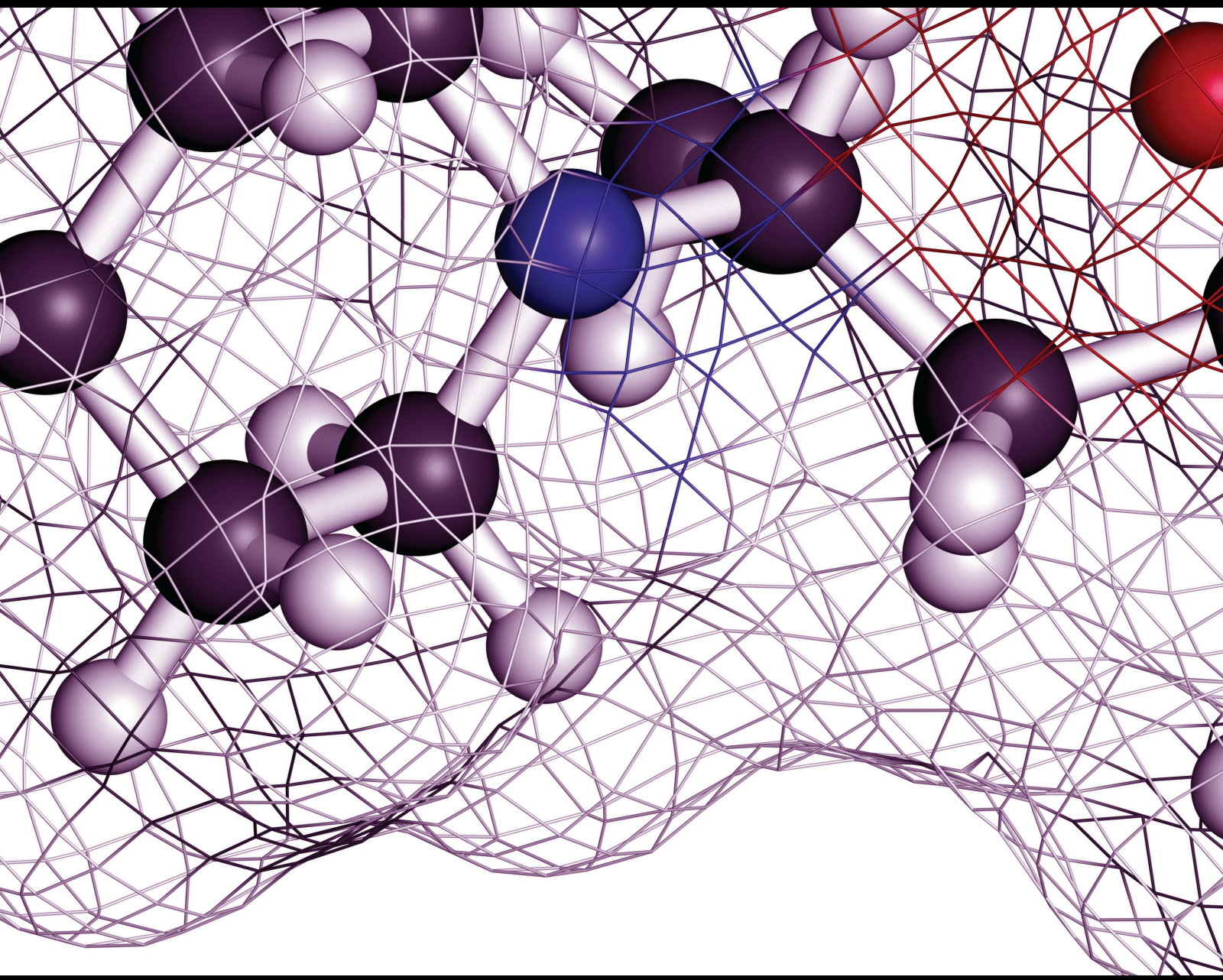
Pain Research and Management

Emerging Basic and Clinical Studies on Musculoskeletal Pain and Management

Lead Guest Editor: Hai-Qiang Wang
Guest Editors: Giustino Varrassi and Wei-Lin Jin



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Editorial

Emerging Basic and Clinical Studies on Musculoskeletal Pain and Management

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In parallel with life-threatening major diseases such as cardiovascular events, cancers, and diabetes, chronic pain is another leading source of global people's sufferings and disabilities [1]. Pain in the musculoskeletal system seems to be the most common phenotype. More in detail, low back pain is a typical and common disease [2], remaining as top cause of years lived with disability for decades, as revealed by the Global Burden of Disease Study 1990 through 2017 [3]. Patient-reported outcome measures (PROMs) are established indicators reflecting clinical symptoms and pertaining severities. PROMs in musculoskeletal diseases may be studied using the visual analogue scale (VAS), Oswestry disability index (ODI), and EuroQol five dimensions questionnaire (EQ-5D). A linking measure between PROMs and clinical manifestation of patients is the threshold of minimal clinically important difference (MCID) [4]. Other linking modalities detecting pain as phenotypes are novel functional diagnostic imaging [5, 6] and genetic studies identifying underlying genotypes [7]. A number of issues still remain challenging for researchers and physicians, including universal classification schemes [8, 9], diagnostic modalities and criteria [10], and novel treatment strategies for musculoskeletal pain [11, 12]. Accordingly, this special issue seeks to cover musculoskeletal pain-related basic and clinical studies.

In this special issue, readers find eight articles, covering a wide spectrum of musculoskeletal pain. In detail, there are five articles focusing on the management of pain (one on neuromodulation therapy for chronic pain, by R. Staelin et al.; a randomized controlled trial of surgical methods for multilevel lumbar spine stenosis, by S. A. Hamawandi et al.; myofascial physical therapy for chronic pelvic pain syndrome, by K. Grinberg et al.; local ropivacaine pain control for ankle fracture patients, by B. L. Li et al.; and a comparative study for the management of masticatory muscle pain, by B. Saranya et al.). An article by Y. Wang et al. addresses the recovery process for patients with lumbar disc herniation undergoing percutaneous endoscopic lumbar discectomy. One article presents the clinical outcome prediction for adolescents undergoing spinal fusion surgery. One article profoundly analyzes the state-of-the-art of available evidence regarding lateral epicondylitis by K. L. Ma et al. In terms of body regions, there are two articles focusing on extremities (the ankle and elbow; B. L. Li et al. and K. L. Ma et al.), three articles on the spine (S. A. Hamawandi et al., D. D. Ocay et al., and Y. Wang et al.), one on the pelvis (K. Grinberg et al.), and one on the head (B. Saranya et al.). One of the articles is not related to body parts, but describes the potentialities of the neuromodulation therapy (R. Staelin et al.).

Collectively, this special issue presents emerging evidence for musculoskeletal pain in various aspects. In consideration of the high prevalence of pain, it deserves a great attention by the readers.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

Authors' Contributions

Hai-Qiang Wang has drafted the manuscript. GV has reviewed the text, with the unconditional support of the Paolo Procacci Foundation. Both authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this editorial, took the responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Hai-Qiang Wang
Giustino Varrassi

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Research Article

Management of Lateral Epicondylitis: A Narrative Literature Review

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Lateral epicondylitis, also termed as "tennis elbow," is the most common cause of elbow pain and dysfunction, mainly resulting from repetitive gripping or wrist extension during various activities. The exact pathogenesis remains largely elusive with putative tendinosis, a symptomatic degenerative process of the local tendon. It is usually diagnosed by clinical examinations. Sometimes, additional imaging is required for a specific differential diagnosis. Although most cases can be self-healing, the optimal treatment strategy for chronic lateral epicondylitis remains controversial. This article presents a landscape of emerging evidence on lateral epicondylitis and focuses on the pathogenesis, diagnosis, and management, shedding light on the understandings and treatment for healthcare professionals.

1. Introduction

Lateral epicondylitis (LE) was first described in the English literature by Runge in 1873 [1]. It was described as chronic symptomatic degeneration of the forearm common extensor tendon attachment at the humeral ectocondyle. It is one of the most common overuse syndromes in primary medical care. LE affects 1% to 3% of the population, mainly those middle-aged people without gender difference [2]. LE can produce a great social and economic burden due to lost workdays and can even disable some patients from working for weeks [3, 4]. Despite advances in the treatment of LE, there is still a lack of established standards. It is generally self-limiting, and most cases require no treatment, with up to 80% cases recovering within one year [5]. Patients with refractory symptoms may require further conservative or surgical treatments.

2. Pathogenesis

The exact etiology of LE has not been well identified. However, it is commonly associated with repetitive microtrauma from excessive gripping or wrist extension, radial deviation, and/or forearm supination [6, 7]. The extensor carpi radialis brevis (ECRB) is the most frequently affected muscle. The pronator and other extensor carpal muscles are also commonly affected [8]. In addition to the factor of excessive mechanical forces, the unique origin of ECRB in the lateral aspect of the capitellum places the tendon at risk for repeated undersurface abrasion during elbow extension and flexion [9]. LE was originally considered as an inflammatory process, especially in its initial phases. Repetitive microtrauma resulting from overload or overuse can cause collagen fibril rupture and the activation of the innate immune system [10, 11]. However, histopathological studies have shown that there is absence of inflammatory cells in biopsies of chronic LE [12, 13]. Accumulating evidence identifies it as tendinosis, a symptomatic degenerative process characterized by an abundance of fibroblasts, vascular hyperplasia, and unstructured collagen. These findings were termed as angiofibroblastic hyperplasia by Nirschl and Alvarado [14]. The mechanical properties of tendons are commonly determined by the

structure of protein molecular and the composition of the extracellular matrix [15]. Strain upon a tendon normally promotes cross-linkage and collagen deposition [13]. In situations of repetitive stretching, multiple microtears of the tendon potentially cause an irreversible denaturing of matrix proteins and proliferation of fibrous tissue [16]. Over time, these scar tissues are vulnerable to repetitive forces, with subsequent further tears. High-frequency cyclical trauma and immature repair result in more severe tears, with consequent alteration and failure of musculotendinous biomechanics and worsening of symptoms [17].

Emerging evidence indicates a significant link between the strain degree of tendons and the extent of injuries [18, 19]. Strains less than 4% generally allow the tendon restore its original length after unloading, but the collagen fibers begin to fail when the strains are more than 4%, and it will be prone to rupture when the strains are over 8%. Kraushaar and Nirschl [13] described four stages of tendinosis, facilitating the recognition of the degenerative process of LE (Table 1). Notwithstanding the main cause is degeneration, additional pathophysiological mechanisms also contribute to the development of tendinosis. LE patients with painful symptoms often involuntarily lead to "underuse" or stress shielding of affected tendons, which subsequently results in structural weakening of the tendon, making it more sensitive to injury [18]. Meanwhile, increasing shear forces promotes fibrocartilaginous formation at tendon enthesis, which contributes to weakening at the tendon-bone junction and initiating development of tendinosis [20].

Histopathological studies have shown defects and necrosis inside the tendon fibers within tendons in patients with chronic LE, which is ascribed to strong association with underuse of the affected limb due to pain-related immobilization [20]. In addition, inadequate tendon angiogenesis and continuous muscle contraction can lead to tendon ischaemia, which further aggravates the development of tendinosis [21].

As for the pain machinery of LE, most studies ascribe the pathogenesis of LE to neurogenic etiology based on several lines of evidence indicating the presence of nerve fibers with reactivity to neuropeptides, including substance P (SP) and calcitonin gene-related peptide (CGRP) [22–24]. Ljung et al. [22] observed 5 patients with LE and 4 patients with medial epicondylitis (ME) by immunohistochemistry, indicating that the SP/CGRP innervation was present in the pathologic tendon tissues of LE as well as ME patients. Neurokinin-1 receptor immunoreaction was noted as varicose fibers in the form of a single fiber or nerve bundles. Thus, the findings present emerging evidence for a possible neurogenic pathogenesis of LE and ME. Uchio et al. [23] concluded that neuropeptides (SP and CGRP) and cytokines (interleukin-1α (IL-1α) and tumor growth factor-β (TGF-β)) might be involved in the pathogenesis of LE. However, further studies are needed to clarify the intrinsic relationship between neuropeptides and cytokines. Furthermore, Han et al. [24] studied the mRNA levels of neuropeptides and cytokines in LE with corticosteroid injection treatment. *In vivo* study found that the expression of SP mRNA was maximally inhibited by corticosteroid triamcinolone acetonide (TAA) at 24 hours but recovered at 72 hours. CGRP mRNA and IL-1α mRNA were inhibited at 24 and 3 hours, respectively. Consequently, the reaction mechanism of the corticosteroid for relieving pain in LE is mainly achieved by inhibiting the expression of neuropeptides and cytokines. Besides, a significant positive correlation between CGRP and IL-1α was also noted after 72 hours of TAA treatment, implicating the role of neurogenic inflammation in the pathogenesis of LE.

3. Clinical Evaluation

Patients often complain of pain or burning around the lateral epicondyle of the humerus, which frequently radiates down the forearm and sometimes extends proximally to the upper arm. This pain is usually triggered or exacerbated by a variety of activities involving wrist extension under resistance, such as grasping objects or twisting towels [25, 26]. The degree of the pain often ranges from mild to severe degrees and from intermittent to persistent, which seriously affects patients' daily life quality. In addition, patients often complain of weakness on gripping and difficulty in lifting [27]. During physical examinations, marked tenderness is usually inspected at the origin of the ECRB in the lateral epicondyle [28]. The pain can be exacerbated with resisted wrist extension, middle finger extension, and forearm supination with the elbow in the extended position. Usually, normal elbow motion can be preserved even in some severe cases [26].

Nirschl and Ashman [29] proposed a classification system and thus separated LE into seven phases based on the level of pain (Table 2). Although there is no complete correlation between histological lesions and clinical features of each phase, their supposed theoretical correlation is helpful to guide the treatment of LE.

4. Diagnosis

Most cases of LE can be clinically confirmed by thorough history inquiry and physical examinations. The contents of medical history collection usually include occupation, hand dominance, daily behaviors and habits, duration of symptoms, date of prior episodes, number of recurrences, inducing or aggravating factors, treatment modalities, and tobacco use. The duration of symptoms and number of recurrences are two key important factors to determine the stage of LE [30].

Any test capable of triggering the typical symptoms of LE can be considered as an effective examination modality for diagnosing LE. Resistance of the middle finger extensor can cause elbow pain due to selective recruitment of the ECRB tendon [31]. Resistance of wrist extensors with full elbow extension and pronation can reproduce the pain in mild-to-moderate cases [25]. Special tests are commonly used during the physical examination, such as the chair test, Cozen's test, and Mill's test [32, 33]. Chair test requires the patient to lift a chair with the shoulder adducted, elbows extended, and forearms pronated. Pain on the lateral epicondyle indicates lateral epicondylitis. Cozen's test requires the patient seated,

Table 1: Pathologic stages of lateral epicondylitis.

Stage	Degenerative changes of tendinosis
I	Peritendinous inflammation with no pathological alterations
II	Involving pathological alterations such as tendinosis or angiofibroblastic degeneration
III	Involving pathological changes and complete structural failure
IV	Involving fibrosis, soft matrix calcification, and hard osseous calcification, in addition to the features of stage II or III

Table 2: Clinical classification of lateral epicondylitis phases.

Phase	Description of pain changes of different phases
I	Mild pain after activity, usually recovers within 24 hours
II	Mild pain more than 48 hours after activity, no pain during activity, can be relieved with warm-up exercises, and recovers within 72 hours
III	Mild pain before and during activity, no significant negative impact on the activities, and can be partially relieved with warm-up exercises
IV	Mild pain accompanies the activities of daily living and has negative impact on the performance of activities
V	Harmful pain unrelated to activities, great negative impact on the performance of activities but does not prevent the activities of daily life. Need complete rest to control the pain
VI	Persistent pain despite complete rest and can prevent the activities of daily life
VII	Consistent pain at rest, aggravated after activities, and disturbed sleep

Notes: the pain in phases I and II is usually self-limiting with due care and protection; the pain in phases III and IV usually needs some nonoperative treatments; and the pain in phases V–VII is more likely to require operative treatment.

with the elbow extended, forearm maximal pronation, the wrist radially abducted, and the hand in a fist. Then, the examiner moves the wrist to dorsal flexion and moves the wrist towards palmar flexion. Mill's test requires the patient seated, elbow extended, and forearm pronated. Then, the examiner moves the wrist passively in palmar flexion and hereby stretching the extensors.

Besides, grip weakness is also been considered as an effective test, with 83% accuracy in determining LE [27]. However, when clinical symptoms cannot be well defined based on physical examination and history, diagnostic imaging may be needed. Although negative findings are usually noted for radiographs, useful information can be obtained in terms of revealing bone diseases, such as arthropathy, osteochondral defects, loose bodies, and calcifications of ECRB origin [26]. Although CT is more sensitive than MRI in identifying tears of capsule, it is rarely used in the diagnosis of LE because of ionizing radiation [34].

Ultrasound is considered as an efficient, noninvasive, and relatively cost-effective imaging method for LE [35]. There are a variety of findings on ultrasound for identifying degenerative changes of the tendons attached to the region of the lateral epicondyle, which includes bone irregularities, calcific deposit, thickening, thinning, and tears of affected tendons or capsule [36]. Moreover, neovascularization can also be detected by ultrasound. If none of these findings is detected, LE can be probably ruled out [37].

In comparison with ultrasound, MRI can provide a better view of the complete anatomical structures of the lateral epicondyle [38]. Primary findings of elbow MRI include signs of abnormal thickening tendon and capsule and increased signal intensity within the common extensor origin. MRI can also identify partial or full-thickness tears of the ECRB, which can influence the need for surgical management and be helpful during preoperative planning [39]. In comparison with ultrasound, however, MRI is of limited diagnostic value in determining the overall extent and size of tendon tearing [40]. MRI is usually considered for the possible intra-articular pathology. It is not recommended routinely owing to its cost and the inconsistence of clinical symptoms with imaging findings [41].

LE is the leading cause of elbow pain; however, similar pain caused by other diseases should be carefully identified to avoid misdiagnosis. These potential diseases mainly include cervical radiculopathy, frozen shoulder, radial tunnel syndrome, lateral plica syndrome of the elbow, posterolateral elbow instability, and inflammatory edema of the elbow muscle. Other causes of pain include low-grade infection or other inflammatory diseases, such as rheumatoid arthritis.

5. Treatment

A variety of treatment options have been recommended for LE. Unfortunately, there are still no universally accepted therapeutic modalities. However, the treatment of LE usually has five therapeutic goals: controlling elbow pain, preserving movement of the affected limb, improving grip strength and endurance, restoring normal function of the affected limb, and preventing further deterioration [26]. Nonoperative treatment remains the priority and mainstay for most patients with LE. Surgical intervention is available for recalcitrant cases.

5.1. Nonoperative Treatment. Nonoperative treatment can significantly resolve the symptomatic LE in 90% of cases [42, 43]. Nonoperative care usually includes activity modification, physiotherapy, nonsteroidal anti-inflammatory medications, bracing, extracorporeal shock-wave therapy, and acupuncture. With a promising result, biotherapy

method has been very popular in recent years, including autologous blood injections (ABI) and platelet-rich plasma injections (PRP).

5.1.1. Activity Modification. Modification of activity and avoidance of overwork are essential components for any treatment protocol. Turning the palm up while lifting and avoiding palm-down exercises can transfer the force away from the lateral epicondyle to the medial epicondyle and help alleviate lateral elbow pain. Besides, LE patients should be advised to correct adverse living habits and stay away from some inciting activities. The principle of RICE (rest, ice, compression, and elevation) can be helpful to relieve pain at the initial stage.

