HLA-A genotype information will provide evidence for drug selection.

(2) Oxcarbazepine: The most common adverse effects are rash, dizziness, headache, and drowsiness. The total incidence of adverse effects is 45.22%, most of which are mild and will alleviate or disappear after 3 to 4 wk. Oxcarbazepine does not affect liver drug enzyme metabolism and has linear PKs, and at the same time has less effects on cognitive function than barbiturates. Oxcarbazepine also can cause a severe rash, such as life-threatening SJS and toxic epidermal necrolysis, with a lower incidence than carbamazepine (1 to 6/10000 *vs* oxcarbazepine is 0.5 to 6/1000000)[27]. Unlike carbamazepine, the correlation between oxcarbazepine's SJS or toxic epidermal necrolysis with HLA-B1502 has not been consistently reported[28].

(3) Side effects of intravenous lidocaine: Drowsiness, paresthesia, muscle tremor, convulsions, fainting, confusion and respiratory depression, hypotension, bradycardia, and other adverse effects. Extreme high blood concentration can cause slow atrial conduction velocity, atrioventricular block, and inhibit myocardial contractility and reduce cardiac output. Precautions of intravenous lidocaine: infusion should be in an environment with monitoring and rescue conditions. During the medication, blood pressure, electrocardiogram, and other vital signs should be monitored. The concentration, total dose, and rate of infusion should be strictly controlled. Lidocaine has slow metabolism and accumulation effect in the body, hence can cause poisoning and convulsions.

Side effects of the 5% lidocaine patch are moderate skin reactions such as erythema and rash. Even with three patches per day for 12 h or even four patches for 18 h, the blood concentration of lidocaine is still very low. However, the use of lidocaine patches should be avoided in patients with oral class I antiarrhythmic drugs such as mexiletine and patients with severe liver impairment. Lidocaine gel is effective in both herpes-related neuralgia and tactile pain and is ineffective against human immunodeficiency virus neuropathy. Patients who are allergic to amide local anesthetics or other ingredients in the product are contraindicated.

(4) BLA: No drug tolerance, no addiction, no gastrointestinal adverse effects. Very few patients may experience transient mild palpitation, nausea, numbness of the lips, and palpitations. The response is transient and can be relieved after stopping the treatment. Pregnant and lactating women, children, and those allergic to this product are prohibited. The interval between the two doses should be no less than 6 h.

Calcium channel modulators

Clinical indications: Indications for calcium channel modulators are mainly NPP including peripheral NPP such as herpes zoster neuralgia, diabetic peripheral

neuralgia, CRPS, central NPP such as stroke pain, and pain after spinal cord injury. It is also considered a complementary treatment for cancer pain[29]. Gabapentin is commonly used in the treatment of herpes zoster neuralgia, diabetic painful neuropathy, cancerous pain, and TN. Pregabalin has good effects on the treatment of PHN, diabetic peripheral NPP, fibromyalgia, and others (Table 2).

Administration and dosage: Gabapentin usually starts at 300 mg daily, three times a day, and needs to be titrated slowly to an effective dose. The usual dose is 900-1800 mg per day. Pregabalin is a new-generation drug developed on the basis of gabapentin. The initial dose is 150 mg daily, twice daily, and the common dose is 150-600 mg per day. To avoid dizziness and drowsiness, you should follow the principle of the first dose at night, using a small amount, gradually increasing the amount, and slowly reducing it.

Drug side effects and precautions: (1) Common adverse effects of gabapentin include dizziness, drowsiness, ataxia, and peripheral edema. Symptoms of withdrawal include disturbance of consciousness, disorientation, non-specific gastrointestinal reactions, hyperhidrosis, tremor, *etc.* Precautions: Because it is excreted from the kidney as a prototype, patients with renal impairment should take reduced dose. Hemodialysis can accelerate the clearance of gabapentin, so patients with hemodialysis should take increased doses to maintain an effective concentration. There is no clear evidence that gabapentin can be used in pregnant women, and it is contraindicated in lactating women because the drug can be secreted through lactation.

(2) Pregabalin adverse effects include peripheral edema, PR interval extension, dizziness, somnolence, ataxia, headache metabolism, language barriers, tremors. Endocrine adverse effects are body weight increase, the occurrence rate is 4% to 12%; the muscular skeletal adverse effect is elevated creatine kinase levels, myoclonus and case-reported stripes muscle dissolution; pregabalin treatment occasionally causes liver enzyme transient increase with mild level, saliva deficiency, constipation, thrombocytopenia, blurred vision, diplopia, amblyopia, *etc*.[30]. Precautions: For patients with liver damage, there is no need to adjust the dosage. The recommended dose is applied for patients with CCR ≥ 60 mL/min. In cases of patients with renal dysfunction, the dose should be adjusted. For a patient undergoing hemodialysis treatment, the dose of pregabalin should be adjusted daily according to renal function. During treatment, patients should be monitored for depression, suicidal thoughts or behaviors, and any abnormal changes in mood or behavior.

CONCLUSION

The CASP organized first-line pain management experts from China to write an expert consensus as a reference for using ion channel drugs. Here, we reviewed the mechanism and characteristics of sodium and calcium channel drugs, and developed recommendations for the therapeutic principles and clinical practice for carbamazepine, oxcarbazepine, lidocaine, BLA, Pregabalin, and gabapentin. We hope this guideline provides direction for clinicians and patients when they use ion channel drugs for the management of NPP.

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EXPERT CONSENSUS

Expert consensus of the Chinese Association for the Study of Pain on pain treatment with the transdermal patch

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Abstract

Chronic pain lasting more than 3 mo, or even several years can lead to disability. Treating chronic pain safely and effectively is a critical challenge faced by clinicians. Because administration of analgesics through oral, intravenous or intramuscular routes is not satisfactory, research toward percutaneous delivery has gained interest. The transdermal patch is one such percutaneous delivery system that can deliver drugs through the skin and capillaries at a certain rate to achieve a systemic or local therapeutic effect in the affected area. It has many advantages including ease of administration and hepatic first pass metabolism avoidance as well as controlling drug delivery, which reduces the dose frequency and side effects. If not required, then the patch can be removed from the skin immediately. The scopolamine patch was the first transdermal patch to be approved for the treatment of motion sickness by the Food and Drug Administration in 1979. From then on, the transdermal patch has been widely used to treat many diseases. To date, no guidelines or consensus are available on the use of analgesic drugs through transdermal delivery. The pain branch of the Chinese Medical Association, after meeting and discussing with experts and based on clinical evidence, developed a consensus for promoting and regulating standard use of transdermal patches containing analgesic drugs.

Key Words: Transdermal drug delivery systems; Pain; Transdermal patches; Topical; Nonsteroidal anti-inflammatory drugs; Analgesics

Core Tip: Currently no international guidelines or consensus are available on the treatment of pain using transdermal patches. With the help of experts and based on recent clinical evidence, the pain branch of the Chinese Medical Association formulated China's expert consensus on "transdermal pain treatment in China," while considering China's national conditions with a view to regulate and promote the standardized use of the transdermal patch containing analgesic drugs.

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INTRODUCTION

According to the International Association for the Study on Pain, "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Chronic pain refers to pain lasting or

recurring for more than 3 mo[1]. Chronic low back pain is one of the leading causes of disability in the Chinese population[2,3]. Hence, treating chronic pain safely and effectively is one of the important clinical problems. In recent years, the research and development of new drugs for chronic pain *via* oral, intravenous and intramuscular delivery are not satisfactory, but transdermal delivery of analgesic drugs has made great progress[4].

Currently, no international guidelines or consensus are available on the use of transdermal analgesic drugs. Therefore, this article summarizes China's expert consensus on "transdermal pain treatment in China," with a view to regulate and promote the standardized use of the transdermal patch containing analgesic drugs. The consensus was formulated by the pain branch of the Chinese Medical Association with the help of experts and using recent clinical evidence.

OVERVIEW OF TRANSDERMAL DRUG DELIVERY SYSTEM

In the transdermal drug delivery system (TDDS), the drug enters systemic circulation through the skin and capillaries at a certain rate to achieve a systemic or local therapeutic effect[5,6]. TDDS in the broad sense includes all topically administered formulations such as ointment, patch, cataplasm, aerosol, coating, *etc.*, whereas TDDS in the narrow sense refers to the transdermal patch[7]. The history of transdermal drug delivery dates back thousands of years. In ancient China, leaves and grass stalks were used to smear the skin and wounds. More than 1500 prescriptions are available in the treatise on external treatment of emergency Guangsheng in the Ming and Qing dynasties[8]. In the modern era, the scopolamine patch for the treatment of motion sickness was the first transdermal patch to be approved by the Food and Drug Administration (FDA) in 1979. From then on, the transdermal patch has been widely used to treat many diseases[9].

CLINICAL CHARACTERISTICS OF TDDS

Advantages of TDDS

Compared with other routes of administration, transdermal administration has many advantages, as summarized in Table 1[10,11].

Absorption and factors influencing skin absorption

Traditionally, transdermal drugs are absorbed by passive diffusion. The stratum corneum, the outermost layer of the skin, is the main rate-limiting barrier for transdermal drug transport. Factors affecting transdermal absorption include physicochemical properties (molecular weight, solubility, partition coefficient and dissociation constant, PKA), carrier properties and skin conditions (Table 2)[10,12]. The rate and extent of drug absorption through skin can be calculated using the following formula:

$$\text{Log } P = -2.7 + 0.71 \times \log \text{Ko/w} - 0.0061 \times \text{M}$$

Where, Ko/w = oil-water partition coefficient and M = molecular weight[9-11].

Systemic and local effects of TDDS

In TDDS for systemic delivery, the drug from TDDS gets transported to the subcutaneous capillaries through the skin without accumulating in the dermis. Once the drug reaches systemic circulation, it exhibits its therapeutic action. Examples of such TDDS include fentanyl transdermal patch, buprenorphine transdermal patch and scopolamine transdermal patch[10,13].

In TDDS, the drug is transported to the subcutaneous tissue through the skin and then to the deeper tissue to exert local action. Some of the TDDS for local action include nonsteroidal anti-inflammatory drugs (NSAIDs) transdermal patch, capsaicin patch and lidocaine patch[10,13].

Structure and development of the transdermal patch

According to the characteristics of its dosage form, the transdermal patch can be roughly divided into three generations (Table 3). The first generation of transdermal patch is the most representative transdermal patch[14].

The structure of a TDDS includes four layers: (1) an impermeable backing layer to protect the system from invasion of external substances and to prevent the loss of

Table 1 Advantages of transdermal drug delivery system administration

Advantages
Simple administration and improved patient compliance
Avoids hepatic first pass metabolism
Avoids direct interaction of drugs with food or other drugs in the gastrointestinal tract, which may affect drug absorption
Helps in controlled drug delivery and reduces frequency of dosing
Reduces dosage and side effects
Can be removed from the skin surface immediately
Has physical form, characteristics and identification marks so that it can be easily and quickly identified in an emergency (such as when the patient is unresponsive, unconscious or comatose)

Table 2 Factors influencing drug percutaneous absorption[10,12]

Influencing factor	Effect on transdermal drug absorption
Drug concentration	Generally, the amount of drug absorbed per unit area per unit time increases with the increase in TDDS drug concentration
Drug distribution coefficient	Drugs with both water-soluble and fat-soluble properties can be effectively absorbed through the skin. The water-soluble properties of drugs determine the concentration of the drug at the absorption site and the partition coefficient affects the rate of drug transport at the absorption site
Drug molecular weight	The ideal relative molecular weight for transdermal administration is 400 Da or less
Carrier factor	The main effects of carriers on percutaneous absorption include solubility of drugs in carriers and change of drug distribution coefficient by carrier
Site of application and time	The larger the application area (TDDS) and the longer the application time, the more the drugs are absorbed
Skin conditions	Hydration of skin helps increase percutaneous absorption. TDDS can form a closed water barrier with evaporating sweat to increase the hydration degree of the skin. It can be applied to the thin cuticle, with better absorption through the skin. When the skin is damaged, the drug will directly enter the subcutaneous tissue and capillaries, which may affect the properties of TDDS

TDDS: Transdermal drug delivery system.

Table 3 Development of transdermal patch[14]

Classification	Characteristic
First-generation transdermal patch	The drug should have suitable properties (highly potency, low molecular weight and lipophilic) to solve the problem of low oral bioavailability, to reduce the frequency of drug administration or to achieve stable drug administration
Second-generation transdermal patch	This generation of patch can promote and improve the percutaneous absorption of small molecule drugs by means of a chemical penetration enhancer, ion introduction or ultrasound
Third-generation transdermal patch	These patches help to promote percutaneous absorption of macromolecules, including therapeutic proteins and vaccines

drugs or evaporation of skin moisture; (2) a drug storage or framework system to store and release drugs; (3) a liner that protects the patch during storage, which has to be removed prior to use; and (4) an adhesive layer to keep the patch in contact with the skin[10]. The adhesive layer can be divided into peripheral type and surface type. Peripheral type refers to applying a circle of pressure-sensitive adhesive on the periphery of the TDDS drug part. In surface type, TDDS is completely covered with finger-sensitive adhesive coating. Of the two types, the surface type of adhesive layer is the most common[10].

Only two types of TDDS were available before 1990: reservoir type and matrix type. After 1990, the adhesive dispersion type was introduced. In the adhesive dispersion type, the drug is dispersed in the adhesive layer itself; this helps to reduce the layers to two or three[15]. Since 1999, the FDA has not approved a reservoir type because of the risk of uncontrolled drug release from the reservoir. Most of the existing patches in the

United States market (72%) are of the adhesive dispersion type[16].

Complications with application of patch

Dose adjustment is the main challenge faced in the use of a transdermal patch because only fixed dosages are commercially available[17]. In theory, an alternative option to reduce the dose is cutting the patch. However, cutting the patch may result in altering the structure of the patch, which may result in altering drug release, especially controlled release, and the quality of the adhesive layer[18] Cutting the microdrug reservoir of the patch can damage the microparticles of the drug, which leads to inaccuracy of dose evaluation[17,18]. A comparative study on the use of the clonidine patch (Catapres TTS) in sections and as a whole reported difficulty in predicting absorption degree and rate of drug release after cutting the patch, and the incidence of abnormal (too high or too low) blood concentration increased significantly with sections of patch. For most analgesic drugs, it is recommended to refer to the relevant instructions provided by the manufacturer[19].