5.1.2. Physiotherapy. Various physiotherapy modalities are recommended for the treatment of LE. Traditional treatment options include electrotherapeutic and non-electrotherapeutic modalities, aiming for improving function and reducing pain by stretching and strengthening the affected wrist extensors [44–48]. Recently, eccentric exercise (EE) has gradually been a first-line conservative treatment for LE. EE is executed via stretching the musculotendinous unit with an applied load [49]. Clinical trials have demonstrated that the EE has superior efficacy in the treatment of LE, in comparison with therapeutic ultrasound, [50] bracing, [51], and a combination of multiple interventions [52]. Although the EE has a promising outcome, the exact mechanisms underlying EE in treating LE remain ambiguous due to varied eccentric programs and undefined optimal dosing [53].

5.1.3. Anti-Inflammatory Medications. Five recent placebo-controlled trials demonstrate that topical nonsteroidal anti-inflammatory medications are effective within four weeks in the treatment of LE [54–58]. There have been no consensuses on the superiority of oral versus topical NSAIDs in pain control, though oral NSAIDs may cause gastrointestinal adverse effects [59]. Hay and colleagues reported that corticosteroid injection was superior than NSAIDs in improving patients' outcomes within four weeks, without long-term benefits at 12 months [43]. Other studies also found that despite of its short-term pain relief, corticosteroid injection is inferior than watchful waiting or physical therapy at one year follow-up [60, 61]. Notably, repeated injections of the corticosteroid may result in iatrogenic tendon rupture and muscle atrophy. Therefore, clinicians should be alert to the abuse of corticosteroids in the treatment of LE on account of poor long-term efficacy and potential adverse effects [62].

5.1.4. Counterforce Braces. Counterforce bracing has been popular in the treatment of LE for decades. Using counterforce braces can significantly alleviate pain by pressing on the forearm extensor muscles and then inhibiting and dispersing the stress on the origin of affected ECRB, thereby facilitating its self-repair [29]. Biomechanical studies have shown that immobilizing the forearm with braces can significantly lessen the stress on the ECRB origin [63]. The latest randomized controlled double-blind trial shows that the use of counterforce brace can significantly decrease the frequency and severity of pain for 2–12 weeks and improve the elbow function at 26 weeks, compared with the placebo group [64]. In addition to counterforce braces, cock-up wrist braces during activities of daily living can limit wrist extension and firing of the ECRB tendon, allowing the injured tendon to heal [65].

5.1.5. Extracorporeal Shock-Wave Therapy. Extracorporeal shock-wave therapy (ESWT) is one of the commonly used physical therapy modalities for treating LE, in spite of conflicting results in the available literature. The mechanism of ESWT has not been completely clarified, possibly including direct stimulation of healing, neovascularization, direct suppressive effects on nociceptors, and a hyperstimulation mechanism blocking the gate control [66]. ESWT may not reverse the pathology of LE but improve the symptoms of LE. ESWT is not appropriate for acute LE but is recommended when symptoms persist for more than 6 months or when other conservative treatments fail [67].

5.1.6. Acupuncture. Acupuncture is a green, simple, inexpensive, and beneficial treatment for musculoskeletal diseases, especially for dysfunction and pain symptoms [68]. However, current data from evidence-based medicine indicate conflicting results. Two systematic reviews have not concluded whether acupuncture was effective for LE [69, 70], whereas three systematic reviews suggest that acupuncture is very effective in relieving LE pain in the short term, with the long-term results remaining unclear [71–73].

5.1.7. Autologous Blood Injection (ABI). Local ABI has been proved effective and widely used for treatment of LE. There are two hypotheses for the mechanism of ABI. On the one hand, ABI works by initiating the inflammatory response around the affected tendon, which may result in cellular and humoral mediators to induce a healing cascade [74]. On the other hand, ABI allows delivery of growth factors inducing fibroblastic mitosis, triggering stem cells, and angiogenesis, probably promoting angiogenesis and collagen formation [75]. Current evidence suggests that ABI can achieve good outcome in the short term; however, no benefit has been found in the medium- or long-term follow-up [76, 77]. In addition, it should be noted that ABI has high risks of injection site pain and skin reaction. Accordingly, its indications should restrict to those recalcitrant cases when other modalities of treatment are less effective.

5.1.8. Platelet-Rich Plasma (PRP) Injection. PRP has gained popularity in recent years in the treatment for LE. The exact mechanisms of PRP remain unknown. There are theories attributed to platelets releasing high concentrations of platelet-derived growth factors enhancing wound healing, bone healing, and tendon healing [78]. However, available

studies have reported conflicting results, which make it difficult to draw clear conclusions on PRP for LE. The latest systematic review manifested that PRP injection has no obvious effects on the treatment of chronic LE [79]. Several studies have shown that PRP does not provide significant benefits over corticosteroids, ABI, or even saline injections [80–82], whereas other studies reported better results with pain relief and function improvement [83, 84].

5.2. Operative Treatment. Surgical intervention can be an option for patients with persistent pain and disability that have failed appropriate nonoperative management.

The number of patients requiring surgical treatment is estimated about 4% to 11% [85]. There are mainly three surgical approaches, i.e., open, percutaneous, and arthroscopic techniques. The surgical focus is to debride the degenerated portion of the ECRB with or without repairing the ECRB tendon [86, 87]. Evidence in the literature indicates fair to good results for these procedures, presenting surgeons with many options for treatment. However, there have been no definite understandings for the mechanism of good outcome.

5.2.1. Open Surgery. Open surgery involves a small lateral incision with dissection and degenerated tendon identification. After debridement of denatured tendon tissues, the main structure of the tendon can be repaired, lengthened, and fixed by drilling or decortication of the lateral epicondyle [88, 89]. Nirschl and Pettrone [90] reported 88 elbow surgical cases out of clinical series of 1,213 patients which involved excision and repair of the ECRB tendinosis tissue. The short-term outcomes of the original procedure were described as good to excellent by 85% of patients with an overall improvement rate of 98% and a return to full activity in 85% of patients [90]. In a recent retrospective study, Dunn et al. [91] presented 10- to 14-year follow-up results of the Nirschl surgical technique for 83 LE patients with 92 elbows. Eighty-four percent of elbows were reported little or no pain, and 92% patients returned to normal elbow range of motion, while 93% of patients could return to their sports. The overall improvement rate was 97%.

Coleman et al. [92] reported their 15 years of experience in treating refractory LE. Amongst 158 consecutive patients treated with open surgery, 94.6% achieved good or excellent results at an average follow-up of 9.8 years. Although the results of open surgery are positive, there is also a risk of instability of the elbow since excessive dissection of the LE may injure the lateral ligaments.

5.2.2. Percutaneous Surgery. Percutaneous surgical approach is mainly used for releasing the common extensor tendon origin at the lateral epicondyle. This technique has been demonstrated to be safe, reliable, and cost-effective [93, 94]. Good midterm outcomes in pain relief have been widely reported with a percutaneous surgical approach [9596]. However, Pierce et al. [97] reported that arthroscopic and open techniques achieved a better prognosis than the percutaneous surgical approach for the treatment of LE.

In recent years, a novel technique termed as ultrasound-guided percutaneous tenotomy (UGPT) has been reported as a safe and effective procedure for the treatment of LE, with durable improvements in terms of symptoms, function, and ultrasound imaging at 1-year follow-up [98]. Barnes et al. [99] reported similar outcomes for 19 patients with chronic, refractory lateral, or medial elbow tendinopathy up to 1 year after the procedure. This novel procedure requires the assistance of the TX1 Tissue Removal System (Tenex Health, Lake Forest, CA), which is performed through an approximately 5 mm incision and uses ultrasonic energy to remove diseased tendon tissue in the damaged region, creating an acute inflammatory reaction and facilitating tendon healing [100].

Seng et al. [101] reported 20 patients with refractory LE treated with UGPT through TX1 Tissue Removal System. The results demonstrated that UGPT procedures could provide sustained pain relief and functional improvement for recalcitrant cases at 3-year follow-up.

Boden et al. [102] compared the effects of PRP and UGPT procedures in the treatment of medial and LE. No statistically significant difference was found between the two treatment modalities. They concluded that PRP and UGPT procedures were both effective in aspect of pain relief and the improvement of function and life quality.

5.2.3. Arthroscopic Surgery. Elbow arthroscopy has been used for the treatment of LE as well. It was first described by Baker and considered as a minimally invasive and efficient surgical procedure [103]. The major advantages of this procedure are quick return to work and the ability to treat the potential intra-articular pathology through visualization of the entire elbow joint. Baker et al. [103] reported that 87% of LE patients undergoing elbow arthroscopy had good long-term follow-up results. Various studies have shown a lower complication rate of arthroscopic treatment than that of open and percutaneous approach [104–106]. However, recent systematic review studies reported a compromise result, demonstrating no differences among open, arthroscopic, and percutaneous surgical techniques for LE regarding the duration of return to work, complication rate, or patient satisfaction [97, 106]. Although there are generally positive results, elbow arthroscopy is thought to have a demanding learning curve with potentially risks of damage to the radial nerve and the lateral ulnar collateral ligament [107–109].

6. Conclusions

LE is a common cause of pain and disability affecting patients aged between 35 and 55 years. Most cases have a self-limiting course of between 12 and 18 months. However, symptoms can be persistent and refractory, thus needing interventional measures. Nonoperative treatment remains the priority and mainstay for LE. Most cases can be well treated with multiple nonoperative treatments, with as high as 90% success rate. However, there is no evidence

suggesting the superiority of nonoperative treatment options. When nonoperative treatment fails, three surgical interventions will be recommended for patients with lateral LE, including open, percutaneous, and arthroscopic approaches. Similarly, no conclusions on the effectiveness of surgical interventions can be reached mainly due to a lack of high-quality evidence and inconsistent outcome measures.

Data Availability

The updated article data in the literature used to support the findings of this study are from previously reported studies and datasets, which have been cited. The processed data are listed as Table 1 and Table 2.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Kun-Long Ma and Hai-Qiang Wang conceived the study together. The manuscript was written by Kun-Long Ma and revised by Hai-Qiang Wang.

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Research Article

Local Infiltration Analgesia with Ropivacaine Improves Postoperative Pain Control in Ankle Fracture Patients: A Retrospective Cohort Study

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Purpose. The study aimed at investigating the effect of local infiltration analgesia (LIA) with ropivacaine on postoperative analgesia for patients undergoing ankle fracture surgery. *Methods*. Consecutive patients were retrospectively included and analysed according to their medical records from July 2014 to August 2018 in a tertiary hospital. Inclusion criteria were patients undergoing open reduction and internal fixation (ORIF) for ankle fractures under general anaesthesia. Moreover, patients should have received intravenous patient-controlled analgesia (iPCA) or LIA + iPCA for postoperative pain relief. The primary outcome indicator was visual analogue scale (VAS) from 8 hours to 48 hours after surgery. Secondary outcomes included postoperative opioid requirement, need for rescue medication, opioid-related adverse effects, and wound complications. *Results*. In total, 89 consecutive patients were included in the study. There were 48 males and 41 females. The average age was 44.6 ± 7.0 years, and VAS scores were significantly lower in the LIA + iPCA group at 8 hours after surgery (1.51 ± 0.58 cm vs 4.77 ± 1.83 cm, $p < 0.001$). The time to first tramadol consumption was longer (580 ± 60.9 minutes vs 281 ± 86.4 minutes, $p < 0.001$), and the number of patients who need tramadol was lower in the LIA + iPCA group (18 vs 26, $p = 0.04$). There was a statistically significant reduction in morphine consumption (25.1 ± 6.3 mg vs 73.4 ± 8.2 mg, $p < 0.001$) and opioid-related side effects in the LIA + iPCA group (4 vs 10, $p = 0.023$). No major wound complications were noted in either group. However, there were 2 cases with superficial wound necrosis in group LIA + iPCA and 3 patients with superficial wound necrosis in group iPCA, and all cured by local wound care. *Conclusions*. The retrospective cohort study indicates that LIA with ropivacaine can provide better early postoperative pain management with a reduction of VAS scores for ankle fracture surgery. Patients receiving wound infiltration also experience decreased opioid consumption, a lower rate of analgesia-related side effects, and comparable wound complication rate.

1. Introduction

Severe postoperative pain has multiple detrimental effects on patients' recovery and quality of life. Patients with poorly managed pain are more prone to experience delay in physical activity and discharge after surgery, interfering with the participation in rehabilitation programs, eventually leading to unsatisfactory outcomes [1]. Updated management of postoperative pain mainly consists of iPCA. Compared with conventional intramuscular injections, iPCA improves postoperative pain relief and potentially reduces the hospital stay by enhancing patients' restoration [2]. Opioids are the most commonly used iPCA drug, with high effectiveness for alleviating moderate-to-severe postoperative pain without ceiling effects [3]. However, these drugs may lead to numerous opioid-related adverse effects, such as pruritus, vomiting, and nausea [3, 4].

Whereas iPCA remains the most commonly used technique for relieving postoperative pain, there has been an increased utilization of local infiltration analgesia (LIA) at the surgical site in the past decade [5]. The resurgence of LIA can be attributed to the availability of long-duration anaesthetics (e.g., ropivacaine and liposome bupivacaine). LIA has been reported to improve the quality of analgesia, decrease the morphine consumption, and reduce hospital stay [6]. However, the efficiency of this technique for postoperative pain relief is not always excellent. Miu al. reported that surgical site infiltration with ropivacaine did not significantly reduce pain or opioid consumption after thyroid surgery [7]. It is believed that the efficacy of local anaesthetics is highly correlated with surgical procedures [8]. Despite the redundancy of studies exploring the efficacy of LIA in various types of surgical procedures, few studies have addressed the use of local anaesthetics in ankle fracture surgery to date.

Therefore, we designed this retrospective cohort study aiming at evaluating the efficacy of LIA and iPCA in patients undergoing isolated ORIF of ankle fractures. The primary outcome was the VAS up to day 2 after surgery. Secondary outcomes included postoperative opioid requirement, need for rescue medication, opioid-related side effects, and wound complications. We hypothesized that the addition of LIA with ropivacaine after ankle fracture surgery would result in adequate pain control, significant decrease in opioid consumption, a lower rate of analgesia-related side effects, and comparable wound complication rate compared iPCA alone.

2. Materials and Methods

2.1. Study Design and Setting. This study was approved by the Institutional Ethics Review Board of Binzhou People's Hospital. We retrospectively reviewed the medical records of all patients who underwent ORIF of ankle fractures at Binzhou People's Hospital between July 2014 and August 2018. We choose this time period because LIA became widely adopted in our hospital as an adjunct to postoperative pain control since 2016. As well, surgical techniques, anaesthesia procedures, and other pain management protocols were unchanged during the study period. Eligible subjects were patients undergoing ankle fracture surgery with general anaesthesia alone at our centre. Exclusion criteria were pathologic or paediatric fracture, open fracture, history of chronic pain, and patients with more than one part of injuries to the body. To eliminate confounding bias related to surgical types, we excluded patients treated only with isolated percutaneous screw fixation. The ankle fractures were classified into three types according to the location of fractures: lateral malleolar fractures, bimalleolar fractures, and trimalleolar fractures. Clinical databases were reviewed to determine demographic characteristics, including age, gender, fracture type, surgery time, and incision length.

2.2. Surgical Techniques. All surgeries were carried out between 7 to 14 days after admission to decrease the incidence of soft tissue complications. Surgical procedures were performed under general anaesthesia. All surgeries were performed by senior Orthopaedic surgeons. The ankle fractures were treated via different operative approaches (e.g., medial approach, lateral approach, posterolateral approach, or modified anteromedial approach) depending on fracture types and the location of major fragments. Fractures were fixed in a standard manner, with screw-plate system, cannulated screws, and tension band wiring.

2.3. Aftercare. Included patients were divided into two groups according to the regimens of postoperative pain relief: either LIA + iPCA or iPCA. The LIA was with ropivacaine (0.5% ropivacaine, total amount was between 15 ml and 30 ml depending on length of surgical incision) injected into the dermis and subcutaneous tissue surrounding the incision. The procedure was conducted by the surgeon before incision was sutured. All patients received the same iPCA pain control regimens. An intravenous patient-controlled analgesia pump was connected to patients postoperatively. The pump contained morphine with a bolus of 0.5 ml and a lockout interval of 10 minutes.

Since the Orthopaedic ward adopts a pain management mode, the nurses routinely evaluate the patient's postoperative pain intensity by a 10-cm horizontal visual analogue scale (VAS, 0 cm = no pain, 10 cm = maximum pain) every eight hours for two days. The VAS is a numeric rating scale tool for assessing pain intensity in which 0 indicates no pain at all and 10 indicates worst pain imaginable. If patients complained of poor pain management despite the use of iPCA, they were administered 50 mg of intramuscular tramadol as rescue medication.

The total dose of morphine administered via iPCA was examined when the pump was removed 2 days after surgery.

Further information concerning opioid-related adverse effects (nausea and vomiting) was collected from patients' medication records. Any complications relating to wound were also recorded.

2.4. Outcome Measures. The primary endpoint variable was the visual analogue scale (VAS) from 8 hours to 48 hours after surgery. Secondary outcome variables included postoperative opioid requirement (morphine via iPCA) and need for rescue medication in the 48 hours after surgery, opioid-related side effects, and wound complications.

2.5. Sample Size. Postoperative VAS score was used to calculate the least sample size. On the basis of previous researches, we used a minimal clinical significant change in VAS score of 1.8 cm [9] and a standard deviation of 1.69 cm [10, 11]. With an alpha level of 0.05, a power of 90%, and an anticipated dropout rate of 20%, the least needed sample size per group was 23 patients.

2.6. Statistical Analysis. IBM SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, USA) was used to perform statistical analysis. Means and standard deviations

(SD) were used to evaluate the continuous variables. The Kolmogorov–Smirnov normality test was used to test whether continuous variables were normally distributed. Depending on the results of the Kolmogorov–Smirnov normality test analysis, either Student's t-test or Man–Whitney U tests were performed. Categorical data and frequencies were analysed by Pearson's chi-square test or Fisher exact tests where appropriate. A p value less than 0.05 was considered statistically significant.

3. Results

Between July 2014 and August 2018, 103 patients underwent ORIF of ankle fractures at our hospital. A total of 89 patients were available for the final analysis of our study. 39 patients (44%) received iPCA alone, 50 patients (54%) received LIA and iPCA. There were no significant differences between the two study groups with respect to age, gender, fracture type, surgery time, and length of surgical incision (Table 1).

In terms of postoperative VAS score, the LIA + iPCA group had significantly lower score (1.51 cm ± 0.58 cm) at 8 hours compared with the iPCA group (4.77 cm ± 0.83 cm) ($p < 0.001$). There was no significant difference between the two treatment groups regarding the VAS score since 16 hours after surgery (Table 2) (Figure 1).

As for postoperative morphine requirement in the 48 hours after surgery, the mean (±SD) total morphine consumption was 25.1 (±6.3) mg for the LIA + iPCA group compared to 73.4 (±8.2) mg for the iPCA group, and this was a significant difference ($p < 0.001$) (Figure 2).

The time to first tramadol consumption was 580 ± 60.9 minutes in the LIA + iPCA group compared to 281 ± 86.4 minutes in the iPCA group ($p < 0.001$) (Figure 3). There was a significant difference between groups on the number of patients who need intramuscular tramadol as rescue medication in the first 48 hours after surgery (18 vs 26 for the LIA + iPCA and iPCA groups, respectively, 36% vs 67%, $p = 0.04$) (Figure 4).

We noted a significant reduced incidence of postoperative nausea and vomiting ($p = 0.023$) in the LIA + iPCA group (8%) compared with patients in the iPCA group (26.6%) (Figure 5).

There were 5 cases of superficial wound necrosis noted after surgery, 2 (4%) in group LIA + iPCA and 3 (7.7%) in group iPCA ($p = 0.45$) (Figure 6). All cases were cured by local wound care without antibiotic application. No major wound complications occurred, and none of the patients needed reoperations for wound complications in both groups during the inhospital stay. We found no adverse drug related events of ropivacaine in the LIA + iPCA group.

4. Discussion

Poorly managed postoperative pain after ankle fracture fixation surgery not only leads to an increase in hospital stay and a decrease in life quality but also elicits worse functional outcome [12–14]. Tremendous efforts have been made on controlling postoperative pain, such as opioid therapy and multimodal analgesic techniques. Amongst these treatment modalities, peripheral nerve block has gained popularity as an adjunct to postoperative pain control in ankle fracture surgery. Blumenthal et al. found that in major ankle surgery operations, a combination of continuous popliteal and femoral nerve block significantly relieved postoperative pain and postoperative morphine consumption [15]. In a systematic review of regional anaesthesia for foot and ankle surgery, Pearce et al. reported that the peripheral nerve block was associated with high levels of patient satisfaction and substantial reduction in hospital costs [16]. Although the peripheral nerve block is effective, technical difficulties related to the placement of catheters and potential complications (such as nerve injury and systemic toxicity) have led to its routine use restricted to a limited number of institutions [3, 17]. Studies have demonstrated that the use of peripheral nerve block to improve postoperative analgesia is very limited worldwide [18, 19].

In recent years, LIA has been increasingly used for postoperative pain relief in a variety of surgical procedures, including abdominal, cardiothoracic, and orthopaedic. The reported advantages of this technique include favourable safety profile, reduced morphine consumption, improved pain control, and simplified technical procedures. Studies have shown that LIA may be an effective alternative to the peripheral nerve block in pain relief Lefevre et al. conducted a prospective cohort study to compare the efficacy of postoperative analgesia with femoral nerve block and LIA in patients undergoing ligament reconstruction surgery [20]. They found that the femoral nerve block is less effective than LIA on early postoperative pain relief. Several studies have shown that LIA results in better pain control, superior knee

Table 1: Demographic data.

Variable	LIA + iPCA ($n = 50$)	iPCA ($n = 39$)	p value
Age (y)*	44.1 ± 6.8	45.3 ± 7.3	0.426
Gender (M/F)†	28/22	20/19	0.658
Surgery time (min)*	101.7 ± 25.1	95.4 ± 20.9	0.210
Incision length(cm)*	15.3 ± 7.2	16.7 ± 5.8	0.325
Number of fractures			
Lateral malleolar fractures†	7	3	0.437
Bimalleolar fractures†	28	20	
Trimalleolar fractures†	15	16	

*Values are expressed as means ± SD. †Values are given as the number of patients. p values based on the independent t-test or Pearson chi-square test.

Table 2: Postoperative VAS scores (cm).

Variable	LIA + iPCA	iPCA	p value
VAS 8 h	1.51 ± 0.58	4.77 ± 1.83	<0.001
VAS 16 h	3.47 ± 1.02	3.63 ± 1.53	0.556
VAS 24 h	3.02 ± 1.14	3.11 ± 1.26	0.725
VAS 32 h	2.65 ± 0.78	2.79 ± 0.92	0.440
VAS 40 h	2.83 ± 0.61	2.79 ± 0.72	0.777
VAS 48 h	2.46 ± 0.59	2.45 ± 0.51	0.933

Values are expressed as means ± SD. p values based on the independent t-test.

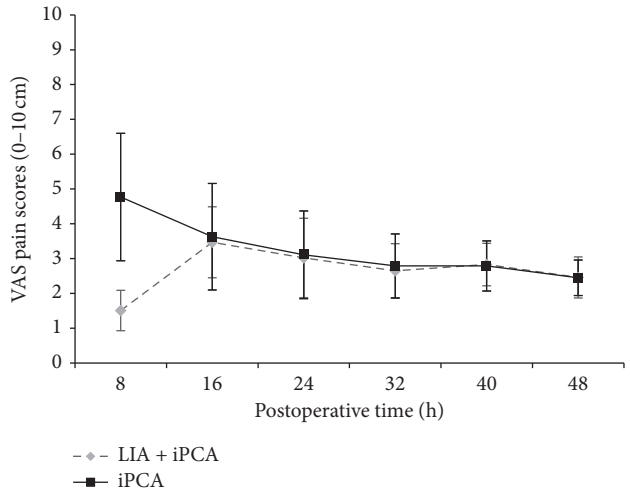

Figure 1: The pain scores (means and SD) after ORIF of ankle fractures, as rated on 10-cm VAS. The LIA + iPCA group had significantly lower VAS score 8 hours after surgery ($p < 0.001$).

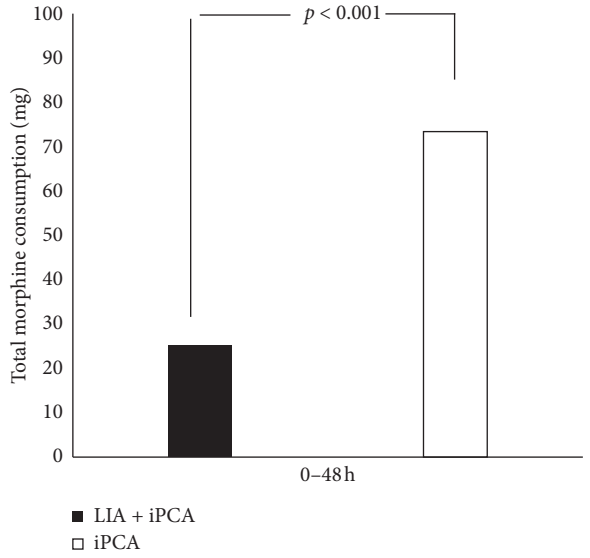

Figure 2: Mean (SD) total morphine consumption in the 48 hours after surgery.

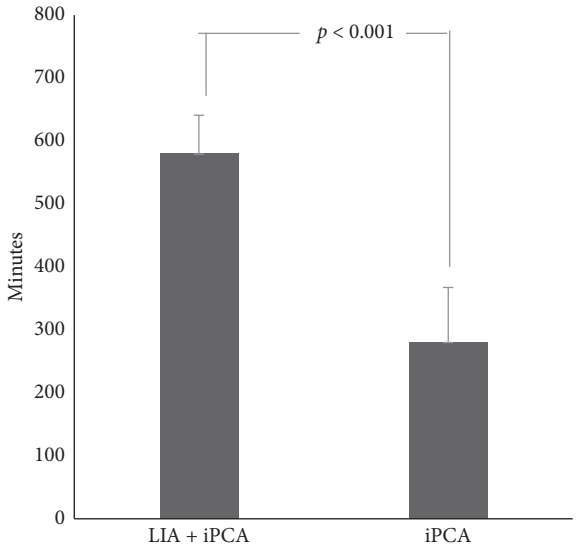

Figure 3: The time to first tramadol consumption after surgery ($p < 0.001$).

function, and more rapid discharge from hospital, comparing with peripheral nerve block techniques of pain relief for both THA and TKA [21–23].

However, the efficacy of local anaesthetics is highly correlated with surgical procedures and local anaesthetic agents. Miu et al. reported that surgical site infiltration with ropivacaine did not significantly reduce pain or opioid consumption after thyroid surgery [6]. To our knowledge, few studies to date have explored the efficacy of LIA with ropivacaine after ankle fracture surgeries.

Ropivacaine is a new amino-amide local anaesthetic agent introduced into clinical use in the early 1990s [24]. It has been advocated as a preferred local anaesthetic for LIA by many investigators [25, 26]. Due to the vasoconstrictive properties of ropivacaine capable of decreasing systemic absorption, it was considered to produce a long-lasting local anaesthetic block that effectively manages postoperative pain [27, 28]. Ropivacaine shows a more favourable clinical safety profile than bupivacaine, with decreased cardiotoxicity and central nervous system toxicity [29–31]. For local infiltration, the recommended dose of ropivacaine should be no more than 200 mg, with a volume less than 100 ml. The does used in this study is 75 to 150 mg. We observed no signs of local or systemic toxic reactions, supporting the administration of bupivacaine.

In this retrospective cohort study, we investigated the postoperative analgesia efficiency of LIA with ropivacaine in ankle fracture surgery. Our results demonstrated that LIA with ropivacaine in ankle fracture surgery was associated with dramatic reduction of early postoperative pain, less opioid consumption, decreased number of patients who need rescue medication, and longer time to first rescue medication after the surgery.

The significant reduction of early postoperative pain scores, less postoperative opioid consumption, and less rescue tramadol administration in the LIA + iPCA group confirms the better postoperative pain control provided by local infiltration analgesia in ankle fracture surgery. Our results are consistent with the reports of Kalogera et al. who reported a significant reduction in patient-controlled analgesia use and rescue medicine requirement after LIA [32]. However, we failed to show any significant reduction in VAS scores with the use of local infiltration analgesia after 8 hours post-surgery. We believed that this could be due to the fact that LIA mainly reduces the immediate postoperative pain. Beatrice et al demonstrated that LIA lower visual analogue scale scores at 1, 3, and 6 hours after surgery, while less morphine was needed even at 12 hours after surgery [4].

There are a number of limitations existing in our study. First, due to the retrospective and nonrandomized design of this study, our results may have been affected by confounding or unrecognized variables. Second, we were unable

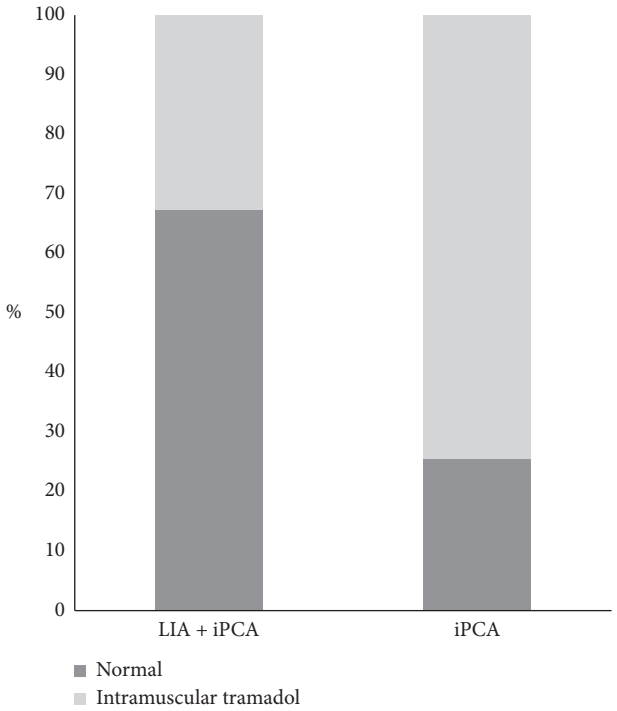

Figure 4: The percentage of patients who need intramuscular tramadol as rescue medication in the first 48 hours after surgery ($p = 0.04$).

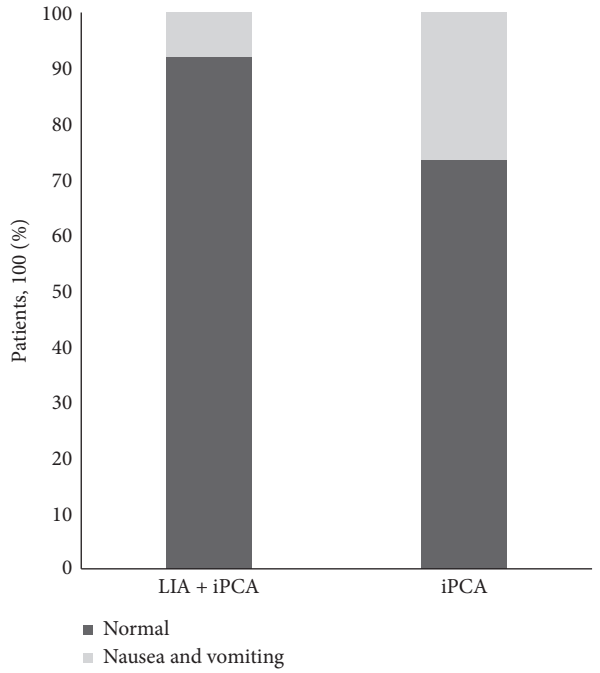

Figure 5: Percentage of nausea and vomiting patients in the 48 hours after surgery ($p = 0.023$).

to record the opioid consumption at every time point that VAS scores were evaluated. Therefore, the LIA action duration was unclear. Additionally, lack of long-term clinical evaluation, such as an assessment of whether LIA is associated with less chronic pain, was conducted in our study.

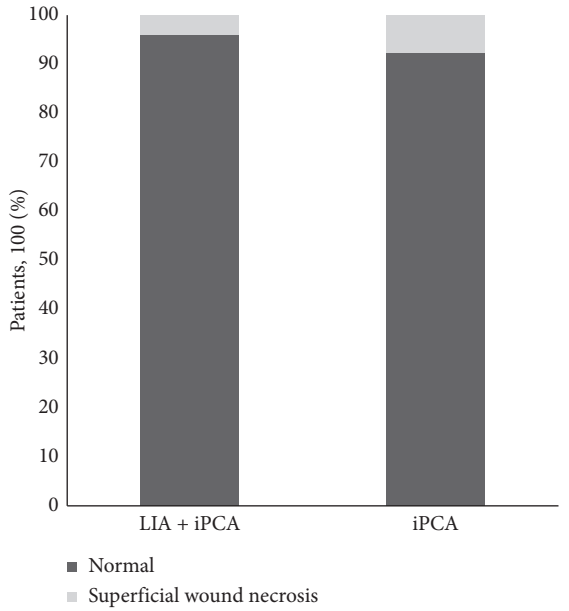

Figure 6: Percentage of superficial wound necrosis patients after surgery ($p = 0.45$).

Nevertheless, our retrospective cohort study presents beneficial line of evidence on the efficiency of LIA in the pain management of ankle fractures.

5. Conclusions

Local infiltration analgesia is a safe and valuable postoperative pain management technique in patients undergoing ankle fracture fixation surgery. Patients who receive wound infiltration can experience a significant decrease in early postoperative pain, reduction in opioid consumption, a low rate of analgesia-related adverse effects, and comparable wound complication rate.

Data Availability

The datasets used to support the current study are available from the authors upon reasonable request.

Disclosure

Bao-Liang Li and Xizhe Liu contributed equally to this work and should be considered co-first authors.

Conflicts of Interest

All the authors declare that they have no conflicts of interest.

Authors' Contributions

Hai-Qiang Wang conceived the study and revised the paper. The authors Bao-Liang Li and Xizhe Liu contributed equally to the article and drafted the manuscript. Wenqian Zhang collected the raw data. Lihua Cui, Mingshan Wang, and Hui Pang performed surgeries. Bao-Liang Li and Hai-Qiang Wang analysed the data. All authors read and approved the manuscript.

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Clinical Study

Predicting Acute Postoperative Pain Trajectories and Long-Term Outcomes of Adolescents after Spinal Fusion Surgery

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Objectives. Acute pain trajectories are associated with long-term outcomes such as persistent pain and functional disability in adults. However, there are limited data on acute postoperative pain trajectories in the pediatric population. The aims of this study were to investigate acute postoperative pain trajectories, their predictors, and their impact on long- term outcomes in adolescents with idiopathic scoliosis. *Methods*. We evaluated the preoperative pain intensity, use of analgesics, psychosocial measures and physical functioning of adolescents scheduled to undergo spinal fusion, and their average 6-hour self-reported pain intensity scores for their entire hospital stay. Six months after surgery, baseline variables were reassessed. We used growth mixture modeling to conduct acute postoperative pain trajectory analysis and to identify predictors of pain trajectories. Generalized linear models were conducted to determine whether acute pain trajectories predict long-term outcomes. *Results*. One hundred and six patients were included in the best-fitted acute pain trajectory model that included four classes that differed in initial pain intensity and rates of change over time. Preoperative pain catastrophizer status and use of analgesics significantly predicted pain trajectory membership. Furthermore, at the 6-month follow-up, patients experiencing moderate-to-severe pain in the acute postoperative period were more likely to report higher levels of pain severity, use pain medication, and miss a greater number of school/work days due to back pain in the last three months. *Discussion*. Preoperative assessment and analyzing the progression of pain in the acute postoperative period can help identify those at risk of negative long-term outcomes after surgery.

1. Introduction

Chronic postsurgical pain is defined as pain that persists for over three months, well after the surgical tissues have healed [1]. Spinal fusion surgery with instrumentation is performed on pediatric patients with adolescent idiopathic scoliosis (AIS), a 3-dimensional deformity of the spine with pronounced single or double curving of the spine [2]. Spinal fusion surgery with instrumentation is an invasive and extensive surgery such that persistent pain is a common postoperative complication [3]. This is highly worrisome as pain can lead to negative consequences such as prolonged emotional distress, long-term pain medication usage, and delayed recovery from surgery [4, 5].

Acute postsurgical pain has been shown to predict chronic pain and opioid use in children and adolescents [6, 7]. Moreover, the persistent nature of postoperative pain may delay rehabilitation [4, 8]. The days following surgery are therefore a critical period where the dynamism of acute pain has an impact on long-term outcomes. Kwan et al. (2017) reported on average pain intensities at 12–24 hour intervals for up to 2 weeks after surgery in a cohort of AIS patients [9]. While pain was considered in relation to time, enormous variability existed in the outcomes at each time point, suggesting heterogeneity of the study population and the presence of multiple subgroups.

Given the heterogeneity present in these populations, patient subgroups with unique pain trajectories may be determined using trajectory analysis. These probabilistic latent class models can capture the progressive change of pain over time [10] that is unique to specific subgroups of individuals. In adults after total hip arthroplasty, Pagé et al. (2016) identified 4 pain trajectories in the acute postoperative period [11]. Importantly, preoperative variables such as pain and anxiety predicted pain trajectory membership. Pain trajectories were in turn associated with long-term outcomes such as pain and functional disability.

Recently, our group conducted acute postoperative opioid consumptions trajectories and their impact on long-term outcomes in a large pediatric cohort of patients undergoing spine surgery [12]. Our findings revealed that patients experiencing mild pain in the acute postoperative period were low-opioid consumers, while those experiencing moderate pain were high-opioid consumers. In addition, the trajectory analysis showed that despite high-opioid consumption, a specific group of adolescents experienced moderate pain that continued to increase up until their hospital discharge (5 days after surgery). In these patients, the analgesic effect of opioids may not have been sufficient enough to provide adequate pain control, thus confirming the need for more personalized pain management. Therefore, the objective of this study was to investigate further this cohort of adolescent patients undergoing spinal fusion surgery by conducting pain trajectory analyses to evaluate if specific acute postoperative pain experiences exist in these patients, to assess the impact of unique acute postoperative pain experiences on long-term outcomes, and to identify predictors of trajectory membership to different postoperative pain experiences.

2. Materials and Methods

2.1. Study Design. The analyses conducted were part of a larger study approved by the Institutional Review Board of McGill University (A08-M71-17B). Adolescents between 10 and 18 years old with idiopathic scoliosis and scheduled to undergo posterior spinal fusion surgery were prospectively recruited and consented at the Shriners Hospitals for Children-Canada between 2013 and 2018. Exclusion criteria included children unable to speak, write, or read English or French, children diagnosed with developmental delay, and children with major chronic medical conditions. Study variables were assessed at baseline (7–10 days before surgery), at postoperative hours 1 to 120 from the moment the patient leaves the operating room (averaged every 6 hours), and at follow-up 6 months after surgery.

2.2. Questionnaires. At baseline, patients completed the Pain Catastrophizing Scale-child (PCS-c) questionnaire to assess their mental state in relation to actual and/or anticipated pain. Patients who received a total score of 30 or greater out of 52 on the PCS-c questionnaire were considered pain catastrophizers [13]. Preoperatively, patients completed the Scoliosis Research Society-30 (SRS-30) questionnaire which has been validated to assess the quality of life and outcomes for individuals with scoliosis scheduled to undergo spinal surgery [14]. Given that pain is the primary outcome variable, we evaluated specific questions separately. These questions included (1) pain experienced in the past 6 months, (2) pain experienced in the last month, (3) pain experienced at rest, (4) current level of activity, (5) sick days from work/school over the past 3 months due to back pain, and (6) medication usage for pain from the following options: none, nonopioids (e.g., Tylenol), or opioids (e.g., Dilaudid). The same SRS-30 variables were reassessed at the patients' 6-month follow-up appointment, instead of a numerical rating scale (NRS) for pain because chronic pain is defined as persistent and/or recurrent pain lasting at least 3 months or longer [1], and there is a lack of evidence for a recommended self-report measure of chronic pain in children and adolescents [15]. The separate questions in the SRS-30 capture the experience of the pain within the last 6 months after their surgery.