Application site of patch: transdermal analgesic drugs can be applied at two application sites. Opioid transdermal patch is generally fixed on the chest, abdomen or upper arm because of its systemic effect. Topical patches with local effects such as topical NSAID patches, 8% capsaicin patch, 5% lidocaine patch and other patches are generally applied to the pain site[17,18].

COMMON CLINICAL TDDS

Transdermal NSAIDs

NSAIDs act by inhibiting prostaglandin synthesis and reduce persistent hyperalgesia by inhibiting cyclooxygenase activity to play an analgesic and anti-inflammatory role[20,21]. Compared with NSAIDs administered systemically, topical administration of NSAIDs reach therapeutic concentrations at the pain/inflammation site while maintaining low serum levels and potentially minimizing adverse effects related to high systemic absorption[20-22].

The advantages of topical NSAID application depend on the ability of the drug to penetrate the skin and reach the site of action. Different NSAIDs have different penetration abilities. Table 4 summarizes the pharmacokinetic properties of different topical NSAIDs[23-29]. According to studies reported, for a drug to be formulated as a TDDS, it should have ideal properties such as a partition coefficient (log *P*) of 1 to 4, molecular weight of < 400 Da, lipophilic, highly potent, low melting point and short half-life[6,30,31]. The peak plasma concentrations of NSAIDs vary greatly, but their concentrations in synovial fluid were much more stable than those in the plasma[32]. The plasma concentration of NSAIDs through topical delivery is about 1% to 10% of that of systemic administration. However, whether the concentration of NSAIDs in the local tissue of the application site is higher than that of systemic administration remains uncertain[32]. Most studies show that the concentration of NSAIDs in the deep tissue of the application site (such as the skeletal muscle and synovium) is equivalent to that of systemic administration. In addition, topical administration of NSAIDs in elderly patients may result in increased plasma concentration, which may be due to reduced drug clearance and thin skin[31,32].

Topical NSAIDs can be used in different diseases such as acute sprain/strain, low back pain, chronic musculoskeletal pain and neuropathic pain[13,21,22,31-33]. A review showed similar efficacy with topical and oral NSAIDs in the treatment of chronic skeletal muscle pain[34,35]. When NSAIDs alone are not effective in treating moderate to severe pain or multisite pain, combination therapy with other analgesic drugs helps in effective treatment. When a combination of topical and oral NSAIDs is used, attention should be paid to avoid an overdose[36-40].

NSAIDs for topical application can be in the form of ointment, gel, gel paste and patch. Some studies compared topical NSAID patches with ointments and gelatin formulations. The results showed that the permeability of patches was better than that of gelatin and ointments. Compared with ointments, patches had better adherence[41-44].

Adverse effects with topical NSAIDs can be cutaneous and systemic adverse reactions. The incidence of cutaneous adverse reactions is about 1% to 2%, which include erythema, pruritus, irritation, fever or burning sensation and contact dermatitis. Most of the cutaneous adverse reactions were reported to be mild and disappeared after drug withdrawal[45-47].

Table 4 Pharmacokinetic characteristics of topical nonsteroidal anti-inflammatory drugs patches[23-29]

	Loxoprofen sodium	Ketoprofen	Diclofenac sodium	Flurbiprofen	Indometacin	Ibuprofen
Log *P* value	1.97	2.94	4.31	3.81	4.42	3.51
Cmax in ng/mL	61.20	891.36	0.81	43.00	27.00	556.00
Tmax in h	82.30	7.60	16.90	20.00	16.00	14.40
$T_{1/2}$ in h	7.8	NA	NA	13.90	11.55	NA

Transdermal opioids

The commonly used opioid transdermal patches in China are the fentanyl transdermal patch and buprenorphine transdermal patch[13]. Table 5 represents the pharmacology of opioid transdermal patches[48-52].

Fentanyl transdermal patch

Fentanyl is a strong opioid analgesic. Its analgesic intensity is about 100 times that of morphine, and its transdermal penetration ability is 43 times that of morphine. Because of its ideal properties such as small molecular weight (337 Da), highly lipophilic properties and no biotransformation in the process of transdermal penetration, it was the first analgesic drug formulated as a TDDS[49]. The fentanyl transdermal patch was approved by the FDA in 1990 for the treatment of chronic pain[13]. Other than chronic pain, it is also used for neuropathic pain and cancer pain[50].

Buprenorphine transdermal patch

Buprenorphine, a semisynthetic derivative of dimethylmorphine, is a partial agonist of the μ opioid receptor and antagonist of the κ receptor. The buprenorphine transdermal patch was approved by the FDA in 2010 for pain treatment. It is used for moderate to severe cancer pain, skeletal muscle pain, neuropathological pai, and visceral pain. As with fentanyl, buprenorphine is also not recommended in the treatment of acute and breakthrough pain[4,13,51,52].

Compared with fentanyl and other opioids, buprenorphine transdermal patch has lower neurotoxicity, especially in the elderly or patients with Alzheimer's disease. Another significant advantage of the transdermal buprenorphine patch is that no dosage adjustment is needed in patients with renal insufficiency[13].

Opioid transdermal patches can significantly reduce pain and gastrointestinal related adverse effects such as nausea, vomiting and constipation and reduce the proportion of patients discontinuing treatment due to adverse reactions. However, in the treatment of chronic low back pain and knee and hip arthritis opioids (including opioid transdermal patches) were reported to have no significant difference in relieving pain and improving body function, while more adverse reactions were reported when compared with NSAIDs[53-57].

Capsaicin transdermal patch

Capsaicin is a selective transient receptor potential vanilloid receptor, subtype 1 agonist that activates the nociceptive sensory nerve fibers (C- and Ad-fibers) of transient receptor potential vanilloid receptor, subtype 1 in the skin, resulting in enhanced sensitivity to stimuli, burning sensation and erythema. Exposure to a single high dose or repeated exposure to low dose of capsaicin can lead to the non-functioning of nociceptors[13,58].

Studies reported absorption of 1% capsaicin into the epidermis and dermis after an hour of patch application. The absorption of capsaicin is directly proportional to the surface area and time of application. Skin temperature was also found to have an influence on the absorption of capsaicin. The results of a population pharmacokinetics study showed that peak plasma concentration (1.38 ng/mL) of an 8% capsaicin patch was attained after 1.46 h. Moreover, capsaicin has a high protein-binding capacity (93%-94%). After absorption, it is mainly metabolized in the liver by P450, and the elimination half-life is 1.64 h[59,60]. The transdermal patch available is 8% capsaicin at a dosing frequency of one patch per day. Capsaicin is used for the treatment of neuropathic pain. Better results were reported with capsaicin than placebo in the treatment of post herpetic neuralgia and diabetic peripheral neuralgia[61,62].

Table 5 Pharmacology of fentanyl and buprenorphine transdermal patches[48-52]

	Fentanyl transdermal patch	Buprenorphine transdermal patch
Absorption	Bioavailability, 92%; Plasma protein binding, 79%-87%; Cmax, 2.6 μg/L; Effective time, 12.7-16.6 h; Peak time 38.1 h; AUC, 117 μg/L; H (0-72 h)	Bioavailability, 50%; Plasma protein binding, 96%; Cmax, 305 pg/mL; Onset time 21 h; Peak time, about 60 h; AUC, 20228 pg/mL
Metabolism	Metabolized by CYP3A4 in the liver, and the metabolites are basically inactive	Metabolized by CYP3A4 in the liver
Elimination	The half-life of the transdermal patch is about 17 h (13-22 h)	The half-life of the transdermal patch is 25.3 h
Mechanism	μ opioid receptor agonist	μ opioid receptor partial agonist, δ opioid receptor agonist, weak κ opioid receptor antagonist, ORL-1 agonist
Indication	Moderate to severe chronic pain and intractable pain treated with opioid analgesics	Chronic pain beyond the control of nonopioid analgesics
Dosage form specification	2.1-, 4.2-, 8.4- and 12.6-mg paste; Four specifications, lasting for 72 h	5-, 10- and 20-mg paste. Each paste is used for 7 d
Adverse reactions, > 10%	Nausea, headache, constipation, dry mouth, drowsiness, fuzzy consciousness, powerlessness, sweating	Erythema, pruritus, nausea

AUC: Area under the curve; ORL: Opioid receptor like; TDDS: Transdermal drug delivery system.

Lidocaine transdermal patch

Lidocaine is a voltage-gated sodium channel blocker (mainly Nav1.7 and 1.8). It can reduce the ectopic negative charge, increase the threshold of peripheral ectopic discharge and reduce the pain transmission by stabilizing the membrane potential of neurons on abnormal excitation of Aδ and C fibers to have an analgesic effect. In addition, the lidocaine patch also has an analgesic effect on pain from injurious sources[13,63].

Transdermal lidocaine majorly penetrates local tissues through the skin, and very little is absorbed into systemic circulation (about 3% ± 2%); hence, adverse reactions related to systemic administration can be avoided. Patients with severe impairment of heart, kidney and liver function should be cautious with lidocaine use. It is contraindicated in pregnant women and patients allergic to local anesthetics[13,64,65].

The lidocaine patch is generally well tolerated even after long term use. The most common adverse events include erythema, pruritus, rash, burning sensation, dermatitis, edema and other skin reactions. The lidocaine patch is used in the treatment of neuropathic pain, but there is no high-quality evidence to prove its clinical efficacy[64-69].

Other transdermal patches

The ketamine transdermal patch and dextromethorphan transdermal patch are common nonbarbiturate anesthetics. They are peripheral N-methyl-D-aspartate receptor inhibitors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor inhibitors. They also inhibit voltage-gated Na^+ and K^+ channels[63].

Ketamine transdermal patch (25 mg/24 h) is used to relieve postoperative pain. The 4% dextromethorphan hydrochloride is formulated with 4% lidocaine and 10% trolamine salicylate (Permavan) and used to treat pain, but its efficacy and safety have not been determined. At present, neither of the two transdermal patches have been approved for marketing[70,71].

The bupivacaine transdermal patch is also under development. Compared with the lidocaine patch for 12 h, the bupivacaine patch can be applied once every 3 d and can be used for post herpetic neuralgia treatment. The United States bupivacaine transdermal patch (Eladur) is under investigation[71].

Rotigotine and amitriptyline are commonly used in the treatment of neuropathic pain. At present, the rotigotine transdermal patch (listed in Europe and the United States in 2007 and in China in 2018) and amitriptyline transdermal patch are available. The rotigotine transdermal patch can improve chronic pain in Parkinson's disease[72]. However, neither of the drugs has been approved for pain treatment[73].

Clonidine, a α_2 adrenergic receptor agonist and imidazoline receptor agonist, is used in antihypertension, acute and chronic pain management and sedation. However, the clonidine transdermal patch is currently approved only in the treatment of hypertension. The analgesic effect of the clonidine patch is related to the α_2 receptor in the skin and the imidazoline receptor in the peripheral nerve endings, but clonidine

use in the treatment of neuropathic pain is insufficient[71,74-77].

CONCLUSION

Based on expert opinions and careful assessment of the existing evidence, the classification and definition of grade evidence were summarized in Tables 6 and 7, while the consensus recommended by experts was summarized in Table 8. This consensus can help clinicians to use transdermal patches in pain management more effectively.

Table 6 Quality classification and definition of grade evidence

Quality level	Definition
High (a)	Very sure that the true effect value is close to the effect value estimation
Medium (b)	There is a moderate degree of confidence in the value of effect; the real effect value may be close to the estimated value, but there is still a possibility that the two are not the same
Low (c)	There is limited confidence in the effect estimates; the true effect values may not be the same as the effect estimates
Very low (d)	There is little confidence in the estimated effect; the true effect value may be quite different from the effect estimate

Table 7 Grade recommended strength classification and definition

Recommended strength	Explanation	Expression method	Expression method
Strong recommendations to support the use of an intervention	The advantages of the intervention measures outweigh the disadvantages	Recommended	1
Weak recommendations to support the use of an intervention	Interventions may have more advantages than disadvantages	Recommended use	2
Weak recommendations against the use of an intervention	Interventions may do more harm than good or the relationship between the advantages and disadvantages is not clear	Not recommended	2
Strong recommendations against the use of an intervention	The disadvantages of the intervention measures are obviously greater than the advantages	Not recommended	1

Table 8 Consensus statement of Chinese experts on pain treatment with transdermal patch

Consensus opinion	Recommended strength level of evidence
The effect of the transdermal patch in pain treatment is clear. It has the advantages of reducing adverse drug reactions and improving patient compliance	1A
NSAID transdermal patch is effective in the treatment of chronic skeletal muscle pain with few side effects, which is recommended as the first choice for the treatment of chronic musculoskeletal pain	1A
NSAIDs can be used as a combination therapy for neuropathic pain	2C
When the efficacy of transdermal NSAIDs alone is not good enough, which can be combined with analgesic drugs of another administration route, such as oral NSAIDs	2B
Opioid transdermal patch is effective in the treatment of chronic pain, but it should not be used as the initial treatment for chronic pain due to addiction and adverse reactions	1B
Opioid transdermal patch should not be used in the treatment of acute or breakthrough pain	1A
When other first-line treatment drugs are ineffective, 8% capsaicin patch can be considered for chronic pain related to peripheral neuropathic pain	1B
When other first-line treatment drugs are ineffective, 5% lidocaine patch can be considered for chronic pain related to peripheral neuropathic pain	2B

NSAID: Nonsteroidal anti-inflammatory drug.

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EXPERT CONSENSUS

Expert consensus of Chinese Association for the Study of Pain on the radiofrequency therapy technology in the Department of Pain

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Abstract

On the basis of continuous improvement in recent years, radiofrequency therapy technology has been widely developed, and has become an effective method for the treatment of various intractable pain. Radiofrequency therapy is a technique that uses special equipment and puncture needles to output ultra-high frequency radio waves and accurately act on local tissues. In order to standardize the application of radiofrequency technology in the treatment of painful diseases, Chinese Association for the Study of Pain (CASP) has developed a consensus proposed by many domestic experts and scholars.

Key Words: Radiofrequency therapy; Standard radiofrequency therapy; Pulsed radiofrequency; Bipolar radiofrequency therapy; Expert consensus; Pain

Core Tip: With the acceleration of global aging process, the number of patients with pain disorders is increasing. Radiofrequency therapy is an effective method for the treatment of pain related diseases. This paper reviews the basic principle, mode, parameters, and possible complications of radiofrequency technology.

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INTRODUCTION

Radiofrequency (RF) therapy is a kind of technology that uses special equipment and puncture needles to accurately output ultra-high frequency radio waves to act on local tissues, which can play the role of thermocoagulation, incision or nerve regulation to achieve the treatment of pain disorders. This minimally invasive treatment can be divided into standard radiofrequency (thermocoagulation) mode and pulsed radiofrequency (PRF) mode. Since the 19th century, animal experiments have used electric current to damage the nervous system. By the middle of the 20th century, the first radiofrequency generator with commercial application value came out[1], which made the radiofrequency therapy technology applied in clinic. In 1997, Dutch physician Sluijter *et al*[2] proposed PRF technology for the first time. PRF has great potential and application value in the treatment of painful diseases because it has no nerve injury, no hypoesthesia, soreness, burning pain and dyskinesia caused by nerve thermal dissection. It is the further development and supplement of traditional radiofrequency therapy technology. On the basis of continuous improvement and development in recent decades, the clinical application of radiofrequency therapy technology has been widely developed, and has become an effective means to treat all kinds of intractable pain.

In order to clarify the characteristics, advantages and disadvantages of RF therapy and to further standardize its application in the field of pain treatment, the proposed consensus was formulated specifically by several domestic experts and scholars organized by the Chinese Association for the Study of Pain (CASP).

BASIC PRINCIPLES OF RF THERAPY

RF therapy instrument (RFTI) generates RF current, which circulates through the body tissues between the tip of the working electrode in the affected area and the dispersion electrodes in other parts. The RF current flows through the tissues and generates a constantly changing electric field, which exerts a force on the electrolyte ions in the tissues and makes the ions move back and forth quickly. The friction and impact of ion currents in tissues generate magnetic field/heat, which is manifested as field effect/thermal effect in tissues[3]. The temperature sensor at the tip of the RF electrode transmits the temperature signal of the treatment area back to the RFTI in real time. When the temperature of the treatment area reaches the pre-set temperature, the RFTI will automatically adjust the current intensity to maintain constant temperature of the working area, avoid fluctuations, and finally achieve the purpose of treatment[4].

The field effect and thermal effect of RF determine the effect of RF therapy has been controversial. The direct current was commonly used in the early stage of RFTI, and its therapy effect was primarily derived from the thermal energy transformed by the resistance energy consumption of human tissues. Following the appearance of high-frequency alternating current RFTI, the thermal energy in the treatment area was mainly generated by the collision of the tissue molecules between the working electrode and the dispersion electrode resulted from alternating current. The molecular structure and physicochemical properties of pain-causing factors may be changed by molecular collision, leading to changes in the compliance of nerve conduction and the permeability of nerve cell membrane simultaneously, thereby producing therapeutic effects. Being restricted by the knowledge on direct current RF previously, more attention were paid to RF thermocoagulation in the early stage. With the in-depth understanding of the work principle of alternating current RF and the relationship among the three important parameters (frequency, field intensity and temperature), the role of PRF mode has been emphasized in recent decades. In PRF therapy mode, the PRTI emits electric current in the form of pulse, which is conducive to the maintenance of lower temperature of tissues around the needle tip. In this regard, it can exert superiority in long-term alleviation of pain and reduce the risk of complications from standard RF thermocoagulation. In recent years, in-depth research of clinicians and researchers has resulted in outstanding achievements, multiple newly established RF models have been emerging, such as unipolar and bipolar water-cooled RF, unipolar and bipolar manual PRF, four-needle RF, *etc*., all of which have achieved satisfactory therapeutic outcomes[5].

COMMONLY USED RF THERAPY MODES AND PARAMETERS

RF therapy mode[6]

Standard RF therapy mode: Standard RF therapy mode (SRFTM) is also known as RF thermocoagulation or continuous RF mode, which is a continuous, low-intensity energy output mode. Current-induced thermal effects of SRFTM can block the transmission of pain signals owing to its effect on protein degeneration and nerve fiber destruction.

PRF therapy mode: PRF therapy mode (PRFTM) is a high-voltage and low-temperature radio frequency mode formed by discontinuous and pulsed current around the nerve tissue. The RFTI emits intermittent pulsed current to the needle tip, which exert an analgesic effect by the field effect caused by rapid voltage fluctuation of voltage near the nerve tissue. Simultaneously, the tip temperature of electrode is kept at 42 °C, which may not induce destruction on the motor nerve function. PRFTM can achieve analgesic effect without thermal nerve detachment effect.

Bipolar RF therapy mode: Bipolar RF therapy mode (BRFTM) consists of two electrodes to form a radio frequency circuit, which can produce a wider RF therapeutic area. According to different parameters and treatment objectives, it can be further divided into two types of bipolar standard RF and Bipolar PRF.

RF therapy parameters

The parameters commonly applied in RF therapy techniques include: needle tip temperature (℃), RF time (s), impulse frequency (H), output voltage (V) and pulse width (the duration of each RF current emitted, ms)[7].

SRFTM: During standard RF therapy, the nerve fibers conducting pain and

temperature can be destroyed when the temperature in the treatment area exceeds 60 ℃, and all nerve fibers can be destroyed no selectively when temperature higher than 85 ℃. Accordingly, appropriate RF temperature can be selected according to the therapeutic purpose[6].

PRFTM: The PRF parameters proposed earliest are the electrode tip temperature at 42 ℃, pulse frequency of 2 Hz, pulse width of 20 ms, output voltage of 45 V and therapy duration of 120 s[2]. In recent years, high-voltage long-term PRF (increasing output voltage and pulse time in PRF) have been applied in clinical practice. Supported by previous literature, it was reported that satisfied therapy effect could be realized when the bipolar pulse parameters pre-set as electrode tip temperature of 42 ℃, pulse frequency of 2 Hz, pulse width of 20 ms, output voltage of 50-90 V, and therapy duration of 900 s[8].

Bipolar SRFTM: In standard bipolar RF therapy, the needle tip distance can be set according to the length of the exposed end of the RF needle, the position relationship between the two needles, the therapeutic site and purpose. The distance between the two needle tips is usually 4-10 mm. To increase the thermotherapeutic effect, a wider banded damaged area can be produced by heat coagulation at 90 ℃ for 120-150 s[6].

PRINCIPLES OF RF THERAPY

(1) Patients are identified as having pain in the corresponding innervated area; (2) Pain seriously affects patients' daily life or work; (3) Conservative treatments such as drugs are ineffective, or patients cannot tolerate the occurred adverse reactions; (4) Diagnostic nerve block is effective and pain is distributed locally; (5) Before treatment, the temperature and range of injury should be accurately predicted according to the patient's condition, and should be selected and controlled in the process of treatment; (6) The nerve should be accurately located under electrical stimulation and electrical resistance monitoring; (7) Repeat RF therapy can be adopted for patients with recurrent pain; (8) The following parameters should be strictly controlled during RF therapy: (a) Temperature The temperature of PRF is 42 ℃, and standard RF is about 85 ℃[9,10]; (b) Treatment duration of RF The treatment duration of standard RF is generally 60-90 s per cycle, in a total of 2-3 cycles; and better therapeutic outcome can be realized with the duration of PRF therapy of 6min[11,12]; (c) Size and shape of RF electrode The therapy range depends on the thickness and length of the exposed electrode; (d) Tissue property The electrode position can be determined according to the tissue resistance; and (e) Test sensory and motor tests should be performed before treatment to determine the relative position between RF needle and the nerve; (9) PRF therapy for pain should be initiated as early as possible, and the starting time of standard RF therapy remains to be studied in the future[13]; (10) In the course of standard RF therapy, local anesthetics should be applied topically to relieve the pain caused by thermocoagulation; (11) Standard RF therapy should be used cautiously for nerves containing motor components to avoid the risk of damage to the motor function; (12) At present, there is still no gold standard for parameter setting of RF therapy, and massive high-quality studies are needed to provide the optimum therapeutic parameters; (13) It should be considered cautiously that cardiac arrest may occur in patients with pacemakers during RF therapy; (14) In patients with spinal cord electrical stimulator, it is necessary to prevent the spinal cord from being implicated by electrical current passing in the direction of the spinal nerve stimulator during RF therapy; and (15) Before RF therapy, the coagulation function of patients should be checked without abnormality, with additional confirmation of no infection at the puncture site and the whole body, and without mental disorder.

COMMON SITE OF RF THERAPY

The application of RF therapy in peripheral nerves

RF therapy of spinal nerve roots[14]: RF puncture of spinal nerve roots should be conducted under the imaging guidance. The needle tip should be applied at the upper 1/3 of the corresponding intervertebral foramen. Unlike other spinal nerves, the sacral nerve should be punctured into the corresponding sacral foramen. After the tip reaches the target, sensory and motor tests should be conducted, which can induce

numbness, pain, abnormal sensation or muscle beating in the corresponding innervation area. Appropriate RF therapy mode of spinal nerve roots should be selected according to the pain situation. PRF can be used to treat postherpetic neuralgia, nerve root pain, post-nerve injury pain, postoperative incision pain, *etc.* In addition, patients with cancer pain often receive standard radiofrequency therapy, but the motor function of the corresponding innervated area and the motor dysfunction that may be caused by standard radiofrequency should be carefully evaluated to determine whether it has an intolerable impact on the patient's life.

RF therapy of nerve trunk: (1) The trigeminal branch[15]. Trigeminal nerve includes maxillary nerve, mandibular nerve, supraorbital nerve and infraorbital nerve, *etc.* Standard RF or PRF will be selected according to the condition in the actual clinical practice. The puncture of maxillary nerve usually adopts the subzygomatic arch approach. The position of the foramen rotundum should be determined under the guidance of X-ray or other images, and the direction of the tip should be adjusted according to the guidance of imaging. When the needle inserting about 5-6 cm depth, it can reach the external orifice of foramen rotundum, and radiating pain will appear in the distribution area of maxillary nerve. The puncture of mandibular nerve should be guided by image through the subzygomatic arch approach (puncture depth of about 5-6 cm) or through the traditional Hartel anterior approach (puncture depth of about 5-8 cm) under the guidance of imaging. Radiating pain may occur in the distribution area of the mandibular nerve when puncture needle touching mandibular nerve. Supraorbital nerve puncture can be performed through the supraorbital foramen approach, and the supraorbital nerve can be reached when it is inserted into the skin of 0.5-1 cm in depth vertically. Infraorbital nerve puncture is performed through the infraorbital foramen approach. The suborbital foramen can be entered when it is inserted into the skin of 1-3 cm in depth at an oblique-posterior-superior direction. The puncture depth can be maintained at just about 1-2 cm to avoid injury to the eyeball. Sensory and motor tests should be carried out after the puncture needle reaches the target nerve. Sensory tests can induce numbness or pain in the corresponding innervation area. During the exercise test, the other trigeminal nerve branches have no motor response except that the mandibular nerve can induce mandibular beating. Standard RF parameters include temperature at 60-80 ℃ for a duration of 60-90 s. PRF parameters are temperature at 42 ℃, duration of 120-240 s, pulse width of 20 ms, and frequency of 2 Hz, in a total of 2-3 cycles. RF of trigeminal nerve branches can be used to treat trigeminal neuralgia, trigeminal neurogenic pain, trigeminal post-herpes zoster pain, cancerous facial pain, and atypical facial pain, *etc* [16]; (2) Glossopharyngeal nerve[17]. Under the guidance of imaging, the needle should be penetrate vertically toward to styloid process from the midpoint of the line between the apex of mastoid process and the mandibular angle. The styloid process can be normally encountered by the needle at about 1.5-3 cm depth, and then slipped slightly forward and upward about 0.5 cm to reach the lower part of the jugular foramen. During the location of the glossopharyngeal nerve *via* sensory and motor tests, sensory test can induce throat numbness or pain and motor test can induce cough. The position of the needle should be adjust in the case of diaphragm twitch. RF of glossopharyngeal nerve should give priority to PRF, with similar PRF parameters as those mentioned before. The RF of glossopharyngeal nerve can be used for the treatment of glossopharyngeal neuralgia, pharyngeal and laryngeal cancer pain, and and pharyngeal and laryngeal pain caused by tumors of skull base; (3) The dorsal ramus of spinal nerve[18]. The posterior branches of the spinal nerve include 31 pairs composing of the cervical, thoracic and lumbar nerves. The posterior branches of the cervical nerve and the lumbar nerve are often selected for RF therapy. The posterior branch of C1 nerve is the suboccipital nerve, which is the motor nerve, and the posterior medial branch of C2 nerve is the occipital great nerve. The PR target of the posterior branch of cervical nerve below C3 nerve locate at the midpoint of the corresponding joint column. The PR target of the posterior branch of the lumbar nerve locate at the junction of the superior articular process root and transverse process of the corresponding vertebral body. During the puncture, the needle should be punctured to the target of the posterior branch of the corresponding spinal nerve under the guidance of imaging. Sensory and motor tests should be carried out after the needle tip reaches the target position. Sensory test can induce numbness, acid distension or pain in the corresponding innervation area, and motor test may cause paravertebral muscle beating. The standard RF or PRF can be applied on the posterior ramus of spinal nerve, with similar parameters as those mentioned before. RF of the posterior ramus of the spinal nerve is applicable for the treatment of neck and shoulder pain, lumbar and leg pain, lumbar facet joint syndrome, compression syndrome of the posterior ramus

of the spinal nerve, *etc*.; and (4) Other peripheral nerves. With the popularity of PRF, the therapy is increasingly applied to peripheral nerves, such as occipital and intercostal nerves. Occipital nerve puncture can be conducted under the guidance of ultrasound, with the insertion point located at the midpoint of the line between the posterior mastoid process and the axial spinous process. The puncture should be perpendicular to the occipital bone surface, parallel to the longitudinal axis of the spine, and penetrates into the occipital bone surface slowly. Intercostals nerve puncture can also be performed under the guidance of ultrasound, the puncture needle should be inserted along the lower edge of ribs to the head side (about 20 ° in direction), slipping through the edge of the ribs, and then needling 2-3 mm to reach the subcostal sulcus. Sensory and motor tests should be performed after the needle reaches the target nerve. Occipital nerve RF can be used to treat occipital neuralgia, cervical headache[19], postherpetic neuralgia in the distribution area of C2 nerve, *etc.* Intercostal nerve RF can be used for the treatment of postherpetic neuralgia and postoperative incision pain.