2.3. Perioperative Anesthesia and Analgesia Care. Perioperative anesthesia was standardized for the study. Intraoperatively, patients received intravenous (IV) propofol, remifentanil/sufentanil/fentanyl, ketamine, and dexamethasone. After induction, patients received an intrathecal injection of morphine (5 μg/kg). Postoperatively, all patients received IV patient-controlled analgesia (PCA) (1 : 1) morphine/ketamine of 20 mcg/kg bolus on demand with a 6-minute lockout interval and a maximum dose per hour of 0,1–0,4 mg/kg/h available upon arrival at the postanesthesia care unit (PACU) till the morning of postoperative day three. Throughout the acute postoperative period, acetaminophen and ketorolac were available on a scheduled and PRN basis. Furthermore, opiates were available after PCA on a scheduled and PRN basis.

2.4. Acute Postoperative Pain Assessment. Self-reported pain intensity was assessed by a bedside nurse during the in-hospital period using the NRS 0–10, where 0 indicates no pain, 1–3 indicates mild pain, 4–6 indicates moderate pain, >7 indicates severe pain, and 10 indicates the worst pain imaginable. The NRS has been validated in the pediatric population and is strongly recommended as a self-report measure for acute pain intensity for children and adolescents between 6 and 18 years old [15, 16]. Average self-reported pain intensity was extracted every hour during the acute

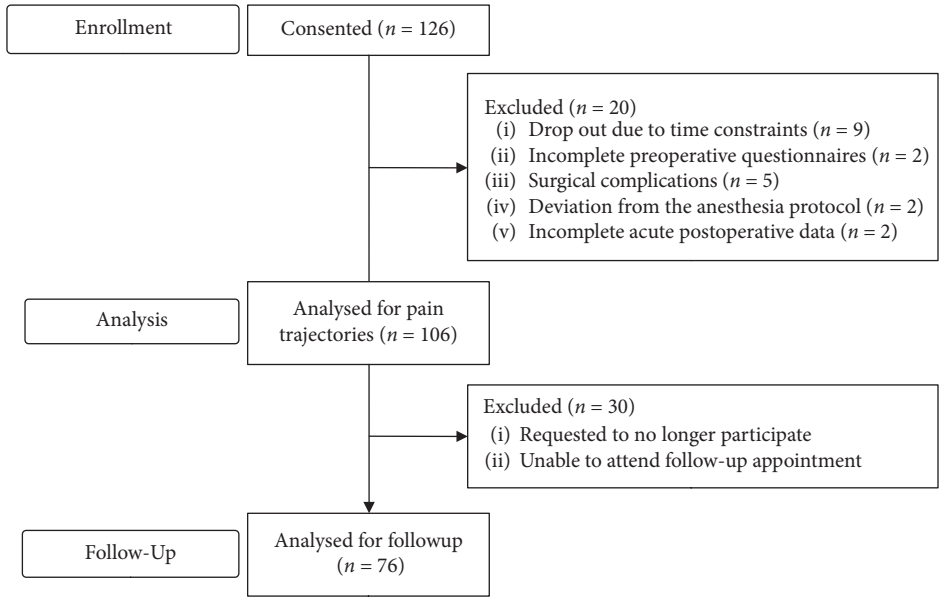

Figure 1: Study flowchart of cohort for the analysis.

postoperative period from the patients' electronic medical charts and average postoperative 6-hour pain intensities were calculated for pain trajectory analysis.

2.5. Statistical Analysis. Growth mixture modeling (GMM) was used to perform acute postoperative pain trajectory analyses similar to previous studies [11, 12, 17]. GMM considers interindividual variability in intraindividual patterns of longitudinal data to identify and model trajectories of unique subgroups within the sample despite possible missing data [10]. Average 6-hour pain intensities were used as the basis of the analyses. Six linear and six linear + quadratic trajectory models were tested using the heterogeneous linear mixed effects (hlme) function of the latent class mixed model (lcmm) package in R version 3.2.1. Selection of the best trajectory model was based on multiple criteria: low values for Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) indicating better fit, high entropy (>80%) reflecting high confidence of group membership, a minimum trajectory class size of 5% of total study population, and parsimony [10, 11, 17]. After the best trajectory model was selected, using the Wald test, pre- and intraoperative factors known to play a predictive role in the acute postoperative pain experience (age, sex, pain medication use, pain severity, pain catastrophizer status, functional activity, largest Cobb angle, number of vertebrae fused, surgery length, blood loss, and intraoperative anesthetic doses) [18, 19] were individually tested as predictors of trajectory membership in the model. Significant variables ($p < 0.05$) were included in the final model. The required minimum sample size of 100 for GMM was based on the theoretical foundations of the study, characteristics of the data, measurement reliability, and group differences [10, 20].

With R version 3.2.1, chi-square test or Kruskal–Wallis H test followed by appropriate post hoc tests was used accordingly to investigate significant differences for reported pain intensity between postoperative days and for perioperative variables between pain trajectory membership. Generalized linear models were conducted to evaluate whether the pain trajectories predict long-term outcomes.

3. Results

3.1. Study Population. One hundred and twenty-six patients consented to participate in the study. However, as depicted in Figure 1, the study population consisted of 106 patients with a mean age of 15.4 ± 2.0 years. Twenty-three patients (25%) were considered to be pain catastrophizers based on their total score on the PSC-c. Within the last 6 months prior to surgery, 9% of the patients reported no pain, 32% experienced mild pain, and 59% experienced moderate-to-severe pain. Additional descriptive statistics are presented in Table 1.

The study cohort experienced constant pain for the duration of the acute postoperative period (Figure 2). A significant increase in average pain intensity in our study cohort was only observed between postoperative days 1 and 4 ($p = 0.0046$).

3.2. Pain Trajectories. Goodness-of-fit indices for the twelve tested trajectory models are presented in Table 2. The simplest model with the best fit (AIC = 6959.67; BIC = 7002.28) contained 4 trajectories, a quadratic term, entropies of >0.8 for 92% of patients, and a smallest class size of 24% of the total study population. Pain trajectory 1 ($n = 26$) and pain trajectory 2 ($n = 29$) were characterized by patients who reported mild and mild-to-moderate pain immediately following surgery, respectively, that remained relatively constant throughout the acute postoperative period. Patients in trajectory 3 ($n = 26$) also reported mild-to-moderate pain immediately following surgery but increased steadily to moderate pain by postoperative day five. Pain trajectory 4

Table 1: Preoperative and intraoperative variables of study patients ($n = 106$).

Preoperative and intraoperative variables	Total patient sample ($n = 106$)	Pain trajectory			
		1 ($n = 26$)	2 ($n = 29$)	3 ($n = 26$)	4 ($n = 25$)
Demographics					
Age, years	15.4 (2.0)	15.7 (2.0)	15.5 (2.1)	14.9 (1.6)	15.4 (2.2)
Sex, *n* (%)					
Male	25 (23.6)	8 (30.8)	7 (24.1)	8 (30.8)	2 (8.0)
Female	81 (76.4)	18 (69.2)	22 (75.9)	18 (69.2)	23 (92.0)
Largest cobb angle, °	56.8 (12.6)	54.2 (14.3)	55.0 (13.1)	60.7 (11.5)	57.6 (10.6)
Pain catastrophizing status					
Total PCS-c score	22.9 (9.8)				
#Pain catastrophizers, *n* (%)					
No	80 (75.5)	24 (92.3)	20 (69.0)	21 (80.8)	15 (60.0)
Yes	26 (24.5)	2 (7.7)	9 (31.0)	5 (19.2)	10 (40.0)
SRS-30 variables, *n* (%)					
#Pain in last 6 months					
None	9 (8.5)	4 (15.4)	0 (0)	2 (7.7)	3 (12.0)
Mild	34 (32.1)	16 (61.5)	8 (27.6)	4 (15.4)	6 (24.0)
Moderate to severe	62 (58.5)	6 (23.1)	21 (72.4)	19 (73.1)	16 (64.0)
Pain in last 1 month					
None	13 (12.3)	7 (26.9)	2 (6.9)	2 (7.7)	2 (8.0)
Mild	29 (27.4)	10 (38.5)	6 (20.7)	6 (23.1)	7 (28.0)
Moderate to severe	64 (60.4)	9 (34.6)	21 (72.4)	18 (69.2)	16 (64.0)
Back pain at rest					
No	17 (16.0)	5 (19.2)	4 (13.8)	6 (23.1)	2 (8.0)
Yes	89 (84.0)	21 (80.8)	25 (86.2)	20 (77)	23 (92.0)
Current level of activity					
Full activities without restriction	45 (42.5)	13 (50)	13 (44.8)	11 (42.3)	8 (32.0)
Light-to-moderate activity	45 (42.5)	9 (34.6)	11 (37.9)	9 (34.6)	16 (64.0)
No activity	16 (15.1)	4 (15.4)	5 (17.2)	6 (23.1)	1 (4.0)
Missed school/work days due to back pain in last 3 months					
0	75 (70.8)	21 (80.8)	22 (75.9)	16 (61.5)	16 (64.0)
1–3	17 (16.0)	3 (11.5)	4 (13.8)	4 (15.4)	6 (25.0)
4 or more	13 (12.3)	2 (7.7)	3 (10.3)	6 (23.1)	2 (8.0)
#Medications for pain, *n* (%)					
None	78 (73.6)	24 (92.3)	23 (79.3)	15 (57.7)	16 (64.0)
Yes					
Nonopioids	22 (20.8)	2 (7.7)	4 (13.8)	9 (34.6)	7 (28.0)
Opioids	6 (5.7)	0 (0)	2 (6.9)	2 (7.7)	2 (8.0)
Anesthetic variables					
Remifentanil, mg/kg	45.6 (22.9)	37.0 (23.3)	45.5 (21.2)	51.7 (23.2)	48.5 (22.4)
Sufentanil, mg/kg ($n = 28$)	0.56 (0.52)	0.26 (0.14)	0.67 (0.65)	0.45 (0.37)	0.79 (0.65)
Fentanyl, mg/kg ($n = 14$)	2.30 (0.55)	2.7 (1.3)	2.2 (0.45)	2.5 (0.35)	2.0 (0.38)
Dexamethasone, mg/kg	0.11 (0.04)	0.12 (0.03)	0.10 (0.01)	0.12 (0.04)	0.12 (0.04)
Ketamine, mg/kg	0.70 (0.57)	0.70 (0.45)	0.73 (0.52)	0.74 (0.50)	0.72 (0.81)
Spinal morphine, mg/kg	5.40 (2.97)	5.28 (2.77)	5.96 (3.92)	5.11 (1.62)	5.19 (3.05)
Total intraoperative opioids (equivalents of morphine), mg/kg	36.1 (17.0)	29.5 (17.7)	36.3 (15.8)	40.7 (17.1)	38.3 (16.6)
Surgical variables					
Surgery length, minutes	264.6 (76.4)	254.7 (71.6)	260.3 (75.8)	277.3 (76.5)	266.5 (84.1)
Blood loss, mL	761.1 (441.2)	769.5 (437.4)	790.5 (509.1)	721.7 (300.0)	759.5 (503.3)
Number of fused vertebrae	10.6 (2.6)	10.2 (2.8)	10.0 (2.9)	11.5 (1.6)	10.9 (2.5)

Data are presented as mean (SD), unless otherwise specified. PCSc: Pain Catastrophizing Scalechild questionnaire, SRS-30: Scoliosis Research Society questionnaire: version 30. #Significant association observed between the variable and pain trajectory membership.

($n = 25$) consisted of patients who reported moderate pain immediately following surgery that remained relatively constant throughout the acute postoperative period. Baseline pain medication use and baseline pain catastrophizing status were significant predictors of trajectory membership in the simplest model and were included in the final model (AIC = 6957.64; BIC = 7016.24) presented in Figure 3. The logarithmic odds that patients were taking pain medication prior to surgery and a member of trajectory 1 instead of trajectory 4 was -1.80 ± 0.86 (Wald $\chi^2 = -2.1$; $p = 0.036$).

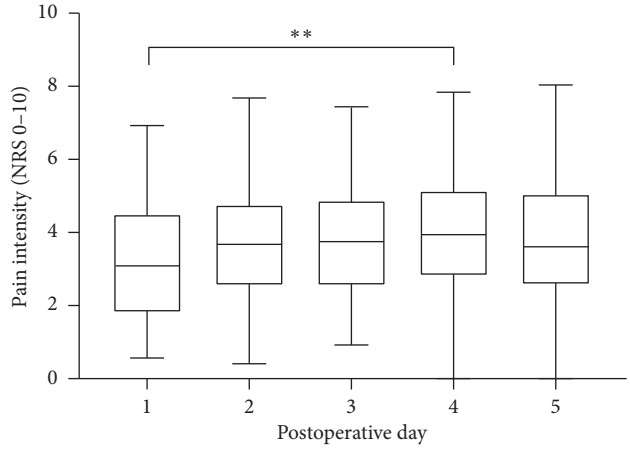

Figure 2: Acute postoperative median pain intensity of patients ($n = 106$). Data are presented as median (middle line), interquartile range (box), and range (whiskers). NRS: numerical rating scale.

Table 2: Goodness of fit indices for the twelve tested trajectory models.

Number of trajectories	Linear			Linear + quadratic		
	AIC	BIC	SC (%)	AIC	BIC	SC (%)
1	8170.13	8178.12	100	8159.95	8170.6	100
2	7346.11	7362.09	43.4	7328.15	7349.46	43.4
3	7057.98	7081.95	26.4	7035.83	7067.79	26.4
4	6982.58	7014.54	23.6	6959.67*	7002.28*	23.6*
5	6933.27	6973.22	11.3	6915.3	6968.57	11.3
6	6908.45	6956.39	7.5	6879.58	6943.5	9.4

*The model with the best fit. AIC: Akaike Information Criterion. BIC: Bayesian Information Criterion. SC: smallest class size.

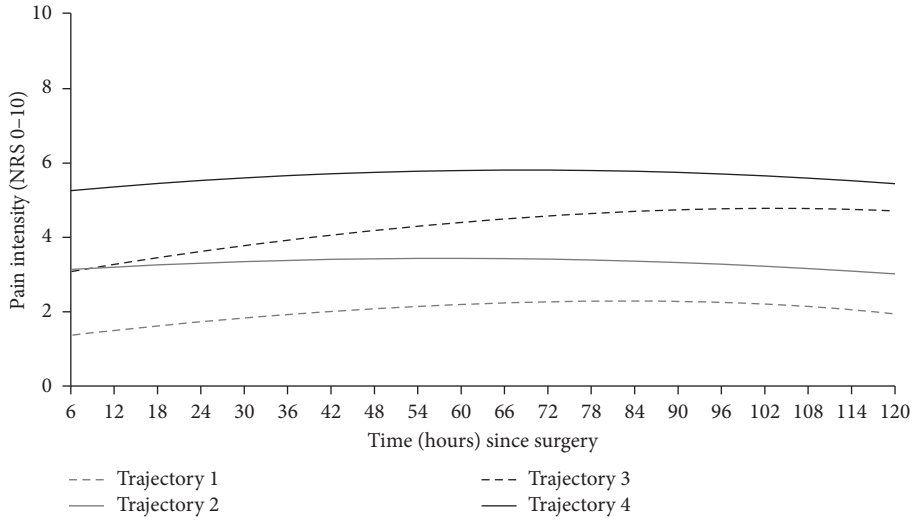

Figure 3: Acute postoperative pain trajectories: trajectory 1 ($n = 26$), trajectory 2 ($n = 29$), trajectory 3 ($n = 26$), and trajectory 4 ($n = 25$). NRS: numerical rating scale.

Furthermore, the logarithmic odds that patients are pain catastrophizers and a member of trajectory 1 instead of trajectory 4 was -1.90 ± 0.82 (Wald $\chi^2 = -2.3$; $p = 0.022$). No significant differences were observed between pain trajectories regarding continuous preoperative and intraoperative variables. A significant association was observed between pain trajectory membership and baseline pain catastrophizing status ($\chi^2 = 8.3$; $p = 0.04$), pain severity in the last six months before the surgery ($\chi^2 = 21.8$; $p = 0.001$), or baseline pain medication use ($\chi^2 = 9.7$; $p = 0.02$). The intercepts, linear, and quadratic slopes of each trajectory and the predicted and raw pain intensity values of each acute

postoperative day are presented in Table 3. Results from the univariate ANOVA of the observed means for each trajectory show that the mean 24-hour pain intensity of each trajectory significantly differed from each other, except between trajectory 2 and trajectory 3 on postoperative day 1 (Table 3).

3.3. Prediction of Long-Term Outcomes. Out of the 106 patients, 30 patients were loss to follow-up resulting in the 6-month outcome variables of 76 patients being analyzed. Long-term outcomes after surgery according to pain trajectory can be found in Table 4. A significant association was observed between pain trajectory membership and the pain severity within the last six months postoperatively ($\chi^2 = 15.8$; $p = 0.02$), the pain severity within the last month from their follow-up appointment ($\chi^2 = 14.7$; $p = 0.02$), the presence of back pain at rest ($\chi^2 = 11.9$; $p = 0.008$), and the number of missed days due to back pain in the last three months ($\chi^2 = 14.6$; $p = 0.02$).

The results from the generalized linear models are presented in Table 5. At the patient's 6-month follow-up, the results display that acute postoperative pain trajectories significantly predicted postoperative 6-month pain experience, the pain experience in the last month, whether they experience back pain at rest, the number of missed school/work days due to back pain in the last three months, and pain medication use (Table 5). Patients experiencing moderate pain in the acute postoperative period were more likely to report higher levels of pain severity, use pain medication, and miss a greater number of school/work days due to back pain in the last three months at their 6-month follow-up appointment.

4. Discussion

Four unique acute pain trajectories were identified that differed in their initial pain intensity and rate of change over time. A moderate-to-severe pain intensity throughout the acute postoperative period predicted negative long-term outcomes. Self-reported pain catastrophizing status and the use of pain medication before surgery predicted higher acute postoperative pain trajectory membership.

In comparison to traditional single and/or mean measures of pain, examining pain in relation to time by trajectory analysis may offer more insight on the impact of different acute postoperative experiences on long-term outcomes [6]. Four unique acute pain trajectories were identified. Visually, patients in trajectories 1, 2, and 4 reported constant pain across the acute postoperative period, while patients in trajectory 3 reported pain that increased with time. This is one of the few studies to conduct probabilistic latent class models which capture the progressive change of pain over time in the acute postoperative period in the pediatric population. In accordance with adult findings following total hip arthroplasty, Pagé et al. (2016) also identified 4 acute postoperative pain trajectories. Interestingly, their study revealed 3 trajectories whose members reported pain that decreased as time progressed and one trajectory whose members reported constant pain [11]. The difference in trajectory patterns between the two studies may be explained by different patient populations, age of study participants, and different surgical scenario [3]. Overall, our findings suggest that pediatric patients experience pain that evolves with time in the acute postoperative period. Furthermore, the identification of multiple trajectories illustrates the presence of latent subgroups in the pediatric population with interindividual differences in pain experience after surgery. Knowledge of these differences warrants the need to consider the variability on pain perception and pain profile following specific surgical procedures and to manage acute postoperative pain as a dynamic event [21].