Peripheral nerve RF therapy: (1) The peripheral nerves of the scalp. Scalp peripheral neuroma has a relatively low incidence but severe pain[20]. RF of scalp peripheral nerve can be considered for patients who are effective but not compliant. With local anesthesia of the puncture point, RF puncture needle should be punctured along the point into the subcutaneous layer with the performance of sensory test at the same time. The puncture should be stopped when the original pain or abnormal feeling is induced, followed by motor nerve test with attention paid to the avoidance of damage to the motor nerve. The RF of the nerve endings of the scalp can be in the form of PRF or standard RF, with the same parameters as before; and (2) Peripheral nerve of stump. It is mainly used to treat patients with residual limb pain and phantom limb pain. Ultrasound-guided puncture is commonly adopted in RF therapy for the treatment of patients with residual limb peripheral nerve. After local anesthesia, patients may usually have pain reactions when the puncture needle was inserted into the residual limb neuroma. Sensory and motor tests should be performed subsequently, of which sensory nerve test can induce original pain or paresthesia, and motor test can stimulate muscle twitches. Standard or PRF may be used. Under standard RF, the parameters are temperature at 60 ℃ within a duration of 90 s, followed by gradual increase in the temperature, every 10 ℃ for a period, until reaching 90 ℃. Multiple cycling treatment should be applied and the surgery should be continued until the presence of strong echo mass in the whole neuroma of the patientindicated by ultrasound[21]. PRF parameters should be set as before.

The application of RF therapy in ganglia

RF therapy of spinal ganglia[22,23]: PRF is generally used in dorsal root ganglion of spinal nerve. Under the guidance of imaging, the RF puncture needle should be punctured to the posterior 1/3 of the intervertebral foramen (below the inferior notch of the upper vertebral pedicle). The C2 dorsal root ganglion is located in the central posterior area of the atlantoaxial joint and its position is fixed. RF puncture needle should be punctured from the back to the central point of the atlantoaxial joint under the guidance of imaging. Sensory and motor tests should be performed after reaching the target of the needle point. Sensory tests can induce numbness or pain in the corresponding spinal innervation area; Motion test can sometimes cause muscle beating in the corresponding spinal innervation area PRF of dorsal root ganglion of spinal nerve can be used to treat postherpetic neuralgia, nerve root pain, cervicogenic headache, pain after nerve injury, postoperative incision pain, *etc.* Standard RF may also be used in patients with cancer pain.

Cranial ganglion RF therapy: (1) Trigeminal gasserian ganglion. RF technology of trigeminal semilunar ganglion has become one of the main treatment methods for primary trigeminal neuralgia[24,25]. The main indications are: (a) Patients with primary trigeminal neuralgia involving branches II and III of the trigeminal nerve, patients with poor efficacy of drug therapy, and those who are unable to continue to be treated with drugs or are not effectively treated of peripheral branches; (b) Atypical facial pain accompanied by pain in the innervation area of trigeminal branches II and III; (c) Involvement of the trigeminal nerve in the advanced cancer pain; (d) Ineffective surgical treatment of secondary trigeminal neuralgia; and (e) Patients with recurrent trigeminal neuralgia. Simple pain in the innervation area of trigeminal branch I, with no trigeminal semilunar RF in principle. RF therapies include standard RF[26] and PRF[27,28]. Brief operation steps are described as follows: The patient should be informed to keep the supine position. In the case of operation guided by X-ray, the projection

angle should be adjusted to 30 degrees at the top of the chin, 21 degrees at the lateral position, and the projection of the foramen ovale on the cheek should be used as the puncture point. When guided by computed tomography (CT), the traditional Hartel anterior approach or modified Hartel anterior approach can be adopted to select the position 2.5-3.0 cm from the lateral side of the diseased side for puncture. Generally, the puncture of the foramen ovale will induce severe facial pain, needle tip fall, and a sense of toughness like penetrating the rubber. Impedance value is commonly in 300-500 Ω; Sensory test can induce pain in the innervating area of the affected trigeminal nerve. According to the motor test, corresponding masticatory muscle movement can be induced in patients with the involvement of trigeminal nerve branch III, but no similar performance in patients with branch II involvement alone. Standard RF parameters should be set as before. Compared with the standard RF, PRF shows milder degree of tissue injury, and lower possibility of complications. However, for primary trigeminal neuralgia, the effect of PRF is worse than that of standard RF, and the long-term effect needs to be further evaluated; (2) Sphenopalatine ganglia. The indications for RF therapy of sphenoid palatal ganglion are as follows[29,30]: (a) Cluster headache; (b) Migraine; (c) Residual forehead headache after treatment for cervicogenic headache; (d) Atypical facial pain in the maxillary nerve region; and (e) Other pain syndromes (poorly located head and face headaches with parasympathetic manifestations of pain, head and face pain caused by head and face tumors, *etc*.). It should be emphasized that RF therapy of sphenopalatine ganglion should be performed until the confirmation of effective diagnostic block. The zygomatic arch approach is usually adopted. The puncture point should be located 3-4 cm in front of the tragus of the affected side and 0.5-1 cm below the zygomatic arch notch. After determining that the puncture needle enters the pterygopalatine fossa under the guidance of imaging, sensory and motor tests should be given respectively. During sensory test, the patient will feel ache and swelling pain in the deep side of the nasal root. During the motor test, the optimum puncture position is at the voltage above 1.0 V with no stimulation of facial twitch. After accurate measurement and localization, PRF mode is commonly used in the treatment of sphenopalatine ganglion. If the standard RF mode is adopted, the treatment parameters should be selected to transit from at 60 ℃ for 60 s to at 70 ℃ for 60 s, and then gradually rise to at 75 ℃ for 120 s, in a total of 1-2 cycles; and (3) Sympathetic ganglia. During RF therapy of sympathetic ganglia, puncture can be performed under the guidance of ultrasound, fluoroscopy or CT. RF thermocoagulation of cervical, thoracic or lumbar sympathetic ganglion can block the transmission of sympathetic nerve excitation and hence exert a therapeutic effect on neuropathic pain and complex local pain symptoms[31]. Lumbar sympathetic neurofrequency thermocoagulation has definite curative effect on intractable pain of thromboangiitis obliterans, diabetic complications of lower limb vascular disease, peripheral neuropathy, complex local pain syndrome and intractable burning pain of lower limbs[32,33]. In view of the extensive effects of sympathetic nerve, PRF with neuromodulatory effects on the cervical sympathetic chain can be used to treat complex regional pain syndrome. RF pulse of lumbar sympathetic ganglion can relieve neuropathic pain of lower limbs. RF therapy of coccygeal ganglion can successfully relieve perineal pain caused by tumors, and which has been reported primarily to be effective for coccygeal pain. However, there is still limited high-quality evidence concerning current use of sympathectomy for neuropathic pain and complex regional pain syndrome. Sympathectomy should be used prudently and is recommended to be selected only when other treatment options are not available.

Application of RF therapy in intervertebral disc

RF therapy of intervertebral disc is a commonly used minimally invasive treatment method and has been relatively mature, with the advantages of simple operation, less intraoperative injury, obvious curative effect, high safety, repeated treatment, less damage to the stability of the spine structure[34]. RF imaging of the intervertebral disc should be performed under fluoroscopy or CT guidance. Single needle RF thermocoagulation can be used to treat discogenic pain. Furthermore, RF combined with low-dose collagenase injection through anterior cervical approach can be used for the treatment of cervical disc herniation[35]. RF ablation nucleoplasty of cervical intervertebral disc may also be used for the treatment of cervical vertigo. RF thermocoagulation of lumbar disc herniation includes single-needle RF, double-needle RF and water-cooled RF. Among them, the water-cooled bipolar RF applies water-cooled system that not only expands the scope of action and improves the effect on the premise of ensuring the safety. PRF of the lumbar disc is a novel technique that may be a therapeutic option for patients with discogenic low back pain.

The application of RF therapy in joints

RF therapy of shoulder joint[36]: PRF has been widely used in the treatment of shoulder joint pain. The scapular nerve PRF is the most widely used one. Systematic evaluation showed that PRF therapy for shoulder joint pain was effective for at least 12 wk without significant complications. However, it is still unclear whether the effect of this therapy is better than other therapies such as intra-articular injection of cortisol hormone and percutaneous electrical stimulation. The subscapular nerve PRF has certain curative effect, and the intra-articular RF also has certain curative effect, but the disadvantage is that there is no support from the results of randomized controlled trials.

RF therapy of sacroiliac joint[37]: It is estimated that 10% to 25% of chronic low back pain is originated from the sacroiliac joint. Conventional RF model has certain effect on the sacroiliac joint pain. In recent years, there have been many attempts to use hypothermic RF mode in clinical practice. However, there are few reports on the application of PRF in sacroiliac joint pain. Bipolar RF can form a band-like damage zone behind the sacroiliac joint, inactivate the joint dorsal nerve, and achieve the purpose of pain treatment.

RF therapy of facet joints[38]: Facet joint disorder is a common cause of low back pain, Interruption of the posterior medial ramus of the spinal nerve by standard RF ablation is an effective approach for pain treatment, and its effect is superior to that of conventional glucocorticoid injection. PRF has also been shown to have a better therapeutic effect, but its pain relief time is shorter than that of the standard RF. It still has good clinical application value in view of its repeatable and non-destructive characteristics.

RF frequency of knee joint[39]: In the treatment of knee osteoarthritis pain, RF therapy has a variety of applications for intra- and peri-articular innervation of the nerve, and have certain therapeutic effects. Intra-articular RF is performed through either direct puncture or under the guidance of arthroscope to ablate intra-articular lesions or PRF regulation. Other RF modalities include RF regulation of the saphenous nerve, sciatic nerve, tibial nerve, common peroneal nerve, and periarticular nerve plexus. In recent years, ultrasound-guided RF therapy has been widely used in knee joint to achieve more accurate and effective treatment.

Application of RF therapy in soft tissue

Soft tissue pain is one of the common diseases in the pain department. There are many causes of soft tissue pain, including primary and secondary pain. Primary factors include sequelae of acute soft tissue damage and pain response induced by chronic soft tissue damage. Secondary common causes include acute or chronic soft tissue injury, secondary muscle spasm or muscle contracture. Accordingly, it may cause nerve damage or innervation disorders, leading to a series of complex biomechanical and neurophysiological effects between vertebrae and joints, thus resulting in a wide range of persistent chronic soft tissue pain.

There are many effective methods to treat soft tissue pain, including acupuncture and moxibustion, massage, manipulation, physiotherapy, silver needle, acupotomy, nerve tissues, *etc*. At present, RF therapy of soft tissue is mainly based on the theory of soft tissue stimulus point or tenderness point and the theory of implicated pain and muscle twitching. The treatment sites mainly focus on the starting and stopping point of the muscle, such as the connection between the muscle and fascia and periosteum, the muscle abdominal position of the muscle, the osteofascial compartment or osteofascial canal, the sepal area between the bone and the muscle fascia, *etc*.

RF therapies for soft tissue pain include standard RF and PRF[40,41]. At present, standard RF is more widely used in the treatment of soft tissue pain than that of PRF. Standard RF therapy can produce high temperature in tissues and damage to the cell by protein coagulation within the treatment range. When RF needle reaches the corresponding treatment point of soft tissues during treatment, it can produce the function of separating tissue adhesion, releasing contracture and promoting local tissue blood supply. Standard RF parameters generally include temperature of 50-80 °C and working duration of 80-120 s, and those of PRF therapy are temperature at 42 °C and working duration of 120-900 s. RF therapy may have broad prospects in soft tissue pain treatment since its tip temperature can be maintained at 42 °C with no any damage to surrounding tissues and nerves.

COMPLICATIONS AND PRECAUTIONS OF RF THERAPY FOR PAIN DISORDERS

Complications[42]

The complications include: (1) Nerve injury; (2) Vascular injury and bleeding; (3) Hypotension; (4) Infection; (5) Skin burn; and (6) Complications of RF therapy in different parts.

Complications of RF therapy for trigeminal neuralgia and semilunar ganglion[43]**:** (1) Facial sensory disturbance. The incidence of facial sensory disturbance is as high as 94% during standard RF thermocoagulation, with most patients presenting with hypoesthesia or numbness. It also provides evidence that pain can only be removed when the sensation in the corresponding trigeminal innervation area decreases significantly or disappears during RF therapy; (2) Eye damage. Eye damage is predominated by hypocorneal reflex (incidence of 3%-27%). Neuropathic palsy is evident in 1%-5%. If corneal reflex is absent, blindfold should be applied or the eyelid should be sutured immediately. The incidence of double vision is estimated to be 0.3%-3%; (3) Trigeminal motor branch injury. The main manifestations for trigeminal motor branch injury are weakness of masseter or pterygoid muscles and masticatory disorders. It can be usually recovered after 6 to 9 wk; (4) Internal carotid artery injury. It is but quite critical, and surgery should be stopped once occurs and replaced by close observation. Patients with severe bleeding should be treated by surgery; (5) Leakage of cerebrospinal fluid. Leakage of cerebrospinal fluid is extremely rate and can form subcutaneous hydrops in parotid ministry mostly. It can be cured commonly by using puncture-aspiration and pressure dressing; and (6) Others. Other situations also include cranial nerve palsy, arteriovenous fistula, meningitis, saliva secretion abnormalities, *etc.*

Complications of RF therapy for disc herniation[44]**:** (1) Intervertebral infection. Sterility should be strictly controlled and antibiotics should be used before and after the operation; (2) Thermal injury of vertebral endplate. The puncture needle should be placed in the middle part of the intervertebral space, with the positive position of the needle tip not exceeding the inner edge of the vertebral arch, and the lateral position should be located at the back 3/4 of the intervertebral space; (3) Electrode broken. Careful examination should be carried out before the operation, and gentle operation should be performed during the operation; (4) Injury of blood vessels. It can lead to retroperitoneal hematoma, lumbar major hematoma, mediastinal hematoma, *etc.*, with an incidence of 1.7%. During the operation, the number of puncture should be reduced as much as possible. After the removal of the puncture needle, the needle channel should be compressed to prevent hematoma from forming in the deep part of the pinhole.