Acute pain trajectories significantly predicted back pain severity experienced 6 months after surgery. In a preliminary study, our group demonstrated that pain intensity on postoperative days 1 and 2 after a spinal fusion surgery was predictive of pain intensity six weeks after surgery [22]. Although interesting, the follow-up period was too short to make conclusions regarding chronic postsurgical pain. Other studies have shown that modeling acute pain trajectories can give insight on pain chronification. Chidambaran et al. (2017) reported that AIS patients who reported chronic pain 3 months and persistent pain one year after spinal fusion surgery had higher pain trends in the acute postoperative period [23]. Therefore, the acute postoperative period may be a crucial point of intervention to prevent long-term postsurgical pain in AIS patients. Interestingly, acute pain trajectory membership predicted the number of missed school/work days due to back pain, but not the current level of activity at the patients' 6-month follow-up appointment. It is plausible that while acute postoperative pain does not predict long-term physical functioning, it may predict the effect of pain on daily functioning/quality of life. Acute pain trajectory membership also predicted the use of pain medications 6 months after surgery. Consistent with our findings, Fassoulaki et al. (2008) found that, in adult patients after breast cancer surgery, average pain intensity in the first nine postoperative hours significantly predicted use of analgesics 6 months after surgery [24]. However, the latter study used a single average pain intensity measure as opposed to a continuous measure of pain by our study. Therefore, analyzing interindividual variability in the acute postoperative period in pediatrics may give more insight on long-term outcomes and the acute period is a crucial period for intervention to prevent persistent pain and long-term pain medication use. Clinicians should manage pain as a dynamic event in the acute postoperative period and identify patients at risk of negative long-term outcomes to intervene early to prevent chronic postsurgical pain.

Use of pain medications prior to surgery predicted pain trajectory membership. Specifically, patients reporting the highest pain ratings were more likely to have been consuming opioids or nonopioid pain medications at baseline than patients reporting the lowest pain ratings. In an adult patient population undergoing total knee arthroplasty, prolonged (>4 weeks) opioid use before surgery resulted in greater pain in the first 6 days following surgery at rest and

Table 3: Description of final pain trajectory model, predicted and raw acute postoperative pain intensity values.

Pain trajectory		Slopes			Predicted values (NRS 0–10)					Raw values (NRS 0–10), mean (SD)				
	n	Intercept	Linear	Quadratic	POD1	POD2	POD3	POD4	POD5	POD1	POD2	POD3	POD4	POD45
1	26	1.21162	0.0277	−0.00018	1.77	2.13	2.28	2.21	1.95	1.57 (0.66)[a,b,c]	1.88 (0.71)[a,b,c]	1.94 (0.49)[a,b,c]	2.40 (1.18)[a,b,c]	1.91 (0.72)[a,b,c]
2	29	3.06402	0.0128	−0.00011	3.31	3.42	3.42	3.28	3.02	3.10 (1.03)[a,e]	3.44 (0.67)[a,d,e]	3.33 (0.55)[a,d,e]	3.32 (0.73)[a,d,e]	3.09 (0.66)[a,d,e]
3	26	2.85109	0.0348	−0.00016	3.59	4.15	4.52	4.71	4.72	3.21 (1.06)[b,f]	4.07 (0.83)[b,d,f]	4.25 (0.64)[b,d,f]	4.88 (0.85)[b,d,f]	4.75 (1.06)[b,d,f]
4	25	5.15001	0.0192	−0.00014	5.53	5.75	5.81	5.71	5.44	5.40 (0.90)[c,e,f]	5.63 (0.85)[c,e,f]	5.74 (0.69)[c,e,f]	5.82 (1.26)[c,e,f]	5.65 (1.18)[c,e,f]
										$F = 73.2$	$F = 104.9$	$F = 182.3$	$F = 58.4$	$F = 84.2$
										$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

Table 4: Long-term outcomes according to pain trajectory membership.

Long-term outcomes	Pain trajectory			
	1 ($n = 19$)	2 ($n = 22$)	3 ($n = 17$)	4 ($n = 18$)
6-month SRS-30 variables, n (%)				
#Pain in last 6 months				
None	9 (47)	2 (9)	2 (12)	2 (11)
Mild	8 (42)	8 (36)	7 (41)	7 (39)
Moderate to severe	2 (11)	12 (55)	8 (47)	9 (50)
#Pain in last 1 month				
None	11 (61)	7 (32)	3 (18)	3 (17)
Mild	8 (44)	8 (36)	9 (53)	7 (39)
Moderate to severe	0 (0)	7 (32)	5 (29)	8 (44)
#Back pain at rest				
No	11 (58)	9 (41)	5 (29)	1 (6)
Yes	8 (42)	13 (59)	12 (71)	17 (94)
Current level of activity				
Full activities without restriction	3 (16)	1 (5)	2 (12)	1 (6)
Light-to-moderate activity	15 (79)	19 (86)	13 (76)	15 (83)
No activity	1 (5)	2 (9)	2 (12)	2 (11)
#Missed school/work days due to back pain in last 3 months				
0	16 (84)	19 (90)	11 (65)	8 (45)
1–3	3 (16)	0 (0)	3 (17.5)	6 (33)
4 or more	0 (0)	2 (10)	3 (17.5)	4 (22)
Medications for pain				
None	16 (84)	15 (68)	11 (65)	9 (50)
Yes				
Nonopioids	3 (16)	6 (27)	6 (35)	6 (33)
Opioids	0 (0)	1 (5)	0 (0)	3 (17)

SRS-30, Scoliosis Research Society questionnaire, version 30. #Significant association observed between the variable and pain trajectory membership.

Table 5: Prediction of long-term outcomes.

Long-term outcomes independent variable	Pain in last 6 months	Pain in last month	Back pain at rest	Current level of activity	Missed school/ work days due to back pain in last 3 months	Pain medication use
Pain trajectory 1	$b \pm$ SE (p value)	$b \pm$ SE (p value	$b \pm$ SE (p value	$b \pm$ SE (p value)	$b \pm$ SE (p value)	$b \pm$ SE (p value)
Pain trajectory 2	2.20 ± 0.87 (0.012)	1.08 ± 0.65 (0.098)	0.69 ± 0.64 (0.28)	1.37 ± 1.20 (0.25)	-0.58 ± 0.97 (0.55)	0.92 ± 0.78 (0.24)
Pain trajectory 3	1.91 ± 0.88 (0.030)	1.86 ± 0.79 (0.018)	1.19 ± 0.71 (0.091	0.34 ± 0.98 (0.73)	1.07 ± 0.81 (0.19)	1.07 ± 0.81 (0.19)
Pain trajectory 4	1.97 ± 0.88 (0.025)	1.93 ± 0.78 (0.014)	3.15 ± 1.13 (0.0053)	1.16 ± 1.21 (0.34)	1.90 ± 0.79 (0.016)	1.67 ± 0.79 (0.033)

while walking than opioid-free patients [25]. Furthermore, a recent meta-analysis on preoperative predictors of poor acute postoperative pain control revealed that preoperative analgesia use was a significant predictor [26]. In our study, pain medications included opioids and nonopioids, where only 5.6% of AIS patients were opioid consumers prior to surgery. We hypothesize that our results may be explained by the phenomenon of opioid-induced hyperalgesia before surgery, where opioid use leads to a decrease in pain threshold and thus a greater experience of pain [27]. The patients who were taking pain medication prior to their surgery may have led to the priming of their nervous system to subsequent pain during the acute postoperative period [28]. However, due to the low proportion of patients consuming opioids preoperatively, it is difficult to correlate our results with this hypothesis. Nevertheless, preoperative intervention to decrease pain medication intake such as emphasizing on nonpharmacological interventions may be suggested instead to reduce the risk of high acute postoperative pain.

Psychological factors are known to affect an individual's pain experience [29]. Pain catastrophizing status was a predictor of trajectory membership such that patients experiencing moderate-to-severe acute postoperative pain were more likely to be pain catastrophizers than patients experiencing mild acute postoperative pain. Although Ferland et al. (2017) could not identify a predictive effect of trait anxiety of AIS patients, or their preoperative anxiety state, on postoperative pain intensity [30], Connelly et al. (2014) reported that AIS patients with greater pain coping efficacy before surgery had a more rapid rate in pain intensity improvement [31]. More evidence shows the importance of mental state before surgery as a major predictor of postoperative pain in pediatrics [32, 33]. It was recently discussed that pain catastrophizing can have an impact on a patient's postoperative pain management through their use

of patient-controlled analgesia (PCA) [34]. The acute postoperative period is an important time period where the patient may feel like they are not in control when in pain. LaMontagne et al. (2003) investigated the effect of cognitive-behavioral intervention on adolescents' pain following spinal fusion surgery. In their study, they observed that videotape intervention combining information of the surgical procedure, the sensations felt after surgery, and information on coping behaviors led to less postoperative pain in adolescents with high preoperative anxiety [35]. Overall, our results suggest that it is primordial in pediatrics to identify before their surgery date pain catastrophizers who are considered to possess maladaptive coping behaviors [29] and intervene via pain counselling/education to reduce the risk of high postoperative pain intensity.

A limitation of the present study was that only the patient's psychological factors were evaluated in isolation to the parental ones. Studies have shown that parental psychological factors also play an important role in their children's response to pain [36, 37]. Rabbitts et al. (2014; 2015) observed that parental pain catastrophizing had a significant impact on pain trajectory membership, such that higher parental pain catastrophizing led to greater pain intensity in the acute postoperative period and late recovery after surgery [38, 39]. Another limitation of this study may be the process in which data were collected as the pain ratings found in the medical charts at an interval of 6 hours were averaged. Trajectories 1–2 and trajectories 3–4 are clinically similar representing mild and moderate pain, respectively, in the acute postoperative period. This may be due to the variability in pain response in the acute postoperative period within each 6-hour interval. Future work evaluating the dynamism of pain intensity in the acute postoperative period with different time intervals should be conducted. Another limitation was the small size of the trajectory groups and the number of patients lost to follow-up at 6 months after surgery. This limitation may have led some pre- and/or intraoperative factors to not have a significant predictive role in trajectory analyses and decreases the predictive effect of acute postoperative pain trajectories on long-term outcomes. Furthermore, increasing the follow-up period to one or two years would be ideal to determine whether the acute postoperative period predicts persistent postsurgical pain in pediatrics similarly to previous studies [3, 23, 40]. Increasing the follow-up period is important in our cohort of patients, because pain may only become present 1 year after spinal fusion surgery in AIS patients [41]. Addressing this issue is important and future work should be conducted with additional patients to improve the strength of statistical analysis of long-term outcomes.

5. Conclusions

In conclusion, in this study of AIS patients, four acute postoperative pain trajectories were identified. Pain catastrophizer status and pain medication use before surgery are significant predictors of acute postoperative pain trajectories. In turn, pain experience in the acute postoperative period has an impact on patients' postoperative 6-month pain experience, number of missed school/work days due to back pain in the last three months, and pain medication use at their 6-month follow-up appointment. Therefore, preoperative assessment of surgical AIS patients and analyzing their progression of pain in the acute postoperative period can help identify who is at risk of negative long-term outcomes after surgery and allow clinicians to intervene early to prevent persistent postsurgical pain and its negative impact on the daily lives of the patients.

Data Availability

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

Conflicts of Interest

The authors declare no conflicts of interest.

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Research Article

Numbness and Weakness Recovered at a Less Extent in Patients with Lumbar Disc Herniation after Percutaneous Endoscopic Lumbar Discectomy

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Background. Patients with lumbar disc herniation (LDH) may present with motor disorders and various sensory disorders, among which pain and numbness are the most common ones. Percutaneous endoscopic lumbar discectomy (PELD) is reported to be both safe and effective. However, most of the previous studies focused on the recovery of pain, and the relief extent of numbness and weakness has rarely been reported. The Sciatica Bothersomeness Index (SBI) is a self-assessment tool for LDH patients. It has demonstrated acceptable reliability, construct validity, and responsiveness. *Objectives*. Our aim was to explore the curative effect of percutaneous endoscopic lumbar discectomy and to compare the various extent of relief among pain, numbness, and weakness. *Methods*. The medical records of patients admitted for LDH from September 2016 to December 2018 were collected, and the patients were followed up for 3 months to evaluate the relief of their clinical symptoms. Preoperative and postoperative total scores and subitem scores of SBI were compared to evaluate the relief of pain, numbness, and weakness. Surgical outcomes of PELD were evaluated by the Nakai score, and patients were divided into two groups accordingly, which were the relief group (excellent and good in the Nakai score) and the less relief group (fair and poor in the Nakai score). Risk factors for PELD outcomes and preoperative presence of numbness and/or weakness were analyzed by the logistic model, and p value less than 0.05 was considered significant. *Results*. A total of 86 patients met the inclusion criteria and acquired 3 months follow-up. Relief extent of pain, numbness, and weakness, was 82%, 41%, and 21%, respectively. There were 71 cases in the relief group and 15 cases in the less relief group. Results of the logistic regression analysis showed that the preoperative pain score of SBI ($p = 0.002$; OR: 1.647 (1.199–2.261)) was a relatively independent risk factor for PELD outcomes, and multiplicativity of duration of preoperative symptoms and imaging grade [$p = 0.004$; OR: 1.015 (1.005–1.026)] was a relatively independent risk factor for preoperative presence of numbness and/or weakness. *Conclusions*. PELD had a good curative effect in the treatment of LDH. Patients of LDH recovered best from pain, followed by numbness and weakness after PELD. Higher level of patients self-reported preoperative pain indicated a better surgical outcome for LDH patients, and preoperative long duration of symptoms together with a severe compression of nerve root significantly increased the risk of presenting numbness and/or weakness.

1. Introduction

Patients with lumbar disc herniation (LDH) usually present with symptoms like pain, numbness, and weakness, which have a negative influence on their social functions [1, 2]. Percutaneous endoscopic lumbar discectomy (PELD) first appeared in 1992 [3] and has been widely used in clinical practice for lumbar spine diseases due to less invasiveness and faster recovery compared with traditional surgery [4–6]. Many studies have reported that PELD could achieve comparative therapeutic effect as traditional surgery. However, most previous studies applied the Japanese Orthopaedic Association (JOA) score, the Visual Analog Scale for Pain (VAS Pain), the Oswestry Disability Index (ODI) score, or the 36-Item Short-Form Health Survey score (SF36) to evaluate surgery outcomes, which mainly provided evidence about patients' recovery of either overall function of neurodeficit, pain, social dysfunction, or quality of life

[7–9], while variable relief extent of symptoms such as numbness and weakness has rarely been reported [10].

Sciatica Bothersomeness Index (SBI) is a self-assessment tool to assess the severity of sciatica. It contains four items, which can evaluate the main symptoms of LDH patients quantitatively, such as pain, numbness, and weakness [11]. It has been applied in previous studies about lumbar disc herniation and has demonstrated acceptable reliability, construct validity, and responsiveness [12, 13]. The purpose of this study was to investigate the curative effect of endoscopic treatment of lumbar disc herniation. The SBI score was used both preoperatively and postoperatively to evaluate the variable extent of relief among pain, numbness, and weakness. We hypothesized that numbness and weakness recovered at a less extent than pain in patients with lumbar disc herniation after percutaneous endoscopic lumbar discectomy.

2. Methods

2.1. Participants. LDH patients admitted for PELD from September 2016 to December 2018 were enrolled in this study. The criteria for inclusion were as follows: (1) complained of unilateral lower limb radiating pain, numbness, weakness, or other symptoms caused by single nerve root compression; (2) with symptoms consistent with preoperative imaging; and (3) with no significant relief of symptoms after 6 weeks of regular conservative treatment. The exclusion criteria were as follows: (1) with lumbar spinal stenosis; (2) and/or with lumbar instability; and (3) with spondylolisthesis or deformity.

2.2. Surgical Procedure. Two approaches for PELD were selected according to disk segments of herniation, which were transforaminal approaches for L45 and interlaminar approaches for L5S1. Surgical procedure was performed by one doctor under local anesthesia with 1% lidocaine, and the patients were laid in the prone position. A cannula was inserted into the spinal canal under the guidance of the C-arm X-ray machine. Free disk fragments were removed as much as possible. Microscopically, free movement of the nerve root and dural sac with the change of abdominal cavity pressure during breathing indicated that the goal of nerve decompression had been achieved.

2.3. Postoperative Management. All patients were treated with neurotrophic drugs routinely after operation and were able to get out of bed with a brace 24 hours after operation. After 3 weeks postoperation, the patients were instructed to return to everyday activities gradually.

2.4. Outcome Measurement. (1) Demographic data included gender, age, and body mass index (BMI); (2) clinical data included duration of preoperative symptoms, the SBI scores for evaluating preoperative symptoms, and the ODI score for evaluating social dysfunction. The SBI score is a patient self-rated instrument usually applied to evaluate the severity of sciatica, which contains 4 items and includes the most common symptoms of LDH patients, such as pain, numbness, and weakness. Each item has a range of score from 0 to 6. The index has labels at the categories 0 (not bothersome), 3 (somewhat bothersome), and 6 (extremely bothersome), which provides a total score from 0 to 24 when summing up the ratings across the 4 items [11]. (3) Imaging data were graded by the Pfirrmann grading system in which nerve root compression was graded into three categories based on preoperative MR images (A: normal or contact; B: deviation; and C: compression) [14]. Evaluation of the image data was completed independently by two attending doctors who had been specializing in spine surgery for at least five years. Any discordance in the evaluation of the image results was discussed, and final agreement was reached before they were recorded for analysis. (4) Follow-up data: all patients were followed up at 3 months after operation. The relief of symptoms was evaluated by the change of the total SBI score and each subitem score. The extent of symptom relief was calculated by the formula (preoperative scores−postoperative scores)/preoperative scores. The curative effect of PELD was evaluated by the Nakai score (Table 1) [15].

2.5. Statistical Analysis. All data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22 (IBM, USA). For all qualitative variables, the total number of patients and the percentage were provided. For quantitative variables, the mean and standard deviation were provided. To reveal the relationship between social dysfunction and different symptoms like pain, numbness, and weakness, correlations between preoperative ODI and the SBI score and its subitem scores were analyzed by the Pearson correlation analysis. The risk factors for curative effect and preoperative presence of numbness and/or weakness were analyzed by the logistic regression model. Factors according to its clinical significance were first assessed individually as predictive variables by the logistic regression analysis, and the final model included all the predictive variables with p values less than 0.2 as covariates, which were further assessed together by the logistic regression. p value less than 0.05 was taken as the criterion for covariates being significant risk factors.

3. Results

A total of 87 patients were enrolled in this study, and one case was lost to follow-up. The 86 enrolled patients included 44 males and 42 females, aged from 21–80, with an average age of 49. Demographic and clinical characteristics of the study patients are listed in Table 2.

Proportions of pain, numbness, and weakness are shown in Figure 1. Pain was the most common symptom, followed by numbness and weakness. Before surgery, 75 (87.2%) out of 86 patients had pain, 61 patients (70.9%) had numbness, and only 37 patients (43%) had weakness. Only 23 patients (26.7%) had all these 3 symptoms at baseline.

Results of the Pearson correlation analysis showed that the ODI score displayed a positive correlation with the

Table 1: Nakai score.

Scoring used in the study	
The patient has resumed work-related and other activities with slight or no symptoms	Excellent
The patient has resumed work-related and other activities but occasionally feels pain in the back or lower limbs after strenuous work	Good
The patient has reduced work-related and other activities because of residual pain in the back or lower limbs	Fair
The patient cannot work or carry out activities of daily living and is considered to be disabled	Poor

Table 2: Demographic, clinical, and imaging characteristics of enrolled patients.

Demographic data	
Age (years)	49 (21–80)
Gender (n, %)	
Male	44 (51%)
Female	42 (49%)
BMI (kg/m^2)	25.2 (3.80)
Clinical data	
Duration of symptoms (weeks)	118 (1–1440)
Preop ODI	49 (22)
Preop SBI total	9.4 (4.35)
Preop SBI pain	3.7 (1.74)
Preop SBI numbness	2.9 (2.08)
Preop SBI weakness	0.7 (1.11)
Imaging grade	
A	32 (37.2%)
B	19 (22%)
C	35 (40.6%)

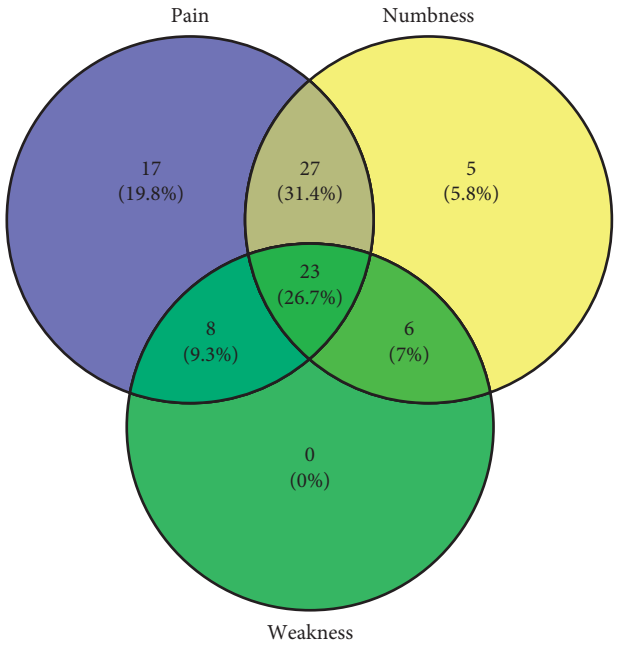

Figure 1: Proportions of various symptoms.

preoperative SBI total score, pain score, and weakness score, while no significant correlations were found between the ODI score and the numbness score (Table 3).

At 3 months after operation, the mean ODI score of the study population was decreased to 16.2 (11.33), $p < 0.001$. The mean SBI total score was decreased to 3.2 (2.32), $p < 0.001$, with a symptom relief rate of 65%. The mean pain score was decreased to 0.6 (0.82), $p < 0.001$, with a symptom relief rate of 82%. The mean numbness score was decreased to 1.6 (1.34), $p < 0.001$, with a symptom relief rate of 41%. The mean weakness score was decreased to 0.5 (0.85), $p < 0.001$, with a symptom relief rate of 21% (Figure 2).

According to the Nakai score, 11 (12.7%) cases had achieved excellent surgical outcomes, while good, fair, and poor were 60 (69.8%), 12 (14.0%), and 3 (3.5%), respectively. Patients were divided into two groups based on the Nakai score, which were the relief group with excellent or good in the Nakai score and the less relief group with fair or poor in the Nakai score. There were 71 cases in the relief group and 15 cases in the less relief group.

Demographics, preoperative clinical data, and imaging grade stratified by surgical outcomes are shown in Table 4. All the predictive variables were first assessed individually, and the significance levels are also listed in Table 4. Gender ($p = 0.193$), BMI ($p = 0.184$), preoperative SBI pain score ($p = 0.002$), preoperative SBI numbness score ($p = 0.08$), preoperative SBI weakness score ($p = 0.186$), preoperative SBI total score ($p = 0.05$), and preoperative ODI score ($p = 0.007$) were included as covariates in the final model of surgical outcomes. Among them, preoperative SBI pain score (odds ratio [OR] = 1.647; 95% confidence interval [CI], 1.199–2.261; $p = 0.002$) significantly increased the probability of relatively good surgical outcomes, while gender ($p = 0.242$), BMI ($p = 0.175$), preoperative SBI numbness score ($p = 0.302$), preoperative SBI weakness score ($p = 0.126$), preoperative SBI total score ($p = 0.525$), and preoperative ODI score ($p = 0.059$) were found to be nonsignificant predictors of the relatively good surgical outcomes and were excluded from the model.

To further explore the risk factors for preoperative presence of numbness and/or weakness, we divided the patients into the numbness and/or weakness group and the pain alone group based on the SBI subitem scores. Patients with SBI numbness and/or weakness scores greater than 2 points were grouped into the numbness and/or weakness group while the rest were in the pain alone group. Demographics, preoperative ODI score, duration of preoperative symptoms, and imaging grade stratified by presence of numbness and/or weakness are shown in Table 5. All the above predictive variables were first assessed individually, and the significance levels are also listed in Table 5. The reason for analyzing the multiplicativity of duration of preoperative symptoms and imaging grade was that they had complex interactions between them which might have influence on each other. Duration of preoperative symptoms ($p = 0.006$), imaging grade ($p = 0.123$), and joint effect of duration of preoperative symptoms and imaging

Table 3: Correlations between the preoperative ODI score and the SBI total score and its subitem scores.

Variables	ODI	
	Correlation coefficient	p value
SBI total	0.654	<0.001*
SBI pain	0.552	<0.001*
SBI numbness	0.148	0.173
SBI weakness	0.241	0.026*

p value less than 0.05 was considered significant.

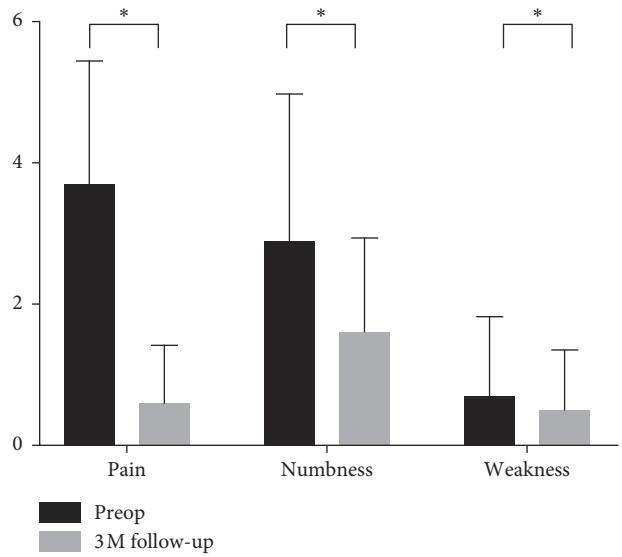

Figure 2: Relief extent of various symptoms at 3 months follow-up. *Indicates $p < 0.05$.

Table 4: Demographics, preoperative clinical data, and imaging grade stratified by surgical outcomes.

Variables	Relief group (71)	Less relief group (15)	p value#
Age, mean (SD)	48.9 (16.47)	51.6 (17.61)	0.572
Male, n (%)	34 (47.9)	10 (66.6)	0.193#
BMI, mean (SD)	25.4 (3.95)	24.0 (2.80)	0.184#
Duration of symptoms, mean (SD)	110 (246.5)	158 (253.72)	0.495
Preop ODI, mean (SD)	52.6 (22)	34.3 (20)	0.007#
Preop SBI total, mean (SD)	9.9 (4.55)	7.4 (2.41)	0.052#
Preop SBI pain, mean (SD)	4.0 (1.56)	2.3 (1.95)	0.002#
Preop SBI numbness, mean (SD)	2.7 (2.14)	3.7 (1.49)	0.08#
Preop SBI weakness, mean (SD)	0.6 (1.11)	1.1 (1.10)	0.186#
Imaging grade A, n (%)	29 (40.8%)	3 (20%)	0.267

For qualitative variables, the total number of patients and the percentage are provided. For quantitative variables, the mean and standard deviation are provided. These predictive variables are first assessed individually; the significance levels are also listed. #Indicates predictive variables included in the final model.

grade (multiplicativity) ($p = 0.004$) were included as covariates in the final model of presence of numbness and/or weakness. Among them, joint effect of duration of preoperative symptoms and imaging grade (odds ratio [OR] = 1.015; 95% confidence interval [CI], 1.005–1.026; $p = 0.004$) significantly increased the probability of presence of numbness and/or weakness, while duration of preoperative symptoms ($p = 0.633$) and imaging grade ($p = 0.341$)individually were found to be nonsignificant predictors and were excluded from the model.

4. Discussion

Patients with lumbar disc herniation usually present symptoms like pain, numbness, and weakness, which have a negative influence on their social functions [1, 16]. Our results showed that 75 (87.2%) out of 86 patients had pain, 61 patients (70.9%) had numbness, and only 37 patients (43%) had weakness. Preoperatively, pain was the most common symptom, followed by numbness and weakness, which was consistent with the results of the previous literature [10].

Table 5: Demographics, preoperative ODI score, duration of preoperative symptoms, and imaging grade stratified by presence of numbness and/or weakness.

Variables	Numbness and/or weakness group (57)	Pain alone group (29)	p value[#]
Age, mean (SD)	50 (16.0)	48 (17.9)	0.486
Male, n (%)	31 (54.3)	13 (44.8)	0.403
BMI, mean (SD)	25.3 (4.08)	24.9 (3.24)	0.690
Duration of symptoms, mean (SD)	171 (290.3)	16 (16.0)	0.006[#]
Preop ODI, mean (SD)	51.3 (23.0)	45.6 (20.0)	0.266
Imaging grade A, n (%)	18 (31.5%)	14 (48.2%)	0.123[#]
Joint effect of duration of symptoms and imaging grade	—	—	0.004[#]

For qualitative variables, the total number of patients and the percentage are provided. For quantitative variables, the mean and standard deviation are provided. These predictive variables are first assessed individually; the significance levels are also listed. [#]Indicates predictive variables included in the final model.

Huang and Sengupta conducted a retrospective study in which they followed up 85 patients who had surgical decompression of the nerve root due to lumbar disease and they found that most of the patients had pain and numbness before surgery. Our results also showed that the preoperative pain score and weakness score correlated with the ODI score, while numbness did not, which indicated that although commonly presented in LDH patients, numbness did not have so much negative influence on their social function as pain and weakness did. This was consistent with our clinical observation. Numbness appeared to be more bearable than pain and caused less social dysfunction.

A great number of studies in the previous literature have reported significant relief of symptoms after decompression surgery [17–20]. Endoscopic procedures for treatment of spinal diseases firstly came out in 1992 and have been widely applied in clinical practice for lumbar spine diseases, as the rapid development of endoscopic technology. Recent studies have reported that they could achieve equal curative effect with less trauma and shorter hospital stay compared to traditional surgeries [3–6]. Our results showed that 71 (82.6%) out of 86 cases achieved good or excellent surgical outcomes which further confirmed that PELD was an effective and reliable method for the treatment of LDH.

However, previous studies mainly provided evidence about patients' postoperative overall functional recovery by employing outcome measurements like JOA, VAS, ODI, or SF36 [7–9]. Various rate and extent of symptoms relief had rarely been discussed. In Huang's research, pain recovered the fastest at the first 6 weeks after surgical decompression, while numbness recovered at a slower pace [10]. We obtained similar results in our study. At 3 months follow-up after PELD procedures, 82% of pain, 41% of numbness, and 21% of weakness were relieved compared with the preoperative symptoms. Pain relieved by the largest extent, which we inferred might be explained from the nerve fiber anatomic point of view. The spinal nerve consists of somatic sensory and motor nerve fibers with various diameters [21]. Damage to sensory Aβ fibers conducting feeling vibrations and touch may result in a general sense of numbness [22, 23], and damage to motor Aα fibers may result in weakness [24, 25]. Both kinds of fibers are myelinated with relatively larger diameters. Pain on the other hand is conducted mainly by unmyelinated thin C fibers and partly by myelinated fibers [26]. Nerve root compressed by LDH would lead to impairment of intraneural microcirculation and tissue inflammatory process, and long-term compression might further induce damage and demyelination of nerve fibers. Decompression by PELD could recover the blood infusion and create a more beneficial environment for nerve fiber regeneration. C fibers recover more quickly and easily than Aα and Aβ fibers as the process of remyelination requires more time [10].

The SBI scores have been used in the previous studies about lumbar disc herniation and have demonstrated acceptable reliability, construct validity, and responsiveness [11, 13]. Three of them were also incorporated in the North American Spine Society questionnaire [12]. Our results showed that the preoperative SBI pain score significantly increased the probability of relatively good surgical outcomes, which indicated that pain was the most significant outcome criteria for patients during the early stage after surgery. Patients with more preoperative pain tended to have more relief of symptoms postoperatively. This was consistent with our common clinical observation that pain relief contributed more to the overall symptoms relief than other symptoms like numbness and weakness, which was also consistent with our previous results that pain relieved by the largest extent. Theoretically, as caused mainly by larger myelinated nerve fibers, numbness and weakness tended to be more difficult to recovery, resulting in a worse surgical outcome. However, given the fact that most LDH patients presented pain simultaneously with other symptoms, it was reasonable that their effects on the surgical outcomes were confounded by pain. While numbness and weakness were not independent risk factors, we believed the results were still meaningful in clinical application because persistent numbness and/or weakness after satisfactory pain relief is commonly seen in patients during the postoperative follow-up [10]. By analyzing the risk factors for presence of numbness and/or weakness before surgery, we found that the joint effect of duration of preoperative symptoms and imaging grade significantly increased the probability of presence of numbness and/or weakness, and the interaction between them was multiplicative, which indicated that preoperative long duration of symptoms together with a severe compression of nerve root would lead to numbness and/or weakness. Long duration of symptoms and severe

nerve root compression may induce deformation and demyelination of nerve fibers distally resulting in numbness and weakness.

This study has some limitations. The reason for following up patients at 3 months after operation was that most symptoms of LDH recovered the fastest at the first 6 weeks and plateaued at 3 months postoperatively according to the previous literature [10]. The results of our study might uncover the extent of symptoms relief at the early stage after operation. Yet, there was still slow improvement of these symptoms even until 1 year postoperatively. Further studies might be needed with a longer follow-up to reveal the overall relief extent of various symptoms. And the other limitation is that this study is a retrospective analysis of prospectively collected data, which may have potential biases of a retrospective study.

5. Conclusion

In patients with LDH, pain was the most common symptom, followed by numbness and weakness. PELD had a good curative effect in the treatment of LDH. Patients recovered best from pain, followed by numbness and weakness. Higher level of patients' self-reported preoperative pain indicated a better surgical outcome for LDH patients, and preoperative long duration of symptoms together with a severe compression of nerve root significantly increased the risk of presenting numbness and/or weakness.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

How Does Myofascial Physical Therapy Attenuate Pain in Chronic Pelvic Pain Syndrome?

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Background. Chronic pelvic pain syndrome (CPPS) is a multifactorial disorder comprising structural and functional muscular abnormalities, a dysfunctional pain system, and psychological distress. Myofascial physical Therapy (MPT) that is targeted at improving pelvic muscle functioning is considered a first line nonpharmacological treatment for CPPS, although the precise mechanisms that lead to symptoms alleviation have not yet been elucidated. *Purpose*. This longitudinal study aimed to examine the local and systemic effects of MPT intervention, including biopsychophysiological processes, among CPPS patients. *Methods*. The study included 50 CPPS women. Morphologic assessment of the levator ani and quantitative sensory testing of the pain system were applied alongside with evaluation of pain-related psychological factors using designated questionnaires. All measures were evaluated both before and after MPT in 39 patients. The long-term effects of MPT were evaluated by clinical pain reports obtained at 3 and 9 months following MPT that were compared with a nontreated group of 11 untreated CPPS women. *Results*. Along with an improvement in the clinical pain intensity ($p = 0.001$) and sensitivity to experimental pain tests ($p = 0.001$) following MPT, the results also indicate that MPT has anatomical, psychological, and social therapeutic effects ($p = 0.04$; $p = 0.001$; $p = 0.01$, respectively). Furthermore, clinical pain evaluation at 3 and 9 months after MPT revealed a significant improvement in women who received treatment ($p = 0.001$). *Conclusions*. The findings of this pilot study suggest multisystemic (direct and indirect anatomical, neurophysiological, and psychological) effects of MPT on the multifactorial pain disorder of CPPS and therefore place MPT as a mechanism-based intervention.

1. Background

Chronic pelvic pain syndrome (CPPS) is defined as a multifactorial pain disorder that localizes to the anatomic pelvis, anterior abdominal wall at or below the umbilicus, the lumbosacral back or the buttocks. It is of sufficient severity to cause functional disability that may require medical care [1–6]. Structural and functional muscular abnormalities have been suggested as key features of CPPS pathogenesis, specifically hypertonicity of the pelvic floor muscles [7–10], trigger points (TrPs) in the vulvar area [11–13], and shortening of the levator muscles [14]. There are subgroups of CPPS including provoked vestibulodynia (PVD) referred to pain provoked by touch or during vaginal intercourse (dyspareunia) [15, 16] and painful bladder syndrome (PBS) characterized by pelvic pain and urinary storage symptoms (e.g., persistent urge to void, nocturia, and urinary frequency) [17, 18].

CPPS women also characterize by dysfunctional pain system as expressed by hypersensitivity of the peripheral and central pain systems, as well as dysfunctional pain modulation [3, 19–22] as well as psychological distress [23, 24], manifested as high levels of anxiety, pain catastrophizing, depression, and somatization [22, 25–33]. All these factors and the interplay between them may affect the severity of symptoms presented by chronic pain patients such as those with CPPS [34–36].

Hence, the present study is based on the biopsychosocial health model which links between biological, psychological, and social factors in understanding health and disease [37, 38]. From a biological point of view, this model refers to defects in parts and body parts and to functional impairment of body systems. In the psychological dimension, the model relates to the type of personality, attitudes and beliefs, ability to cope, and emotions such as fear, anxiety, depression, anger, and morbid behavior. In the social aspect, it relates to relationships with family members, friends, and work relations, the framework of work, medical advice, support frameworks, emotional and financial compensation, cultural factors, and socioeconomic factors. The perspective of this model serves to explore the complex mechanisms involved in chronic pain disease [39–41].

The dysfunctional pelvic floor muscle, whether originating from the lesioned muscular tissue or secondary to abnormal functioning of the pain system or psychological distress, is the target of physical therapy. This is mainly in the form of myofascial physical therapy (MPT) [42, 43]. MPT involves skillful, hands-on maneuvers directed towards relaxation, elongation, stretching, and massaging of tightened muscles, as well as the relief of myofascial tender points [44, 45]. In addition to these local effects on the pelvic floor, pain attenuation following MPT may be attributed to processes that occur at the systemic pain level, i.e., in the spinal and supraspinal structures. The latter include changes in the activity of the sympathetic nervous system and induction of pain inhibitory effects via supraspinal pathways [46, 47]. We have recently reported that MPT results in attenuation of vulvar pain and pain evoked at trigger points [48]. However, little is currently known on how MPT works and whether reductions in pain and clinical symptoms are associated with improved functioning of the pain system, as well as psychological well-being. The psychological factors, such as somatization, depression, and anxiety, were altered following pain reduction treatments and most often decreased [12, 22, 27, 36]. However, no studies have yet examined the changes of such parameters following MPT in CPPS patients.

The main goal of this prospective longitudinal preliminary study was to shed some light on the biopsychophysiological processes associated with MPT which lead to pelvic pain relief. Our investigational approach included a comprehensive evaluation of both local (morphological parameters of the levator ani pelvic floor muscle) and systemic changes (pain processing and modulation measures, as well as psychological factors) before and after MPT in CPPS patients. An additional goal was to assess the trajectory of the long-term pain relieving effects of MPT.

2. Methods

The data reported in this paper are part of a longitudinal study that examined the prediction and consequences of MPT in CPPS patients [48].

2.1. Study Participants. In this prospective longitudinal study, women diagnosed with CPPS were recruited from the Urogynecology and Pain Clinics at the Rambam Health Care Campus and the Sex Therapy Clinic at the Lis Maternity Hospital. The nontreated by MPT or any other treatment group included age-matched CPPS women (for more detailed information about the study cohort please refer Grinberg et al., 2017) [3]. Inclusion criteria for CPPS were as follows: age >18 years; for painful bladder syndrome (PBS) that is characterized by pelvic pain and urinary storage symptoms: urinary frequency ≥10 times per 24 hours, including one night-time voiding, and complaints of bladder pain ≥3 months [17, 18] for provoked vestibulodynia (PVD); and a distressing genital pain condition provoked by touch and one of the most common causes of pain during intercourse (dyspareunia) in premenopausal women [15, 16]: pain intensity during intercourse ≥4 on a 0–10 numerical pain scale (NPS) during the previous month. Patients were excluded from the study if they had a history of pelvic cancer or radiation therapy; had undergone pelvic or abdominal surgery; suffered from a urinary tract infection within the last month; or had fibromyalgia, irritable bowel syndrome, a neurological disorder, diabetes, or pregnancy. Sociodemographic and medical data including age, marital status, religion, employment status, duration of CPPS symptoms, and pharmacological treatments were recorded.