Matters needing attention[45]

The premise of RF therapy: (1) Patients with localized pain and effective diagnostic block; (2) Patients with identified local sources of pain, such as pain in the innervation areas caused by facet joints, intervertebral discs, musculoaponeurosis, tumors, or other causes; (3) Patients with chronic pain who are unable to respond to non-invasive conservative treatment, to respond well to medication, or to tolerate or unwilling to use medication due to side effects of medication or treatment; (4) Patients with pain that has affected the normal life or work, such as interfering with sleep, or the patient with psychological abnormalities, such as anxiety, depression and anger that need to implement behavior therapy; (5) Patients who require RF therapy due to ineffective results by other conservative treatment; and (6) Patients without contraindications for puncture therapy, such as coagulation dysfunction, and those who can be cooperative to the treatment.

Patients with pacemakers and patients with spinal cord electrical stimulators: (1) Patients with pacemakers should be aware that cardiac arrest may occur during RF therapy; and (2) Patients with spinal cord electrical stimulators need to prevent the spinal cord from being implicated when the electrical current passes along the direction of the spinal nerve stimulator during neck operation.

The hemodynamic in the elderly: The hemodynamic in the elderly is unstable, additional attention should thus be paid since RF therapy of the posterior root node may affect the blood supply to the adjacent spinal cord due to changes in local blood circulation, resulting in incomplete paralysis of the opposite side of the RF site.

GRADING OR RATING THE QUALITY OR STRENGTH OF EVIDENCE

The qualitative modified approach to grading of evidence and guide for strength of recommendations are shown in Table 1 and Table 2.

CONCLUSION

To sum up, the current domestic and foreign RF therapy technology is no longer simply thermal coagulation damage, but replaced by non-destructive PRF therapy with increasingly more extensive range of use, thus expanding the application of RF therapy technology in the treatment of chronic pain diseases. In this paper, the basic principle of RF technology, commonly used RF modes and parameters, principles and locations of RF technology application, as well as the possible complications and matters needing attention are summarized based on the literature of RF therapy at home and abroad and the experience of some experts. The consensus of RF therapy technology of doctors in the Department of Pain is reached eventually, which will play a normative and guiding role in the treatment of painful diseases by RF technology in China.

Table 1 Qualitative modified approach to grading of evidence[46]

Grading	Qualitative	Evidence
Level I	Strong	Evidence obtained from multiple relevant high quality randomized controlled trials for effectiveness
Level II	Moderate	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials
Level III	Fair	Evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures

Table 2 Guide for strength of recommendations[47]

Strength	Recommendations
Strong	There is high confidence that the recommendation reflects best practice. This is based on: (1) strong evidence for a true net effect (*e.g.*, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: (1) good evidence for a true net effect (*e.g.*, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: (1) limited evidence for a true net effect (*e.g.*, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

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MINIREVIEWS

Contributions of aversive environmental stress to migraine chronification: Research update of migraine pathophysiology

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Abstract

Clinical studies have suggested that internal and/or external aversive cues may produce a negative affective-motivational component whereby maladaptive responses (plasticity) of dural afferent neurons are initiated contributing to migraine chronification. However, pathophysiological processes and neural circuitry involved in aversion (unpleasantness)-producing migraine chronification are still evolving. An interdisciplinary team conducted this narrative review aimed at reviewing neuronal plasticity for developing migraine chronicity and its relevant neurocircuits and providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. Thus, information presented in this review promotes the understanding of the pathophysiology of chronic migraine and contribution of unpleasantness (aversion) to migraine chronification. We hope that it will bring clinicians' attention to how the maladaptive neuroplasticity of the emotion brain in the aversive environment produces a significant impact on the chronification of migraine headache, which will in turn lead to new therapeutic strategies for this type of pain.

Key Words: Migraine chronification; Aversive environmental stress; Migraine pathophysiology; Migraine headache; Roles of unpleasantness; Emotion brain

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Core Tip: In this article, neuronal plasticity for developing migraine chronicity and relevant neurocircuits were reviewed and discussed. Specifically, we focused on providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. New information collected from both preclinical and clinical studies on these aspects may advance our understanding on the chronic migraine pain mechanisms and lead to new strategies for pain treatment.

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INTRODUCTION

Migraine is the third most prevalent disease and the second most severe disabling disorder worldwide[1]. In the United States, it is estimated that over 45 million people are actively afflicted by migraine. Of these, about 4% of them develop chronic migraine annually[2]. The International Headache Society clinically characterizes chronic migraine as recurrent unilateral throbbing headache attacks of moderate to severe intensity and associated symptoms (including facial allodynia, nausea, vomiting, phonophobia and photophobia) occurring episodically for more than 15 d every month for 3 consecutive months[3]. Before or at the same time as a headache, migraineurs could have aura, *i.e.* a transient visual, sensory, or other central nervous system symptoms[3]. Clinical retrospective data show that the development of chronicity (chronification) is frequently related to a wide variety of internal and external triggers, such as physical and/or mental stress, hormonal fluctuations, sleep disturbances, meal skipping, sensory overload, *etc.*[1,3]. Also, such a chronic disorder is associated with greater psychiatric and medical comorbidities[4]. Pathophysiologically, maladaptive responses (plasticity) of dural afferent neurons of the ophthalmic division in the trigeminal ganglia are evident to be an underlying mechanism for migraine headache. This plasticity is modulated by descending pathways from the higher brain centers[5]. Thus, it is proposed that internal and/or external aversive cues produce a negative affective-motivational component whereby maladaptive responses are initiated contributing to migraine chronification. However, our understanding of pathophysiological processes and neural circuitry involved in aversion (unpleasantness)-producing migraine chronification is still evolving. In this article, neuronal plasticity for developing migraine chronicity and relevant neurocircuits were reviewed and discussed. Specifically, we focused on providing the most cutting-edge information on neuronal mechanisms involved in the processing of affective aspects of pain and the role of unpleasantness evoked by internal and/or external cues in facilitating the chronification process of migraine headache. New information collected from both preclinical and clinical studies on these aspects may advance our understanding on the chronic migraine pain mechanisms and lead to new strategies for pain treatment.

LITERATURE REVIEW

An interdisciplinary team conducted this narrative review. MEDLINE and Cochrane databases were reviewed to identify publications relevant to chronic migraine pathophysiology, unpleasantness (aversion), and synaptic plasticity. Publications were selected based on author expertise to summarize our current understanding of the impact of aversive environmental stress on chronic migraine.

MIGRAINE PATHOPHYSIOLOGY

It is well established by a great deal of research work that migraine pathophysiology involves altered excitability of many brain regions, intracranial arterial dilatation, recurrent activation (sensitization) of the trigeminovascular pain pathway, and consequential structural and functional changes in genetically susceptible individuals[6]. The headache of a migraine attack is the major complaint from the migraine sufferers and is thought to originate from activation of nociceptors innervating meninges, large cerebral arteries, and sinuses. Activation of these structures by mechanical, electrical, or chemical (inflammatory "soup" or infectants) stimulation contributes to migraine headache and its most common associated symptoms including nausea, throbbing pain, photophobia, and phonophobia[6,7]. The nociceptive innervation of the meninges and intracranial vasculature consists of unmyelinated and thinly myelinated axons (C- and Aδ fibers) that contain vasoactive neuropeptides, mainly substance P and calcitonin gene-related peptide contributing to neurogenic inflammation. These peripheral nociceptive terminals originate in the trigeminal ganglion and reach the dura mainly through the ophthalmic branch of the trigeminal nerve (V1) and, to a lesser extent, through the maxillary (V2) and mandibular (V3) divisions[8,9]. Innervation of the dura is also supplied by neurons in the upper cervical dorsal root ganglia[10]. Central processes of meningeal sensory afferents enter the brainstem *via* the trigeminal tract and at the same time sends out collaterals that terminate in the spinal trigeminal nucleus caudalis (Sp5C) and upper cervical spinal cord (C1-3), called trigeminocervical pathway. The projections of intracranial (visceral) and extracranial (somatic) primary afferents onto Sp5C neurons are involved in the perception of referred pain in the periorbital and occipital regions (orofacial allodynia)[11]. Ascending projections of Sp5C neurons to several cortical and subcortical areas contribute to a wide variety of symptoms like migraine headache, phonophobia, photophobia, osmophobia, nausea, irritability, fatigue, sleepiness, and exaggerated emotional responses[6,11-13].

Development of neural plasticity in the trigeminovascular pain pathway has been evidently shown to be the underlying migraine pathophysiology. Brief chemical stimulation with inflammatory agents on the dura of rodents can lead to peripheral sensitization of the primary afferent neurons in the trigeminal ganglion and dorsal root ganglia of C2/C3 and central sensitization of the second order neurons in the Sp5C (known as trigeminocervical complex)[11,14]. Central sensitization may extend to the thalamic (third order) neurons. This is proven clinically by finding an exaggerated activation of the cortical and subcortical areas during ictal period of migraine attack in human migraineurs triggered by nitroglycerin and experimentally by finding the increased responses of sensitized thalamic neurons of rats to cephalic and extracephalic skin stimuli after exposing their dura receptive field to inflammatory soup[6,15]. These strongly support there are endogenous inflammatory mediators released during migraine attacks to activate and sensitize peripheral and central trigeminovascular neurons by the mechanism of neurogenic inflammation[16,17].

Peripheral sensitization mediates the throbbing perception of the headache, whereas sensitization of second-order neurons in the Sp5C mediates cephalic allodynia as well as muscle tenderness[18]. In most chronic migraineurs, episodic attacks are associated closely with the triggering of sensitization of the trigeminovascular pain pathway. These neural plastic responses to episodic attacks are initially adaptive and physiological but later become maladaptive and pathological, which would eventually create a vicious cycle leading to the chronicity of migraine headache[7]. However, it still remains debatable how episodic attacks are triggered and initiated. So far the most widely accepted view is that migraines are preceded by visual, motor, or somato-sensory symptoms known as aura that is characterized by a visual perception of light flashes moving across the visual field.

Aura has been suggested to be closely linked to a reversible, transient cortical event, called cortical spreading depression (CSD)[19]. Electrophysiologically, CSD is a slowly propagating wave (2-6 mm/min) from membrane depolarization of neurons and glia followed by a prolonged inhibition (15-30 min) of cortical activity[20]. This distinctive electrophysiological phenomenon has been correlated with the visual aura that precedes the onset of headache in migraine[21,22]. Neurochemically, triggering of CSD has been shown to lead to the local release of ATP, glutamate, potassium, hydrogen ions, calcitonin gene-related peptide, and nitric oxide by neurons, glia, or vascular cells[23]. These molecules in turn diffuse toward the surface of the cortex to irritate persistently (activate) dural nociceptors, triggering a consequential neurogenic inflammation (vasodilatation, plasma protein extravasation, and mast cell degranulation). The release of pro-inflammatory molecules in the meninges due to

nociceptor activation contribute to the pain of migraine[16,17]. Further, the plastic changes in the trigeminocervical pathway by CSD was suggested by showing that CSD induces an increase of c-fos expression in the Sp5C and that neural firing of meningeal nociceptors and central trigeminocervical neurons in the Sp5C are enhanced by CSD[24]. One of the molecular mechanisms has been proposed by the finding that CSD propagation induces the opening of neuronal Panx1 megachannels leading to a downstream cascade of events that include the release of pro-inflammatory molecules in the meninges[25]. These would serve as the triggers of episodic attacks of migraines. Thus, abnormal cortical excitability plays a pivotal role in the predisposition to develop neural plasticity contributing to the recurrent trigeminovascular and/or dural nociceptor activation. These pathophysiological processes are likely associated with the transition of migraine from acute to chronic disorder (chronification).

CONTRIBUTION OF THE UNPLEASANTNESS (AVERSION) TO MIGRAINE PAIN

A number of internal and external cues are suggested to be triggers of episodic attacks of migraines in approximately 75% of patients. These include physical and/or mental stress, menstruation, hormonal fluctuations, sleep disturbances, noise, odors, heat, head/neck movement, neck pain, and sensory overload[26,27]. However, whether these factors are the causes of CSD causing migraine attacks remains to be investigated. It has long been known that negative emotions-induced unpleasantness produces a significant impact on pain perception[28]. Patients experiencing pain caused by many diseases often reported a higher degree of unpleasantness (or aversion) that are reflected as varying degrees of affective symptoms, such as fear, anxiety, anger, depression, and aversion to pain associated environments. Moreover, the negative affect or "bothersome"-like pain significantly impacts the quality of life of the sufferers and leads to the common comorbidities of psychiatric disorders such as depression[29,30]. Clinical studies have provided important evidence that pain-related aversion experiences seem to be not related to pain intensity but to be significantly influenced by the psychological environment in which pain is perceived[31].

UNPLEASANTNESS COMPONENT OF MIGRAINE PAIN

Migraine is a subjective multidimensional conscious experience, and the pain processing and perception are significantly affected by negative emotions. In addition to cephalic allodynia and/or hyperalgesia perceived as headache, a negative unpleasant affective-motivational component (aversion) is clinically very important and named as pain aversion[31]. A number of clinical retrospective data seem to support etiologically that migraine pain is associated with adverse affective and emotional states. For example, the high comorbidity of migraine and depression highlights the importance of negative affect[32]. Also, migraine patients have been identified to be significantly associated with suicide, and literature has proven that migraine patients have a higher suicide risk (about 2.5 times) than patients without migraine[33]. It is widely accepted that stress contributes to the severity and frequency of migraine attacks[26,27]. In laboratory studies using animal models, the reward- and/or penalty-conditioned paradigms, such as conditioned place preference (CPP) and/or conditioned place aversion (CPA), are the common procedures to assess the affective component of pain and then analyze its mechanisms[34]. Animals are conditioned with CPA paradigm where aversive stimuli (like varieties of stress) can "teach" animals to avoid environments (or objects) that are associated with aversive stimuli by psychologically producing negative, unpleasant affect[31] and by behaviorally inducing avoidance or escape[35]. Using CPP paradigm, the conditioned animals learn to differentiate the pain-alleviating environment from pain-producing environment. For example, in animals with migraine-like pain induced by inflammatory mediators applied to the dural membrane, administration of lidocaine elicited animals to develop a CPP[36]. Thus, both CPP and CPA paradigms are demonstrated experimentally to be a useful, effective tool to reveal affective pain and are therefore available to study the psychological mechanisms of affective dimension of pain.

BRAIN REGIONS AND RELEVANT NEURAL CIRCUITRY RESPONSIBLE FOR MIGRAINE PAIN AVERSION

It is well known that pain is processed in discrete but interacting brain structures, which help to produce multidimensional experiences composed of sensory, cognitive, and emotional (subjective) components[37]. However, our understanding of the neural circuitry that mediates the negative affective component of pain is still very limited. The anterior cingulate cortex (ACC) is the region of the brain that has been frequently reported to mediate consistently pain affects and unpleasantness in many types of pain, particularly chronic pain[31,37,38]. The ACC, along with the insular cortex and orbitofrontal cortex, is part of a salience network. This network circuit has a central role in the detection of behaviorally relevant salient stimuli (including pain) and in the coordination of neural resources[39]. Thus, aberrant salience processing in the salience network may contribute to chronic pain. When brain salience systems become dysregulated or disrupted, they may overly respond to certain types of stimuli because they cannot properly filter and process information[40,41]. Thus, the dysfunction of the salience network would be a critical mechanism contributing to chronic pain. Functional imaging analysis has firstly been used to capture the activity of the brain in a migraine cycle that includes preictal, ictal, and postictal phases for migraine attacks[42,43]. Secondly, increasing neuroimaging studies have investigated the brains of migraine patients in responses to painful and other stimuli during interictal periods. Studies have consistently observed increased activation of a network of brain regions collectively known as the "painmatrix" including the primary and secondary somatosensory cortices, ACC, insula, prefrontal cortex, amygdala, thalamus, and others. Also, decreased activation can be observed in areas responsible for pain inhibition (*e.g.*, pons and ventral medulla), thereby suggesting an imbalance between facilitation and inhibition, likely resulting from maladaptive neural plasticity[15,43,44]. Some of these brain regions, like the ACC, prefrontal cortex, amygdala, *etc.*, have been shown to specifically contribute to psychological and/or aversive processing of migraine headache[43]. It is evident that migraine patients viewing pain-related words exhibited enhanced activation in the insular cortex and orbitofrontal cortex compared to healthy control subjects. Further, there is a report of structural deficits in the orbitofrontal cortex and increased functional connectivity between the orbitofrontal cortex and ACC in migraineurs[45]. In an animal model of migraine pain induced by application of inflammatory mediators to the dural membrane, lesions of the ACC prevented the acquisition for place preference produced by injection of lidocaine into the rostral ventral medulla[46]. The important role of the ACC in the integration of the aversive component of pain was also demonstrated by the evidence that a CPA to formalin-induced pain was absent following the lesion of the ACC[47,48]. Migraineurs were identified to have structural and functional cerebral abnormalities (*e.g.*, reduced cortical thickness) in the prefrontal cortex, the rostral ACC, the somatosensory cortex, the orbitofrontal cortex, and insular cortex[45]. In addition to cortical thinning, the functional activity of both the ACC and the insular cortex was significantly reduced in patients with chronic migraine[49].

The amygdala is another important brain region contributing to the mediation of the aversive component of pain because there is overwhelming evidence demonstrating the comorbidity of psychiatric illness with migraine[50]. Also, more than 47% of migraineurs are comorbid with mood and anxiety disorders[51]. The development of disease comorbidity and the progression to chronic migraine are proposed to be a result of stress-induced neuronal plasticity heavily integrated with stress, affect, and pain[28]. An interesting finding by Akcali *et al*[52] suggests that synaptic plasticity within the amygdala may contribute to migraine pain. Their study demonstrated that (1) topical application of N-methyl-D-aspartate to the central amygdala led to a high expression of c-fos in the amygdaloid neurons and CSD; and (2) sumatriptan attenuated c-fos expression that was thought to result from the induction of CSD. An *in vitro* electrophysiological recording on the amygdala-hippocampus-cortex slices further indicated that CSD modulates synaptic transmission of the lateral amygdala producing synaptic plasticity[53]. Human imaging data showed that migraine patients during spontaneous and untreated attacks had significantly higher blood oxygen level-dependent signal intensities in the limbic structures (amygdala and insular cortices)[54]. These findings suggest strongly a pathophysiological mechanism how the CSD is linked to negative emotions-induced unpleasantness, which in turn contributes to migraine pain. Since there is broad transmission from the amygdala to other brain structures facilitating stress and pain response, it is proposed that the sensitization of the amygdala may underlie the progression of migraine symptoms that are comorbid

with mood disorders.

THE ROLE OF UNPLEASANTNESS (AFFECTIVE) IN THE CHRONIFICATION OF MIGRAINE HEADACHE

The transition from acute migraine to chronic status of migraine is called "migraine chronification". It is estimated that approximately 4% of patients with acute migraine develop and become chronic migraineurs[2]. So far the pathophysiology of migraine chronification still remains elusive. Some mechanisms have been proposed including (1) altered trigeminal and cranial autonomic system function; (2) thalamic contribution to central sensitization; (3) dysfunction of the descending pain-modulating network; and (4) medication-associated central sensitization[55]. These proposed views share a common mechanism, *i.e.* sensitization of migraine pain related pathways. As mentioned above, sensitization of trigeminovascular system and higher brain centers contributes to the neuronal plasticity that should be the key to the progression of migraine. Therefore, it is proposed that frequent or persistent exposure to unpleasant (affective) events leads to a synaptic plasticity in these pain pathways, leading to chronicity. Nevertheless, the exact pathophysiological mechanism remains to be clarified, because this sensitization is affected by multiple internal and external triggers. Patients with migraine often show a "lack of habituation", *i.e.* no decrease or even an increase in response following frequent or persistent stimulation[56]. Clinically, this habituation deficit seen in migraine patients has been demonstrated using several tests, including visual evoked potentials, somatosensory and auditory evoked potentials, blink reflex, and laser evoked potentials[56,57]. This migraine-related deficit in the normal habituation phenomenon is suggested to be one of the mechanisms underlying interictal deficits in habituation and the associated changes accompanying migraine chronification. Clinical observations on patients with chronic migraine showed that the habituation pattern during interictal periods is similar to that during a migraine attack. This should explain such chronic disorder as a status of never-ending migraine[58].

Studies at cellular and molecular levels using animal models have provided insights into the mechanisms that lead to and sustain chronic pain. Synaptic plasticity has been reported in several cortical and sub-cortical regions that are known to be involved in the processing of pain aversion. Of these higher centers, synaptic plasticity has been most extensively studied in the ACC[59,60]. Hyperactivation of the ACC is involved in signaling the unpleasantness associated with pain, especially individuals with neuropathic pain and chronic pain conditions[61]. Further, activation of the ACC has also been linked to emotional or psychological pain. For example, experimentally induced sadness, social exclusion, or rejection led to an increase in activity in this cortical region[62]. Thus, the ACC mediates various negative effects, including the unpleasantness of pain in the course of pain chronification.

Long-lasting synaptic plasticity mostly seen in the form of long-term potentiation (LTP) and mediated by excitatory amino acid receptors and their relevant downstream signaling molecules is the major pathophysiological change responsible for chronic pain. Increasing evidence suggests that LTP recorded in the ACC is causally associated with chronic pain[60,63]. Pharmacological studies on the ACC synaptic plasticity by using *in vitro* electrophysiological recordings reveal that LTP exists in at least four different forms: N-methyl-D-aspartate receptor-dependent, L-type voltage-gated calcium channel-dependent, late-phase LTP, and presynaptic LTP[63]. Some of these LTPs may coexist to be involved in chronic pain or affective (*e.g.*, fear) memory[59,60]. The development of pain chronicity seems to be encoded temporally by LTP in the ACC: (1) Synaptic responses in the ACC are potentiated at the time that allodynia develops seen in rodent models of chronic inflammatory pain, neuropathic pain, bone cancer pain, and chronic visceral pain, and LTP is persistently expressed when pain symptom develops[64]; and (2) Although acute nociception is short-lasting, it can trigger persistent synaptic changes associated with the formation of affective memory[65]. Thus, acute pain may engage synaptic plastic mechanisms in the ACC to encode physiologically relevant information about pain-evoked cognitive impairment, which might contribute to the chronification of pain. With the known widespread connectivity among the ACC, as well as other subcortical limbic regions known as "emotion brain" and nociceptive pathways, it may be presumed that the ACC would integrate the processing of pain with the associated emotional and affective events, contributing to the migraine chronification[31]. Internal and/or external environmental stressors would serve as aversive triggers to stimulate these limbic brain areas and

cause a negative affective state that significantly changes pain sensation, which is the main source of pain aversion. When aversive stimuli become frequent or persistent, the emotional brain may develop sensitization, *i.e.* hyper responsiveness. It thus is proposed that central sensitization of emotional brain will be generated through affective learning of aversive environment, which can trigger recurrence of migraine and contributes to the development of migraine chronicity.

SIGNIFICANCE OF STUDYING THE ROLE OF AVERSIVE ENVIRONMENTS IN MIGRAINE CHRONIFICATION

Insights into the plasticity of emotion brain induced by aversive environment are prerequisites to the understanding of the neural basis of chronic migraine headache and how this chronic event develops due to the maladaptive changes in mood and cognitive function caused by environmental stress. Traditionally, the trigeminal ganglia are trigeminovascular structures and are still seen as "gold" targets for controlling migraine pain. However, when the pain becomes chronic, the situation does not always seem to be the case, because more and more evidence shows that some central changes will occur in the course of chronification. Just like aversion memory and other affective learning processes, it is too late to interfere at the periphery if such "bad" memory takes place in the brain. Therefore, clinicians and laboratory researchers should pay more and more attention to how the maladaptive neuroplastic changes of the emotion brain in aversive environment promote the development of the chronic pain state. The results of this study may provide potential new targets for the treatment of this chronic disorder.

CONCLUSION

Migraine pathophysiology in the transition from acute to chronic pain is complex and multifactorial and involves altered excitability of many brain regions, intracranial arterial dilatation, recurrent activation (sensitization) of the trigeminovascular pain pathway, and consequential structural and functional changes in genetically susceptible individuals. Chronic migraine is closely associated with adverse affective and emotional states. Frequent or persistent exposure to unpleasant (affective) events leads to a synaptic plasticity in these pain pathways, leading to chronicity. The achievements from clinical and laboratory studies may provide potential new targets for the treatment of this chronic disorder.

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MINIREVIEWS

Cervical intervertebral disc degeneration and dizziness

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Abstract

Clinical studies have found that patients withcervical degenerative disease are usually accompanied by dizziness. Anterior cervical surgery can eliminate not only chronic neck pain, cervical radiculopathy or myelopathy, but also dizziness. Immunohistochemical studies show that a large number of mechanoreceptors, especially Ruffini corpuscles, are present in degenerated cervical discs. The available evidence suggests a key role of Ruffini corpuscles in the pathogenesis of dizziness caused by cervical degenerative disease (*i.e.* cervical discogenic dizziness). Disc degeneration is characterized by an elevation of inflammatory cytokines, which stimulates the mechanoreceptors in degenerated discs and results in peripheral sensitization. Abnormal cervical proprioceptive inputs from the mechanoreceptors are transmitted to the central nervous system, resulting in sensory mismatches with vestibular and visual information and leads to dizziness. In addition, neck pain caused by cervical disc degeneration can play a key role in cervical discogenic dizziness by increasing the sensitivity of muscle spindles. Like cervical discogenic pain, the diagnosis of cervical discogenic dizziness can be challenging and can be made only after other potential causes of dizziness have been ruled out. Conservative treatment is effective for the majority of patients. Existing basic and clinical studies have shown that cervical intervertebral disc degeneration can lead to dizziness.

Key Words: Cervical intervertebral disc degeneration; Cervicogenic dizziness; Cervical discogenic dizziness; Cervical spondylosis; Neck pain; Mechanoreceptors

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Core Tip: Cervical discogenic dizziness is an emerging and very attractive concept. Degenerative cervical discs are rich in Ruffini corpuscles and prone to inflammatory reactions resulting in dizziness that can be eliminated by intradiscal analgesic block. Based on basic and clinical findings, degenerated cervical discs can be thought as an important source of dizziness.

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INTRODUCTION

Dizziness is a common complaint encountered in clinical practice[1]. Cervicogenic dizziness, which occurs in the cervical spine, is considered to be one of the most common etiologies[2]. It is generally described as "a nonspecific sensation of altered orientation in space, and disequilibrium originating from abnormal afferent activity arising in the neck"[3]. Cervical degenerative disease, or cervical spondylosis, is currently considered to be the most common cause of cervicogenic dizziness[4]. The major pathological feature of cervical spondylosis is cervical disc degeneration. Patients with chronic neck pain often suffer from dizziness[5]. Neck pain and dizziness are two common concomitant symptoms of cervical degenerative disease. When these two complaints present at the same time, do they have any relationship? Can degeneration of cervical intervertebral discs cause dizziness? If so, what are the pathophysiological mechanisms of this dizziness? This narrative review will scientifically answer these topical clinical issues based on existing basic and clinical studiesevidence.

LITERATURE SEARCH

A comprehensive literature search of PubMed and MEDLINE from the inception of the database to February 2020 was performed. The search terms included "cervicogenic dizziness", "cervical dizziness", "cervical vertigo", "cervical disc innervation", and "cervical disc degeneration". References for this review were also identified from the personal libraries of the authors and supplemented by the reference lists of recent reviews and book chapters. Publications relevant to cervical intervertebral disc degeneration and dizziness were selected based on author expertise to summarize our current understanding of the impact of cervical disc degeneration on dizziness.