2.2. Experimental Procedure. The Rambam Medical Center (Haifa, Israel) Review Board, in accordance with the Helsinki Declaration and the IRB of the Haifa University, approved the study. All participants received detailed explanation and provided written informed consent before the start of any testing procedure. All subjects who agreed to participate in the study were instructed to adhere to the study protocol and did not take any medication during treatment. All women were diagnosed by a physician experienced in the field of urogynecology and dyspareunia who performed the clinical evaluation of the pelvic floor and the assessment of vulvar pain (LL and LA). Morphologic assessment of the levator ani was performed by a gynecologist specializing in ultrasonography of the pelvic floor. The psychophysical experimental procedure was conducted during the morning hours by the same investigator (KG) in the Laboratory of Clinical Neurophysiology at the Faculty of Medicine of the Technion (Haifa, Israel).

Women were initially exposed to a training session in order to familiarize them with the psychophysical tests. Thereafter, they completed the sociodemographic and medical history forms and clinical pain and urinary symptoms questionnaires, as well as the psychological questionnaires. They then underwent the psychophysical pain tests. This battery of tests was repeated again on the

same women after completion of the 8 weekly session of MPT.

The study's long-term follow-up was performed after 3 months and again after 9 months (since the end of the treatment). At both time points, patients report their level of pelvic pain intensity using the 0–10 numerical pain scale (NPS) where 0 indicated "no pain" and 10 represented "the worst pain imaginable." CPPS patients who had enrolled in the first stage of the study but decided not to have MPT served as the nontreated group. They were also asked to similarly report their 0–10 level of pelvic pain intensity at 3 and 9 months following the baseline evaluation session.

2.3. Clinical Evaluation of Symptom Severity. The severity of urgency symptoms among the PBS patients was assessed using the validated Hebrew version of the Urgency, Severity, and Impact life Questionnaire (USIQ) [20]. This questionnaire consists of 13 Likert scale items relating to the intensity of urgency symptoms and the severity of frequency symptoms, as well as the impact of these symptoms on daily life. The α Cronbach of the Hebrew version is 0.85–0.90.

The study's approach to evaluating the severity of vulvar pain symptoms and evaluation pain evoked at pelvic TrPs has been detailed in an earlier report [49].

2.4. Morphologic Assessment of the Levator Ani. The length and width of the levator ani muscle was measured by using a specially designed 3D endovaginal ultrasound (BK Medical Ultrafocus machine (Peabody, MA)), device at a frequency of 4–8 MHz, as depicted in Figure 1. This ultrasound imaging was performed while the women was laying in the dorsal lithotomy position and with the hips flexed and slightly abducted, when a probe is inserted into the vagina. No preparation was required, and the patients were recommended to have a comfortable volume of urine in the bladder. This assessment was performed before and after the MPT by a gynecologist who specializes in ultrasonography evaluation. This test has been extensively described in the article of Rostamina et al. and found to be reliable [49].

2.5. Psychophysical Assessment of Pain. In order to examine the changes in pain sensitivity at the spinal and supraspinal level following MPT, noxious stimuli were delivered to the suprapubis area and forearm, respectively. Notably, no side effect was observed after psychophysical testing. The battery of psychophysical tests (see Grinberg et al., 2017) [3] are as follows:

2.5.1. Mechanical Pain Threshold (MPT). This was assessed at the referred area (i.e., the suprapubis area) by using von Frey hairs filaments (VFH; Stoeteling Ltd., USA) that evoke pinprick sensation, using the method of levels in an ascending order starting from the lightest VFH force of 3.7 g [50]. The lightest gram weight filament that evoked pain sensation in two out of three trials was considered to be the MPT.

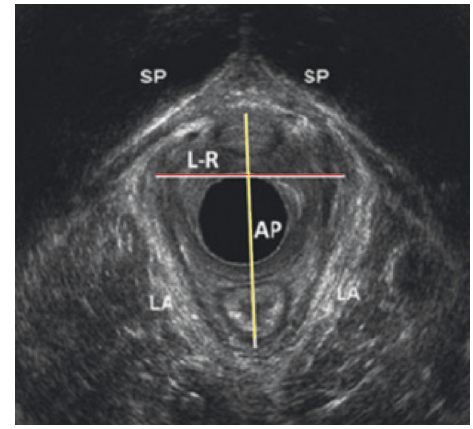

Figure 1: An Hiatus biometry measurement on 3D endovaginal ultrasound, intact levator ani muscle. AP, anteroposterior; L-R, left-to-right width; SP, symphysis pubis; LA, levator ani.

2.5.2. Heat Pain Threshold (HPT). This was measured via the thermal sensory analyzer (TSA, Medoc, Ramat Yishay, Israel) with a 30×30 mm probe, which delivers a contact heat stimulus. Patients received three successive ramps of gradually increasing temperatures delivered to the volar forearm of their dominant hand according to the method of limits [51]. The mean of three successive responses whose variance was less than 0.5°C was calculated as the HPT.

2.5.3. Magnitude Estimation of Painful Mechanical Stimulus. Three stimuli were delivered with a 225 g VFH to the suprapubis area, and women were asked to rate the level of pain intensity on a 0–100 NPS. An average of the three pain ratings was defined as the suprathreshold pain rating.

2.5.4. Magnitude Estimation of Tonic Heat Pain (THP) Stimulation. A thermal stimulus at a temperature perceived to be an intensity of pain rated 50 on a 0–100 NPS (i.e., "pain 50" intensity) was applied to the volar forearm of the dominant hand for one minute. The mean ratings (NPS) of pain at 5, 25, 40, and 55 sec were defined as the suprathreshold pain.

Temporal summation of pain , a sensory phenomenon that represents central sensitization and the functioning of the facilitatory pain pathways:

(a) *Mechanical Temporal Summation (mTS).*Two series of 10 repetitive stimuli with a 160 g VFH were applied to the suprapubis with 2-3 sec interstimulus intervals. The differences in 0–100 NPS pain scores between the last and the first stimulus were calculated for each series and averaged across series to calculate the mTS.

(b) *Heat Temporal Summation (hTS).* Magnitude was calculated as the difference between the last (at 55 sec) and first 0–100 NPS pain scores (at 5 sec) that were given during the one minute of THP.

2.5.5. The Conditioned Pain Modulation Paradigm (CPM). This is an advanced psychophysical paradigm to test the efficacy of a dominant supraspinal descending endogenous

analgesia mechanism, namely diffuse noxious inhibitory control (DNIC) [51, 52]. This mechanism is based on the "pain inhibits pain" phenomenon, which requires a remote noxious "conditioning stimulus" for pain attenuation of the "test stimulus." The test stimulus was the 60 sec THP described above. The conditioning stimulus was a 90 sec immersion of the nondominant hand in a hot water bath (46.5°C) (Heto Cooling Bath, Jouan Nordic A/S, Allerod, Denmark). The test stimulus was first given alone, and pain ratings were obtained every 10 sec. After a 10 min break (to allow for nociceptor recovery to resting state), the patients were exposed to the conditioning stimulus for 30 sec after which they immediately rated the pain intensity of the hot water. Then, concomitantly with the conditioning stimulus (hot water bath), the same test stimulus was delivered again and pain ratings of the test stimulus were again recorded every 10 sec. The CPM effect was calculated as the average pain rating for the test stimulus given with the conditioning stimulus minus the average pain rating of the test stimulus given alone. A negative CPM value was considered to indicate effective endogenous pain modulation.

2.6. Psychological Evaluation. Participants completed a battery of psychological questionnaires including (i) the State-Trait Anxiety Inventory [53] using the validated Hebrew version [54]. The first part of the questionnaire assesses the level of state anxiety, and the second part assesses trait anxiety. Each part includes 20 statements that describe the emotional condition (reliability of 0.82–0.91). CPPS patients were asked to rate their feelings about each sentence on a 4 point Likert scale; (ii) the Hebrew version of the Brief Symptom Inventory (BSI) [55], translated by Canetty et al. [56], which assesses the level of somatization symptoms and consists of 13 self-report questions on psychological distress, (reliability of 0.78–0.91); (iii) the Hebrew version of the Pain Catastrophizing Scale (PCS) [57, 58]. This questionnaire includes 13 items representing the three components of pain catastrophizing: rumination, magnification, and helplessness. Items were rated on a Likert scale ranging from 0 (not at all) to 4 (all the time) with a total score range from 0 to 52, (reliability of 0.86); and (iv) the Beck Depression Inventory (BDI), which assesses both the cognitive and affective symptoms of depression [59]. In the BDI, a score of 0–9 is normal, 10–18 means mild depression, scores of 19–26 represent moderate depression, and scores over 26 are considered to indicate severe depression symptoms (reliability of 0.84).

2.7. MPT Intervention. MPT was carried out with the goal to restore pelvic floor muscle length and strength; release TrPs in the muscles and connective tissues of the pelvic floor, pelvic girdle, and abdomen, using pelvic massages (performed by a specialist woman physiotherapist) [60, 61]; and improve blood flow to the pelvic area [62]. Specifically, the MPT intervention included myofascial TrPs release and connective tissue manipulation techniques (manual stretching of the trigger point region and myofascial release). [63]. Furthermore, during treatment, the women also learned control skills and how to self-train their pelvic muscles to contract and relax [64–66]. In this study, the women were scheduled for 8 weekly 1 hour treatments with one specialist pelvic physical therapist. In addition, the patients were asked to perform a minimum of two self exercises at home (every week) in order to maximize the treatment effect and maintained a self diary. The subjective effectiveness of the MPT treatment was examined 3 and 9 months following treatment termination by asking the women to rate their responses on a 0–10 scale where 0 indicated no improvement at all and 10 represented the most effective response. As mentioned previously, the pain intensity was also examined in this period (3 and 9 months following treatment termination) using the 0–10 NPS scale.

2.8. Statistical Analysis. Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, IL). Paired t-tests were used to examine the differences before and after MPT regarding the anatomical muscle changes. MANOVA repeated measure tests were carried out to examine the differences between the experimental pain parameters and the psychological measures following MPT. In addition, a repeated measure ANOVA followed by preplanned contrasts were conducted to examine differences in pelvic pain scores between women with CPPS who received MPT compared with CPPS women who did not receive MPT. To compare difference in the mean difference in the pain score between the before-and-after values between groups who did and did not undergo MPT, ANOVA test was used (for example, pain at 3 and 9 months, with a variable taking into account baseline pain and a variable for the treatment group). Paired t-tests were carried out to examine the differences between the anatomical structure of the levator ani muscle before and after MPT treatment. All statistical tests were corrected for multiple analyses using Bonferroni correction; $p < 0.05$ was considered as significant.

3. Results

3.1. Clinical Characteristics of the Patient Population. The sample included 39 CPPS patients (21 with PBS and 18 with PVD) who underwent MPT and 11 nontreated CPPS patients. The mean age of the study group was 37.9 ± 15.4 years (range 22–67 years). The mean disease duration was 5.5 ± 9 years (range 1–30 years). As previously reported, there were no significant differences between PBS and PVD patients neither in their clinical pain ratings and consequent effects on daily functioning nor in their psychophysical and psychological parameters ($p < 0.05$) [3]. Six women with PVD also reported urine symptoms, but did not meet the criteria of PBS. The CPPS sample age ranged from 22–67 years, with an average age of 37.9 (SD = 15.4; range: 22–67), disease duration of 5.5 years (SD = 9; range: 1–30), and 53% of the participants single, 41% married, 5% divorced, and 2% widowers. More than half of them had high school education (52%), 46% had an academic degree, and 2% were college graduation. Most of the women were Jewish (93%) and 7% were Christian and Muslim.

3.2. Changes in Outcome Measures following MPT. In line with the reduction in the severity of clinical pain that was recently reported [48], a reduction in USIQ scores was also observed (18.1 ± 4.1 before MPT versus 13.6 ± 3.4 after MPT; $p < 0.001$) together with their impact on daily functions (23.1 ± 7.0 before MPT versus 18.5 ± 7.1 after MPT; $p < 0.01$).

A significant correlation was found between the change in the pain test (CPM test) and the change in the muscle length ($r = 0.661$, $p = 0.037$) and width ($r = 0.671$, $p = 0.034$).

3.3. Changes in Psychophysical Parameters. MPT significantly impacted the experimental pain parameters as shown from analyzing the changes before and after treatment. Specifically significant reductions in pain sensitivity were observed ($F(10, 27) = 5.26$, $p < 0.001$) for the following measures: pain thresholds, suprathreshold rating of heat and mechanical pain stimuli, and CPM magnitude (Table 1).

3.4. Changes in Psychological Parameters. MPT significantly improved all pain-related psychological parameters before and after MPT ($F(5,32) = 5.72$, $p < 0.001$), with improvements in state and trait anxiety levels, pain catastrophizing, somatization, and depression (Table 2).

3.5. Changes in Anatomical Measures. Due to technical problems, data were obtained from only 11 women who were available for the ultrasonographic analysis. An increase in the width of the levator ani ($t = 2.28$, $p = 0.04$) was observed following MPT. However, there were no significant changes in muscle length (Table 3). No significant correlations were found between the change in the length or width of the levator ani and the changes in the clinical pain ratings before and after treatment ($p < 0.05$).

3.6. The Long-Term Effects of MPT on Clinical Pain. Repeated measure ANOVA showed significant improvement in self reports of pelvic pain intensity 3 and 9 months following up MPT as compared with baseline pain intensity ($F(1, 47) = 7.004$, $p = 0.001$), whereas, no significant change in pelvic pain was observed in the group that did not undergo MPT, and patients who completed the treatment demonstrated significant improvement and stable pain alleviations as assessed at 3 and 9 months compared with the reports of pelvic pain obtained at baseline. (Table 4 and Figure 2).

4. Discussion

PVD and PBS represent subgroups of CPPS. They have shared characteristics including muscular abnormalities, a dysfunctional pain system, and psychological distress [3], suggesting a common mechanism-based treatment strategy. Thus, this preliminary study was aimed at investigating how MPT, a pelvic floor-focused treatment, is able to affect biopsychological measures and alleviate symptom severity in women with CPPS from PVD or PBS. The results indicate that MPT has anatomical, neurophysiological, and psychological therapeutic effects alongside long-lasting pelvic pain alleviation. Specifically, MPT works on relieving hypertonicity, reduces the sensitivity to experimental pain, improves the functionality of the endogenous inhibitory system, and decreases psychological distress (i.e., state and trait anxiety levels, pain catastrophizing, somatization, and depressive symptoms). These systemic effects position MPT as a multisystemic therapeutic intervention for patients with CPPS.

Evidence suggests that the MPT approach improves blood flow to the pelvic region and involves the releasing of TrPs [45, 67]. MPT has also been shown to normalize muscle tone, flex the connective and soft tissue around the joints of the pelvic floor, and strengthen the pelvic girdle muscles [45, 68–75]. The fact that women in the current study who were not treated by MPT showed no significant reduction in their clinical pain intensity after 3 and 9 months reinforces the assumption that the short- and long-term effects of MPT cannot be attributed solely to a placebo effect [45, 76]. The combined positive effects on anatomical, neurophysiological, and psychological processes associated with MPT are revealed for the first time in this study.

The anatomical effect of MPT on the width of the levator ani muscle supports the improvements seen in the clinical picture. The levator ani plays a role in supporting the pelvic organs and the functional mechanism of the sphincters. Physical therapy to the pelvic region was focused on imparting patient control of the muscle relaxation and contraction processes, which may contribute to improving muscle relaxation and consequently to changing the muscle width. The literature supports such a causative linkage, as studies have reported a lengthening of the levator ani muscle following MPT in CPPS patients that was correlated with the degree of improvement in clinical pain ratings [45, 77, 78]. The current study did not compare the muscle length and width between women with CPPS and healthy women, which eliminates the possibility to derive any conclusions about a possible anatomical impairment in the muscle prior to the intervention. Yet, it has been suggested that an anatomical defect is one of the mechanisms underlying CPPS that may arise due to stress situations, past events, or perhaps originate from an organic, anatomical, or morphological impairment [4, 32]. An indirect indicator of the anatomical defect might be represented by increased pain ratings in response to contact stimuli at the TrPs, as previously reported in other studies [20, 21], as well as on this cohort [48]. Our findings of reduced pain hypersensitivity following MPT [48], accompanied by the morphological enlargement of the levator ani, may suggest that this anatomical change also contributes to the reduced sensitivity of TrPs.

MPT also affected the systemic pain sensitivity to experimental pain measures. Specifically, we observed an increase in pain thresholds and a decrease in pain ratings in response to noxious stimulation in referred and remote body areas. Two possible central mechanisms may be involved in this treatment-induced plasticity. Firstly we suggest that MPT decreases the level of central sensitization, where sensitization of neurons at the spinal and supraspinal levels contributes to the development and maintenance of referred and remote pain, respectively

Table 1: Differences in experimental pain parameters before and after MPT.

	Pre-MPT	Post-MPT	Mean difference	F	p
MPT (gr.)	5.6 ± 0.5	5.7 ± 0.4	0.1	1.90	0.17
1st supra-m (NPS)	29.7 ± 20.5	20.7 ± 15.6	−9.0	12.50	0.001
10th supra-m (NPS)	41.8 ± 25.5	31.3 ± 21.3	−10.5	15.20	0.000
mTS (NPS)	10.3 ± 15.2	12.2 ± 20.3	1.9	0.24	0.62
HPT (°C)	41.1 ± 2.8	41.9 ± 2.7	0.8	4.81	0.035
Pain 50 (°C)	42.7 ± 2.3	43.2 ± 2.2	0.5	10.60	0.002
Contact THP (NPS)	46.1 ± 13.3	45.6 ± 14.2	−0.5	0.06	0.05
Immersion THP (NPS)	67.0 ± 37.9	72.8 ± 30.7	5.8	1.50	0.12
CPM (NPS)	−0.2 ± 13.9	13.8 ± 12.2	14	34.90	0.000

Data are shown as mean ± standard deviation. MPT, mechanical pain threshold; 1st supra-m, the mean pain rating of the first mechanical stimuli; 10th supra-m, the mean pain rating of the tenth mechanical stimuli; HPT, heat pain threshold; NPS, 0–100 numerical pain scale; mTS, mechanical temporal summation; hTS, heat temporal summation; Pain 50, the temperature that induces a pain of 50/100 on the NPS; Contact THP, the mean pain rating from the tonic heat stimulus of the thermal sensory probe; Immersion THP, the mean pain rating from the tonic heat stimulus of the hot-water bath; CPM, conditioned pain modulation.

Table 2: Differences in psychological factors before and after MPT.

	Pre-MPT	Post-MPT	Mean difference	F	p
Anxiety state	49.4 ± 7.0	46.6 ± 4.9	−2.8	4.42	0.043
Anxiety trait	47.7 ± 4.8	46.0 ± 5.0	−1.7	4.62	0.038
PCS	26.2 ± 13.0	21.2 ± 12.2	−5.0	7.32	0.001
BSI	13.4 ± 8.7	10.1 ± 6.5	−3.3	15.77	0.000
BDI	12.0 ± 6.8	8.0 ± 6.3	−4.0	17.72	0.000

Data are shown as mean ± standard deviation. Anxiety state and anxiety trait, from the State-Trait Anxiety Inventory; PCS, pain catastrophizing scale; BSI, brief symptom inventory; BDI, beck depression index.