DISTRIBUTION OF MECHANORECEPTORS IN CERVICAL DISC

Strasmann *et al*[6] found a great number of Pacinian corpuscles in the longitudinal ligaments and interverbral discs of the cervical spine of small laboratory marsupials. The large number of mechanoreceptors suggests their importance for the detection of changes in position of the cervical spine and head. Mendel *et al*[7] first found mechanoreceptors similar to Pacinian corpuscles and Golgi organs in the annulus fibrosus of human cervical discs obtained at autopsy, which may indicate that the mechanical status of cervical discs is monitored by the central nervous system. Recently, an immunohistochemical study published by Yang *et al*[8] found Ruffini corpuscles in the anterior longitudinal ligaments and outer annulus fibrosus of human normal cervical discs. Ruffini corpuscles were significantly increased in number in the deep tissues of the inner annulus fibrosus and the nucleus pulposus of degenerating cervical discs from cervical spondylosis patients with dizziness compared with cervical discs from patients without dizziness. A small number of Golgi organs were seen in disc tissue samples from patients with dizziness, suggesting that these mechanoreceptors are involved in the development of dizziness. No Pacinian

corpuscles were found in any samples of cervical discs. According to the basic principles of neurobiology, abnormal ingrowth of nerve endings must be associated with abnormal nerve function. It is well known that Ruffini corpuscles normally distribute around joints and sense movement and direction and Golgi tendon organs sense muscle tension. A positive correlation of the increase of Ruffini corpuscles and the occurrence of dizziness in patients with cervical spondylosis has been shown, suggesting involvement of Ruffini corpuscles in the pathogenesis of dizziness caused by cervical spondylosis.

Yang *et al*[9] collected cervical intervertebral disc specimens from patients with chronic neck pain and dizziness for immunohistochemical study. Those patients showed degeneration of the cervical disc on imaging, without cervical disc herniation or nerve root compression, and an increased number of Ruffini corpuscles and substance P-positive free nerve fibers in the degenerative cervical discs compared with normal controls. The distribution of the free nerve fibers was highly consistent with that of Ruffini corpuscles.

DISC DEGENERATION, INFLAMMATION, AND NERVE INGROWTH

Disc degeneration is characterized by elevation of inflammatory cytokines such as tumor necrosis factor (TNA)-, interleukin (IL)-1 /β, IL-6, and IL-17 secreted by the disc cells themselves[10]. These cytokines promote matrix degradation in degenerative discs by producing and activating degradative enzymes, chemokine production, and changes in cell phenotype. Release of chemokines from degenerative discs promotes infiltration and activation of T and B cells, macrophages, and mast cells, further amplifying the inflammatory cascade and release of neurotrophins, nerve growth factor (NGF) in particular[11]. It is now considered that the innervation characteristic of intervertebral disc degeneration is related to the role of NGF[10,11].

Normal intervertebral discs are poorly innervated by only sensory and sympathetic peripheral nerve fibers. Physiologically, proteoglycans in the matrix of the intervertebral disc, especially aggrecans, provide interstitial hydrostatic pressure to counteract nerve and vascular ingrowth into disc[12]. In addition, aggrecan chondroitin sulfate components in normal intervertebral discs inhibit nerve formation. In human degenerative discs as well as in animal models of disc degeneration, the increased expression of NGF in the disc and the breakdown of aggrecans lead to the ingrowth of sensory nerve fibers[12].

CERVICAL SPONDYLOSIS AND DIZZINESS

Clinical studies have found that patients with cervical degenerative disease tend to have concomitant dizziness[13-15]. Cervical degenerative disease is the most common cervical spine disorder in humans[5]. The incidence of complaints of dizziness is 50%-65% in patients with cervical spondylosis[16,17]. Using vibration- and galvanically-induced body-sway posturography assessment, Karlberg *et al*[16] found that patients with cervical spondylosis had poor postural control. The objective findings indicated that balance function was impaired in those patients compared with healthy subjects. Persson *et al*[18] assessed postural performance using posturography in 71 consecutive patients with cervical spondylotic radiculopathy who were randomized to three treatment groups. Surgery (anterior cervical decompression and fusion) achieved significantly improved postural performance and reduced neck pain scores compared with two conservative treatments (physiotherapy and cervical collar). Many clinical studies have shown that anterior cervical decompression and fusion can effectively treat cervical spondylosis patients with cervicogenic dizziness[13-15]. The main indications for surgical treatment of cervical spondylosis are cervical radiculopathy or myelopathy; and after decompression, cervical nerve root and cervical spinal cord conduction are improved. Proprioception is also improved, which may be one of the reasons that anterior cervical decompression improves dizziness[16,18]. Recently, Peng *et al*[15] performed a prospective cohort study to compare the effectiveness of anterior cervical surgery and conservative treatment for cervicogenic dizziness. They found that anterior cervical decompression surgery had a significantly greater effect on dizziness during 12 mo of follow-up than conservative treatment. Because cervical spondylosis is characterized by cervical intervertebral disc degeneration, evidence from the studies described above suggests that cervicogenic dizziness is caused by cervical disc degeneration. Yang *et al*[9] performed a clinical and immunohistochemical

study of patients with chronic cervical pain and refractory dizziness and cervical disc degeneration without disc herniation or radiculopathy on imaging. Resolution or improvement of neck pain and dizziness following bupivacaine injection indicated a symptomatic disc. were significantly reduced or resolved, indicating that the disc was symptomatic. They then performed anterior cervical fusion in those patients. After surgery, the patients experienced a significant reduction in neck pain and dizziness. Thus, it has been proved theoretically and clinically that cervical discogenic dizziness does exist.

PATHOGENESIS OF CERVICAL DISCOGENIC DIZZINESS

The mechanism of cervical discogenic dizziness is not clear. With disc degeneration, there is a net loss of proteoglycans and water from the nucleus, leading to loss of normal structure and to abnormal motion, which can provoke mechanical stimulation. Abnormal stimulation of the mechanoreceptors in degenerated discs can, in certain circumstances, such as inflammation, result in an amplified response called peripheral sensitization. That may explain why some degenerative discs produce dizziness, and others do not[8]. Some mechanoreceptors are more sensitive to mechanical stimuli in inflamed joints than in normal joints[19]. If the discharging characteristics of the mechanoreceptors in a degenerative cervical disc are altered by inflammation and an increase in their number, erroneous signals will is produced[8]. Abnormal cervical proprioceptive inputs are transmitted to the central nervous system, resulting in a sensory mismatch of vestibular and visual information that leads to dizziness and instability[8]. It is because of the strong connection between cervical dorsal roots and vestibular nuclei *via* cervical proprioceptors that the pathology of degenerative cervical disc can be related to dizziness or imbalance[8,9,15,20].

Cervical intervertebral discs have long been considered as a major source of neck pain. Degenerative cervical discs have a rich supply of nerve fibers, are prone to inflammatory reactions, and are susceptible to pain that can be provoked by disc stimulation and can be eliminated by analgesic injection[8,9,21]. A recent review has summarized the evidence that cervical intervertebral disc degeneration can lead to neck pain[22].

Electric stimulation of group III muscle afferents and intramuscular injection of hypertonic saline have been shown to result in significant changes in the activity of γ-fusimotor afferents in leg muscles[23,24]. These observations led Johansson *et al*[25] to propose a pathophysiological model based on nociceptive regulation of the fusimotor system. According to their hypothesis, thin myelinated (group III) and unmyelinated (group IV) muscle afferents can be sensitized by increased concentrations of interstitial potassium, lactic acid, or arachidonic acid caused by static muscle contractions secondary to pain. Both static and dynamic γ-motoneurons are excited by group III and IV muscle afferents, which were strong enough to increase the sensitivity of muscle spindles. This may serve as a positive feedback loop to increase reflex-mediated muscle tension and stiffness. In addition, the connection between second pain neurons and spinal motoneurons can also help increase muscle tension. Increasing sensitivity of muscle spindles can lead to erroneous proprioceptive signals, especially when muscle spindles in different cervical muscles or on different sides of the neck are unevenly sensitized.

Neck pain is reported to have an effect on an alteration of cervical proprioception from muscle spindles[20,26]. A study by Malmström *et al*[27] showed that injecting hypertonic saline into deep cervical muscles of volunteers caused intense, radiating neck pain, resulting in disorientation. The proprioceptive system of the cervical spine, in particular, is extremely well developed, as reflected by an abundance of mechano-receptors, especially from muscle spindles in the deep segmental upper cervical muscles[28]. The mechanisms that control posture involve a wide variety of structures including peripheral afferents, the central nervous system, and the effector muscles[29]. Integration of symmetrical inputs from these afferent systems is essential for normal orientation and balance, and any dysfunction or asymmetry of afferent inputs in these sensory organs can lead to imbalance or dizziness[4]. Proprioceptive signals of the cervical muscles and cervical intervertebral discs play an important role in maintaining and adjusting a person's resting direction and balance during movement, and changes in the proprioceptive signals could cause cervicogenic dizziness[4,9,20].

MANAGEMENT

Like cervical discogenic pain, the diagnosis of cervical discogenic dizziness can be challenging and can only be made after other potential causes of dizziness have been ruled out[4]. Based on the mechanisms of cervical discogenic pain and dizziness described above, the symptom of neck pain for diagnosis of this dizziness is very important. If a patient has a chief complaint of dizziness that is not accompanied by neck pain, a diagnosis of cervical discogenic dizziness may be initially excluded. Similarly, the management of dizziness should be the same as this kind of neck pain[1,5].

Conservative treatments such as nonsteroidal anti-inflammatory drugs, muscle relaxants, manual therapy, and physiotherapy, are effective for the majority of patients[2,4]. Takahashi[2] used muscle relaxants to treat patients with cervicogenic dizziness and stiffness of the neck and shoulders. After treatment, dizziness disappeared or improved significantly in 90% of the patients within 1 wk. Humphreys *et al*[29] compared adult who presented for chiropractic treatment of neck pain with dizziness (n = 177) or without dizziness (n = 228). After 6 mo of follow-up, 80% of patients with dizziness and 78% of patients without dizziness reported clinically relevant improvement. In addition, there were no significant differences between patients with and without dizziness in any of the outcome measures. Reid *et al*[30] assessed the effectiveness of a specific type of spinal mobilization known as sustained natural apophyseal glides for cervicogenic dizziness. They found significant improvement in the severity and frequency of dizziness and relief of neck pain at 6 and 12 wk after treatment.

Some authors encourage the implementation of vestibular rehabilitation for treatment of cervicogenic dizziness[3,31]. It may be assumed that the vestibulo-cerebellar system is better able to compensate for changes in cervical sensory input in cases of cervicogenic dizziness. Therefore, it is believed that vestibular rehabilitation to strengthen the vestibulo-cerebellar system when normal cervical afferent inputs are impaired can improve the ability to adapt to that situation[32]. Studies have reported positive results when combined with manual treatment and vestibular rehabilitation[31].

If a patient with cervical radiculopathy or myelopathy accompanying dizziness does not respond to conservative treatment, anterior cervical surgery can guarantee the reduction of neurologic symptoms and signs and concomitant dizziness[13-15]. If conservative treatment is not effective in a patient with dizziness and painful cervical disc degeneration confirmed by injection of intradiscal bupivacaine, and if cervical radiculopathy or myelopathy are absent, then anterior cervical fusion surgery can provide good therapeutic results[9].

CONCLUSION

Degenerative cervical discs do not always cause dizziness, just as degenerative cervical discs do not always cause neck pain. If a degenerated cervical intervertebral disc does not contain a sufficient number of Ruffini corpuscles and does not have a strong inflammatory response, it may not produce a strong enough proprioceptive afferent impulse. Based on our basic and clinical findings, we have sufficient evidence that degenerated cervical discs are a source of dizziness. Of course, the best evidence we have is from patients who have recovered from dizziness and neck pain after treatment of cervical degenerative diseases. Further basic research is needed to elucidate the nerve conduction pathways in cervical discogenic dizziness and confirm this complex clinical mechanism and to improve diagnosis and treatment.

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ORIGINAL ARTICLE

Observational Study

Clinical efficacy of ultrasound-guided pulsed radiofrequency combined with ganglion impar block for treatment of perineal pain

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Abstract

BACKGROUND

Ganglion impar block alone or pulsed radiofrequency alone are effective options for treating perineal pain. However, ganglion impar block combined with pulsed radiofrequency (GIB-PRF) for treating perineal pain is rare and the puncture is usually performed with X-ray or computed tomography guidance.

AIM

To evaluate the safety and clinical efficacy of real-time ultrasound-guided GIB-PRF in treating perineal pain.

METHODS

Thirty patients with perineal pain were included and were treated by GIB-PRF guided by real-time ultrasound imaging between January 2015 and December 2016. Complications were recorded to observe the safety of the ultrasound-guided GIB-PRF procedure, and visual analogue scale (VAS) scores at 24 h before and after treatment and 1, 3, and 6 mo later were analyzed to evaluate clinical efficacy.

RESULTS

Ultrasound-guided GIB-PRF was performed successfully in all patients, and no complications occurred. Compared with pretreatment scores, the VAS scores were significantly lower ($P < 0.05$) at the four time points after treatment. The VAS scores at 1 and 3 mo were slightly lower than those at 24 h ($P > 0.05$) and were significantly lower at 6 mo after treatment ($P < 0.05$). There was a tendency toward lower VAS scores at 6 mo after treatment compared with those at 1 and 3 mo ($P > 0.05$).

CONCLUSION

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Ultrasound-guided GIB-PRF was a safe and effective way to treat perineal pain. The 6-mo short-term clinical efficacy was favorable, but the long-term outcomes need future study.

Key Words: Ganglion impar; Perineal pain; Pulsed radiofrequency; Real-time ultrasound guidance

Core Tip: Ganglion impar block alone or pulsed radiofrequency alone are effective options for treating perineal pain. However, the safety and clinical efficacy of real-time ultrasound-guided ganglion impar block combined with pulsed radiofrequency (GIB-PRF) remain unclear. In this study, we evaluated thirty patients with perineal pain who received real-time ultrasound-guided GIB-PRF. Ultrasound-guided GIB-PRF was found to be a safe and effective method to treat perineal pain, with a favorable 6-mo outcome.

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INTRODUCTION

Perineal pain is a common complaint, especially in women after delivery[1]. Pain receptors in this region are mainly located within the ganglion impar. Such pain is classified as sympathetic pain, and its treatments include conservative medication, physical treatment, minimally invasive treatment, psychotherapy, and surgical intervention.

Previous studies have reported that ganglion impar pulsed radiofrequency had significant pain relieving effects for refractory perineal pain and coccygeal pain[2,3]. However, the puncture was often guided by X-ray or computed tomography imaging, which have limited effectiveness. The sacrococcygeal joint cannot be precisely visualized by X-ray if the patient has obvious abdominal distension. Although computed tomography can accurately show the position of the puncture needle, it inevitably increases the patient's exposure to radiation[4,5]. In recent years, ultrasound-guided ganglion impar block was found to be an effective way to treat chronic perineal pain[6], but the patients usually needed three or more repeated blocks[7], which indicated a short duration of pain relief following a single ganglion impar block.

A previous case report observed good outcomes after the use of pudendal nerve block combined with pulsed radiofrequency to treat chronic pelvic and perineal pain[8]. However, the clinical efficacy of real-time ultrasound-guided ganglion impar block combined with pulsed radiofrequency (GIB-PRF) remain unclear. Therefore, this study aimed to evaluate the safety and clinical efficacy of real-time ultrasound-guided GIB-PRF.

MATERIALS AND METHODS

Subjects

From January 2015 to December 2016, 30 patients with perineal pain or coccygeal pain who were admitted and treated in Peking University Third Hospital were included in our study. Oral painkillers and conservative treatments were ineffective and an ultrasound-guided GIB-PRF procedure was performed. Patients with pelvic disease or histories of surgery, hip trauma, or sacrococcygeal joint fusion and calcification were excluded. All patients provided written informed consent. The study was performed in accord with the ethical principles of the Declaration of Helsinki, and was approved

by the appropriate ethics committee.

Ultrasound-guided puncture

A sterile steel wire was used to assist the positioning over the skin surface. The wire was held perpendicularly to the probe and placed between the probe and skin (Figure 1A). The steel wire was moved until the "comet-tail" sign behind it with overlapping the surface of the sacrococcygeal joint (Figure 1B), which was the precise puncture point of the needle. During insertion, the lift-thrust method was used to find and trace the position of the needle tip. The needle tip was monitored using real-time ultrasound guidance until it reached the space of the sacrococcygeal joint. At that time, slight force was used to push the needle tip into the ventral sacrococcygeal joint disc, which was accompanied by an obvious sensation of fall-through. A lack of resistance was confirmed by the absence of blood, cerebrospinal fluid, or air in a syringe after injection of a small amount of saline. Anteroposterior and lateral contrast scans by a C-arm X-ray unit confirmed the appropriate position of the needle tip (Figure 2).

Block and pulsed radiofrequency treatment

Sensory stimulation by an all-digital radiofrequency at 50 Hz was started to induce symptoms of perineal pain or discomfort. If the symptoms were consistent with the previous location of pain, the puncture point had reached the position of the ganglion impar. Subsequently, 3 mL of solution containing 0.2% ropivacaine and 2.5 mg diprospan was infused, followed by pulsed radiofrequency treatment for 120 s at 42 ^{o}C. The above procedure was carried out collaboratively by a physician who had specialized in musculoskeletal ultrasound for over 5 years and a surgeon who had specialized in pain therapy for 15 years.

Follow-up

Visual analogue scale (VAS) scores were followed-up at 24 h before and after the treatment, and at 1, 3, and 6 mo after treatment[9]. Surgery-related complications such as rectal perforation, infection, or accidental injection of drugs into the vessels were recorded. These variables were evaluated by resident doctors in the ward or in the outpatient clinic.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corporation, 2011). The data were presented as the mean ± SD for continuous variables. Paired *t*-tests were used to compare VAS scores before and after treatment at each of two time points. *P* values < 0.05 were considered significant.

RESULTS

Characteristics of the study population

The mean age of these patients was 62.1 ± 12.1 years. Among the 30 patients, four were male. The mean duration of pain was 17.7 ± 9.1 mo, with a range from 6 to 36 mo.

Clinical outcomes after real-time ultrasound-guided GIB-PRF treatment

All 30 patients underwent the procedure uneventfully and without complications such as rectal perforation, infection, or accidental injection of drugs into the vessels. Compared with pretreatment VAS scores, the VAS scores significantly decreased ($P < 0.05$) at the four evaluations performed after treatment. Compared with the VAS score at 24 h, those obtained at 1 and 3 mo after GIB-PRF treatment tended to be lower ($P > 0.05$); the scores at 6 mo were significantly lower ($P < 0.05$). In addition, compared with the VAS scores at 1 and 3 mo, the scores at 6 mo after treatment demonstrated a lower tendency ($P > 0.05$, Table 1).

DISCUSSION

GIB-PRF is indicated in patients with perineal pain in whom oral treatment is ineffective, especially those with poor localization of pain, diffuse pain, and symptoms of a burning sensation. The ganglion impar, also called the Walther ganglion or coccygeal ganglion, is located anterior to the sacrococcygeal joint and is a

Table 1 Comparison of visual analog scale scores at different time points before and after the treatment

Variables	Before treatment	After treatment			
		24 h	1 mo	3 mo	6 mo
No. of cases	30	30	30	30	30
VAS	7.7 ± 0.82	5.4 ± 1.7[a]	4.2 ± 2.0[a]	4.3 ± 1.89[a]	3.1 ± 2.85[a,d]

[a]$P < 0.05$, *vs* the visual analogue scale (VAS) score before the treatment.
[d]$P < 0.05$ *vs* the VAS score at 24 h after the treatment.
VAS: Visual analogue scale.

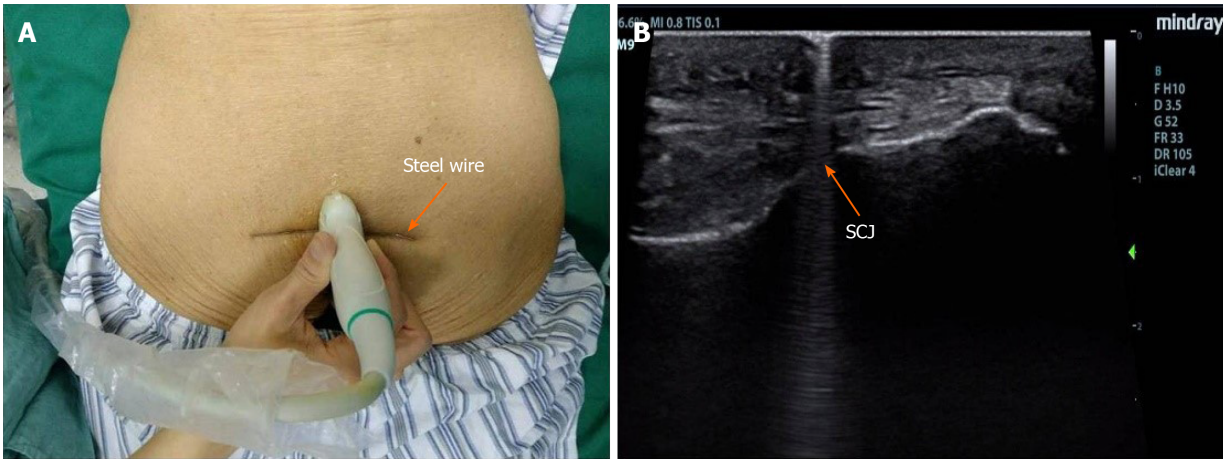

Figure 1 Position of the puncture point on the skin. A: A steel wire was placed perpendicular to the plane of the probe; B: The surface of the skin overlapped, causing a "comet-tail" sign behind the steel wire and the puncture position of sacrococcygeal joint (SCJ) was deeper.

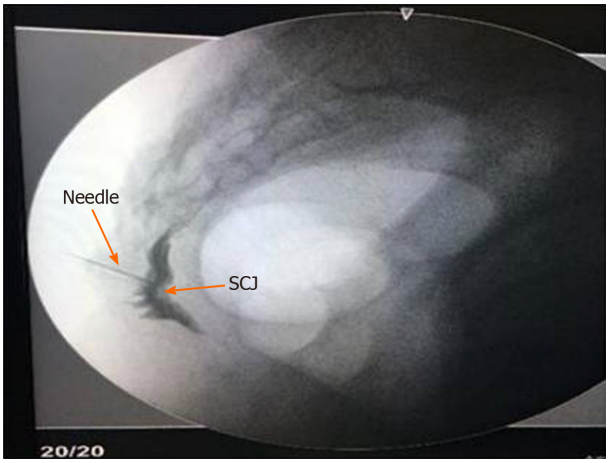

Figure 2 X-ray in the lateral position. Contrast scan showing the position of the puncture needle in the sacrococcygeal joint (SCJ).

retroperitoneal structure[10]. It is close to the rectum and receives sympathetic neurofibers from the sacrococcygeal area. Our study demonstrated that real-time ultrasound-guided GIB-PRF was feasible for treating perineal pain or coccygeal pain, and the key to a success treatment was related to the selection of patients and the tips for ultrasound-guided puncture.

The main principle of pulsed radiofrequency treatment is the generation of a strong electromagnetic field around the tip of the electrode that relieves pain by interfering with the impulse conduction of neurons[11,12], which is one of the effective ways to treat chronic pain. The key step in the procedure is in the precise positioning of the puncture needle within the ganglion impar. X-ray or computed tomography imaging guidance was previously used for the ganglion impar puncture, but the paramedian

puncture pathway, which includes the sacrococcygeal joint, coccyx, and anococcygeal ligament, varies. The reported successful puncture rate free of complications is approximately 70%, but none of the puncture methods was generally accepted as the optimal option[13]. In addition, high-frequency ultrasound is usually used to evaluate muscles, tendons, ligaments, and peripheral nerves in clinical practice, and also in the field of pain therapy[14]. Ultrasound-guided ganglion impar blocks were first reported by Gupta *et al*[15] in 2008 and became an effective treatment for chronic perineal pain[7,16]. However, real-time ultrasound-guided GIB-PRF for treating perineal pain was rarely studied.

Firstly, in our study, the ultrasound-guided method was roughly consistent with that reported by Johnston *et al*[16]. Local, clear ultrasonograms were obtained by Johnston *et al*[16], who used high-frequency probes. In our study, significant thickening of subcutaneous soft tissues in the sacrococcygeal area in obese patients prevented clear visualization of the sacrococcygeal joint because of insufficient penetration of the ultrasound waves when using a high-frequency probe. Therefore, we used a low-frequency convex-array probe to increase penetration. The resolution of superficial structures when using a convex-array probe is relatively poor, however, visualization of the target puncture site in the sacrococcygeal joint was satisfactory, which facilitated successful insertion of the needle.

Secondly, the space within the sacrococcygeal joint is narrow and it forms an arc vertically. Thus, the in-plane view of the puncture is limited, regardless of cross-sectionally or vertically scanning. Therefore, we inserted the needle out of plane, which has the advantages of space savings and a short puncture pathway. Although the needle passage cannot be displayed completely, inserting a needle perpendicular to the skin surface is easier for reaching the target, because of the relatively superficial position of the sacrococcygeal joint and the large vertical space of the articular surface. The distance between the skin and sacrococcygeal joint, as measured before insertion, was used as the reference for the depth of insertion and to avoid deep insertion.

Thirdly, another characteristic of our study was the use of a steel wire as a positioning marker. The slender steel wire was visualized on ultrasonograms as a stripe with strong echogenicity, which results from multiple interference of sound waves reflected off the metal surface, generating the "comet-tail" sign. This method greatly enhanced the accuracy of needle positioning. Therefore a careful selection of patients and tips for ultrasound-guided puncture are important to achieve a successful GIB-PRF in patients with perineal pain.

There were also several limitations in this study. Firstly, a relatively small sample size might have led to negative results, especially about post-treatment complications. In addition, this study cannot make a conclusion about superiority of block alone or pulsed radiofrequency alone *vs* combination of these two treatments, or ultrasound guidance *vs* X-ray guidance, which need further study. Lastly, a follow-up of more than 6 mo after the GIB-PRF is needed.

CONCLUSION

Ultrasound-guided GIB-PRF was a safe and effective way to treat perineal pain. The 6-mo short-term clinical efficacy was favorable. Long-term outcomes need further study.

ARTICLE HIGHLIGHTS

Research background

Despite of the efficacy of ganglion impar block alone or pulsed radiofrequency alone for treating perineal pain, the puncture is usually conducted under the guidance of X-ray or computed tomography imaging. The efficacy of ganglion impar block combined with pulsed radiofrequency (GIB-PRF) for treating perineal pain remains unclear.

Research motivation

This study provides references to the clinical practices of real-time ultrasound-guided GIB-PRF in patients with perineal pain or coccygeal pain.

Research objectives

This study evaluated the safety and clinical efficacy of real-time ultrasound-guided GIB-PRF in treating perineal pain.

Research methods

Thirty patients with perineal pain who were treated by GIB-PRF with guided by real-time ultrasound imaging were analyzed. Complications were recorded to observe the safety of the treatment. VAS scores at 24 h before and after the treatment, and 1, 3, and 6 mo later were performed to evaluate clinical efficacy.

Research results

Ultrasound-guided GIB-PRF was performed successfully in all patients, and no complications occurred. Compared with pretreatment VAS scores, the VAS scores significantly decreased at the four time points after the GIB-PRF. Compared with the VAS score at 24 h after the GIB-PRF, the scores were slightly lower at 1 and 3 mo and significantly lower at 6 mo after treatment. There was a tendency toward lower VAS scores at 6 mo after GIB-PRF compared with those at 1 and 3 mo.

Research conclusions

Ultrasound-guided GIB-PRF was a safe and effective way to treat perineal pain. The 6-mo short-term clinical outcomes were favorable.

Research perspectives

The findings from this study help to establish and provide the groundwork for further studies to compare outcomes of block alone or pulsed radiofrequency alone *vs* the combination of these two treatments and to investigate the long-term outcomes.

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