[79, 80]. It is therefore a fair assumption that in this study, MPT diminished the degree of hypersensitivity at the local level (the pelvic soft tissue), as expressed by a reduction in evoked pain (e.g., TrPs), and thus reduced nociceptive input to the central pain system. The diminished barrage of nociceptive information may have consequently resulted in decreased sensitization at the spinal and supraspinal levels as manifested by the reduced pain sensitivity at referred and remote body areas [20, 81–83].

The second suggested central mechanism is based on the improved endogenous inhibitory capacity following MPT, as demonstrated by an increased CPM response. CPM is the experimental paradigm to test diffuse noxious inhibitory control (DNIC), a descending system that induces top-down modulation on the nociceptive neurons at the spinal level, resulting in a systemic inhibitory effect and pain alleviation. Research has indicated a dysfunctional DNIC system in CPPS [3, 21, 83, 84] and other idiopathic pain conditions [85, 86]. Notably, interventions aimed at pain alleviation (i.e., surgical and pharmacological) have the capability to restore the functioning of the endogenous inhibitory system [85]. For example, Kosek and Ordeberg [87] identified a restoration of the DNIC system in osteoarthritis patients who underwent hip or knee surgery and reported significant pain relief. These results suggest that the dysfunctional pain inhibition is maintained over time by ongoing pain and when the pain is extinguished, and DNIC function may be restored resulting in an attenuation of pain sensitivity. We therefore suggest that following MPT treatment, improved CPM functionality was observed in our patients, probably due to a reduction in the ongoing pain, and such enhanced inhibitory activity contributed to the reduction in the clinical pain.

MPT was also associated with psychological benefits in our patient cohort, as expressed by a reduction in psychological distress and a decrease in the level of state and trait anxiety, as well as decreased ratings of depression, catastrophizing, and somatization after treatment. Previous studies indicate that a reduction in psychological distress can alleviate pain. For example, a decrease in fear, anxiety, and catastrophic thoughts is able to reduce negative feelings and somatic complaints and may affect the response to experimental and clinical pain [36, 58, 88–90]. Furthermore, high levels of catastrophizing have been attributed to clinical pain intensity and experimental pain sensitivity [34, 55, 91, 92]. The literature thus supports the present study's findings of improved pain-related personality factors in parallel with reduced clinical and experimental pain parameters. Conversely, it is also possible that the chain of events is in the opposite direction and that the reduction in clinical pain improved the psychological distress.

It is important to note an additional perspective to interpreting the observed results of MPT in CPPS patients, namely, the patient-physiotherapist relationship. This may hold therapeutic effects that are above and beyond the direct local influence on the muscular system [45, 69]. Such relationships may involve instilling a sense of control, security, and trust, as well as self-efficacy [93], which are invaluable in improving clinical outcomes of chronic pain disorders. Furthermore, frustration resulting from the failure of previous treatments may have led women to develop negative thoughts in relation to their disease, which also manifested as catastrophic thinking when relating to their pain [94]. An appropriate treatment is therefore likely to reduce such catastrophizing and indeed following MPT, improvements were found in the current study on this psychological factor. Lowered catastrophizing thinking may be also achieved due to the improvement of the patients' ability to voluntarily contract and relax the pelvic floor muscles and thus control urine functioning.

Table 3: Anatomical structural differences before and after MPT.

	Pre-MPT ($N = 11$)	Post-MPT ($N = 11$)	Mean difference	T	p
Levator ani length (cm)	5.7 ± 0.7	5.2 ± 0.8	−0.5	1.77	0.11
Levator ani width (cm)	4.3 ± 0.7	4.8 ± 0.9	0.5	2.28	0.04

Data are shown as mean ± standard deviation.

Table 4: Differences in pain scores (after 3 and 9 months) of women with CPPS who received MPT compared with women with CPPS who did not receive MPT.

	CPPS with MPT ($N = 39$)	CPPS with no MPT ($N = 11$)	Mean difference	F	p
NPS at baseline	7.6 ± 1.4	6 ± 1.2	−1.6	3.25	0.31
NPS at 3 months	4.4 ± 2.3	6.5 ± 1.5	2.1	2.91	0.005
NPS at 9 months	4.1 ± 1.5	5.9 ± 1.2	1.8	3.70	0.01

Data are shown as mean ± standard deviation. NPS at 3 months, clinical pain ratings after 3 months on a 0–10 numerical pain scale; NPS at 9 months, clinical pain ratings after 9 months on a 0–10 numerical pain scale. There was a significant improvement in clinical pain scores among women receiving MPT compared to women with CPPS who did not undergo any treatment, as assessed at 3 and 9 months.

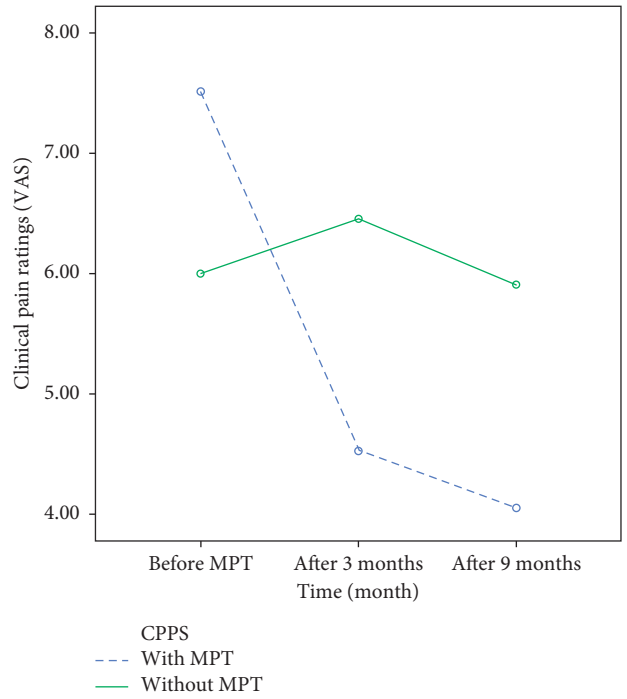

Figure 2: Clinical pain scores (0–10 NPS) of women with CPPS at baseline and following MPT compared with CPPS women who did not undergo MPT; ** $p < 0.01$, *** $p < 0.001$. There was a significant improvement in clinical pain ratings among women receiving MPT as assessed before the treatment ($t = 3.18$, $p = 0.003$) and at 3 ($t = 3.97$, $p = 0.000$) and 9 months ($t = 3.58$ $p = 0.000$) compared with the nontreated group. Baseline differences in clinical pain were controlled.

This leads to the adaption of more efficient coping strategies as well as a better sense of control. With regard to the biopsychosocial model, it is therefore likely that MPT also has cognitive-psychological effects that may improve CPPS symptoms beyond its physical influence.

Several limitations that may influence the significance of the findings should be addressed. First, the relatively small sample size limits the generalization of our findings given the variability in psychophysical and pain-related personality measures. The small sample size was due to the restrictive inclusion criteria which reduced the number of CPPS patients that could be enrolled. Second, due to the fact that the 11 women who did not undergo MPT were not randomly selected and that their assignment to this group was based solely on their reports of clinical CPPS symptoms, this nontreated group is not a "true" control group. In order to present an understanding of the mechanistic processes, a real randomized control group should be obtained and tested with both psychophysical and psychological measures. Therefore, the significance of the findings should be carefully interpreted relating to this pilot study. It cannot be ignored that the ability to make decisive conclusions from the findings of this pilot study is limited.

5. Conclusions

This study sheds light on the indirect neurophysiological and psychological effects of MPT that occurred together with pain alleviation and improvement in functioning. The peripherals and systemic effects of MPT position it as a multisystemic therapeutic intervention for patients with CPPS. This suggestion is in line with the notion that CPPS is a multifactorial and complex pain disorder comprised of multiple biopsychosocial components. Therefore, an intervention such as MPT that has multisystemic effects can be recommended as a mechanism-based intervention for CPPS patients. We suggest that future randomized control studies conducted on larger cohorts of patients may allow the reliability of our results to be addressed.

Abbreviation

CPPS: Chronic pelvic pain syndrome
MPT: Myofascial physical therapy
TrPs: Trigger points
PVD: Provoked vestibulodynia
PBS: Painful bladder syndrome
NPS: Numerical pain scale
USIQ: Urgency, severity, and impact life questionnaire
MPT: Mechanical pain threshold

VFH: Von Frey hairs
HPT: Heat pain threshold
TSA: Thermal sensory analyzer
THP: Tonic heat pain
mTS: Mechanical temporal summation
hTS: Heat temporal summation
CPM: Conditioned pain modulation paradigm
DNIC: Diffuse noxious inhibitory control
BSI: Brief symptom inventory
PCS: Pain catastrophizing scale
BDI: Beck depression inventory.

Data Availability

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

Additional Points

Myofascial manual therapy induces anatomical, neurophysiological, and psychological effects in chronic pelvic pain patients.

Ethical Approval

This study was approved by the Rambam Medical Center Review Board in accordance with the Helsinki Declaration.

Consent

All participants in the study were over 18 years of age and provided written informed consent.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors contributed to the study design. Prof. Lowenstein and Drs. Abramov and Grinberg performed the data collection. Prof. Granot, Dr. Weissman-Fogel, and Dr. Grinberg analyzed the data and wrote the manuscript, and all authors edited it. All authors have read and approved the final manuscript.

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Research Article

Comparison of Transcutaneous Electric Nerve Stimulation (TENS) and Microcurrent Nerve Stimulation (MENS) in the Management of Masticatory Muscle Pain: A Comparative Study

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Introduction. Temporomandibular disorders (TMDs) are a heterogeneous group of pathologies affecting the temporomandibular joint (TMJ), the jaw muscles, or both. Epidemiological studies of TMD reveal a prevalence of 82% in the general population with 48% of them presenting with clinical features of muscle tenderness and difficulty in mouth opening. TMD are considered to be the most common orofacial pain conditions of nondental origin. *Methods*. The patients with TMD were randomly divided into two groups, A and B, based on their VAS scale. Group A consists of two subgroups 1 and 2 each consisting of 15 patients. Group B consists of two subgroups 3 and 4 consisting of 15 patients. Patients in Group A were given TENS for twenty minutes, and the frequency is adjusted as follows: (i) subgroup 1: TENS frequency at a range of 0–5 (VAS measuring 1–5) and (ii) subgroup 2: TENS frequency at a range of 5 and above (VAS measuring 6–10). Patients in Group B were given MENS for twenty minutes, and the frequency adjusted as follows: (i) subgroup 3: MENS frequency at range of 0–5 (VAS measuring 1–5) and (ii) subgroup 4: MENS frequency at a range of 5 and above (VAS measuring 6–10). Each patient was recalled for five consecutive days for the treatment, and the same intensity and frequency were maintained throughout the treatment period. *Results*. The improvement in VAS is seen to be highly significant statistically in MENS subgroup 4 (moderate-to-severe pain). Subgroups 1 and 3 had improvement in VAS which was comparable in both TENS and MENS groups. *Conclusion*. In the present study, it was found that TENS and MENS are equally effective in improving the functional mouth opening. MENS showed better and immediate effect in relief of pain. Microcurrent also has the advantage of being subthreshold, and hence the side effects such as tingling sensation and paresthesia seen to occur in some patients following TENS are absent. TENS and MENS can be considered as the first line of treatment in patients with acute and chronic masticatory muscle pain and also as an effective treatment option in cases of functional mouth opening.

1. Introduction

Temporomandibular disorders (TMDs) are a heterogeneous group of pathologies affecting the temporomandibular joint (TMJ), the jaw muscles, or both. Epidemiological studies of TMD reveal a prevalence of 82% in the general population, and 48% of them presented with clinical features of muscle tenderness and difficulty in mouth opening. TMDs are considered to be the most common orofacial pain conditions of nondental origin. The frequent concurrent presence of other symptoms such as earache, headache, neuralgia, and tooth pain which may be related to TMD or present as ancillary findings makes the assessment of TMD a complex issue [1].

Myofascial pain syndrome (MPS) is diagnosed in nearly a third of patients who have musculoskeletal pain disorders. Accurate diagnosis allows for appropriate therapy whether it is nonsurgical or surgical. Current trends favor conservative

(nonsurgical) therapy, and the surgical interventions have become less aggressive, moving away from open arthroplasty towards arthroscopic procedures [2]. The interrelationship and association of TMDs with various disorders continue to be explored [3]. A number of successful conservative treatment options have been tried for myofascial pain including occlusal splints, physiotherapy, muscle relaxing appliances, pharmacological interventions, physical agents such as thermography, cryotherapy, and ultrasound, complementary and alternative medicine such as acupuncture, and electrotherapy modalities such as transcutaneous electric nerve stimulation (TENS) and microcurrent electric nerve stimulation (MENS) [4]. MENS is a relatively new approach for pain relief and muscle healing, while TENS has been used for pain relief since the sixteenth century.

The use of TENS is based on several interrelated theories on the mechanism of pain transmission and the blocking of those mechanisms. The first one being the gate control theory, the second theory is related to endogenous release of morphine-like substances (endorphin) after electrical stimulation. The third mechanism of action of TENS is related to the automatic and involuntary contraction of muscles.

MENS is a form of electrotherapy current that provides subthreshold or subminimal stimulation lower than 1000 microamps (μA). MENS works on the principle of Arndt–Schulz law. It is theorized that healthy tissue is the result of direct flow of electric current throughout our body. Electrical balance is disrupted when the body is injured at a particular site, causing the electric current to change course. The use of microcurrent over the injured site is thought to realign this flow, thus aiding in tissue repair.

The purpose of this study was to compare the effectiveness of transcutaneous electric nerve stimulation (TENS) and microcurrent electrical nerve stimulation (MENS) on patients suffering from myofascial pain.

2. Materials and Methods

After obtaining clearance from the Institutional Ethical Committee, the present study was conducted in the Department of Oral Medicine and Radiology, Manipal College of Dental Sciences, Mangalore. A total of 60 patients above the age of 18 years with clinically diagnosed masticatory muscle pain were included in the study if they fulfilled the following criteria:

(1) Clinical diagnosis of myofascial pain [4]

(2) Muscle tenderness of any of the muscles of mastication

(3) A complain of pain with a duration of more than 3 weeks

(4) TMJ stiffness and pain

(5) Patients of either gender

(6) Patients who have given informed consent for the study

The exclusion criteria were as follows:

(1) Patients on analgesics or anti-inflammatory medication/physiotherapy/complementary and alternative medicine (CAM) for the same problem

(2) Patients with cardiac pacemakers and implanted defibrillators

(3) Areas over cancerous lesions

(4) Presence of acute infection in the region

(5) Patients who are unwilling to be part of the study

Equipments used for treatment:

(1) TENS apparatus adjusted to 50 Hz, with a pulse width of 0.5 msec at 0–60 mA

(2) MENS apparatus adjusted to 0.5 Hz, 1000 μA

After obtaining subject demographics, a thorough history of the patient was taken. Routine dental checkup of the patient was done and the findings recorded in the proforma. After recording a thorough case history, patients were assessed for TMDs, and clinical diagnosis of muscle pain was established by following the DC/TMD criteria. Radiographic investigations were carried out in cases that raised suspicion of any underlying bony changes of the TMJ. The patients were explained in detail about the treatment protocol and informed consent was obtained. Mouth opening was recorded on the first day before beginning the treatment. The intensity of pain in the affected side was measured by the Visual Analog Scale (VAS) before the beginning of the treatment. The patients were then randomly divided into two groups, Group A and Group B, based on their VAS score.

Group A consists of two subgroups 1 and 2, each consisting of 15 patients. Group B consists of two subgroups 3 and 4 consisting of 15 patients each. The patients were seated in the dental chair, and the electrodes were applied directly on the skin, using a special conducting gel, over the trigger points or in the general area of pain if specific trigger points could not be elicited. Patients in Group A were given TENS for twenty minutes, and the frequency is adjusted as follows:

(i) Subgroup 1: TENS frequency at VAS range of 0–5

(ii) Subgroup 2: TENS frequency at VAS range above 5

Patients in Group B were given MENS for twenty minutes, and the frequency is adjusted as follows:

(i) Subgroup 3: MENS frequency at VAS range of 0–5

(ii) Subgroup 4: MENS frequency at VAS range above 5

Each patient was recalled for five consecutive days for the treatment, and the same intensity and frequency were maintained throughout the treatment period.

Patients were given instructions such as supporting their jaw while yawning and while opening their mouth wide. Bilateral chewing pattern and hot fomentation of the affected side were taught as part of jaw exercises. The VAS was measured every day before starting the treatment. The oral rehabilitation such as correction of high points, restoration of decayed tooth, replacement of missing teeth, and extraction of third molars was done if required after the

Table 1: Genderwise distribution of masticatory muscle pain among the study population. Males are represented by 1 and females by 2.

		Type		
		MENS	TENS	Total
Sex	1	9	9	18
		30.0%	30.0%	30.0%
	2	21	21	42
		70.0%	70.0%	70.0%
Total		30	30	60
		100.0%	100.0%	100.0%

Table 2: Affected side distribution among the study population. Right side is represented by 1, left side by 2, and 3 represents both right and left.

		Type		
		MENS	TENS	Total
Sides	1	14	9	23
		46.7%	30.0%	38.3%
	2	13	17	30
		43.3%	56.7%	50.0%
	3	3	4	7
		10.0%	13.3%	11.7%
Total		30	30	60
		100.0%	100.0%	100.0%

completion of the 5-day treatment. Patients were instructed not to undergo any further treatment for the masticatory muscle pain in the following one month period and were asked to contact the investigator in case of any discomfort or functional limitation. After one month, these patients were recalled, and their VAS and mouth opening were measured. If any of the patients had discomfort or functional limitation, alternate treatments were considered after the 1-month follow-up.

2.1. Statistical Method for Analysis. The data were expressed as mean and standard deviation using 2-way ANOVA. The groups were compared using Student's t-test, and the intergroup statistics were done using post hoc analysis. Statistical analysis was performed using SPSS 17.0 software.

Level of significance: $\alpha = 0.05$.

We compared the P value with the level of significance. If $P < 0.05$, we reject the null hypothesis and accept the alternate hypothesis. If $P > 0.05$, we accept the null hypothesis.

3. Results

Genderwise distribution and commonly affected side correlation in the study population are described in Tables 1 and 2, respectively.

TENS group reveals an immediate and steady increase in mouth opening during the one-month follow-up period, whereas MENS group reveals a statistically significant increase in mouth opening from day three onwards and during the one month recall, after treatment. The average baseline mouth opening of both the groups was comparable as explained in Table 3.

Comparison of pain response (VAS) between the TENS and MENS group from day zero to day five and one month recall as depicted in Table 4 reveals a decrease in pain more markedly in the MENS group especially after day four of the treatment. Patients in the MENS group also showed a significant immediate positive response to treatment in comparison with the TENS group. However the change in VAS is seen to be comparable in both TENS and MENS group at one month recall.

The inter subgroup comparison in the improvement of mouth opening reveals that the improvement in mouth opening was statistically significant in both TENS and MENS group. However, MENS improves functional mouth opening significantly in patients with moderate-to-severe pain (Group B, subgroup 4) when compared with TENS.

The improvement in pain scale was more marked in subgroup 2 (moderate-to-severe pain) in patients under TENS Therapy. Patients in subgroups 1 and 2 showed a 60% reduction in pain by day 4 of treatment. The pain relief at one month recall in both the subgroups is comparable.

The improvement in VAS was seen to be significant statistically in MENS moderate-to-severe pain group (Group B, subgroup 4). In subgroup 3 of Group B (MENS therapy), the improvement in VAS is comparable with the results achieved in subgroup 1 in patients undergoing TENS therapy (Group A).

4. Discussion

TMDs are characterized by a classically described triad of clinical signs: muscle and/or TMJ pain; TMJ sounds; and restriction, deviation, or deflection of the mouth-opening path [5].

There is evidence that the prevalence of TMD signs and symptoms may be high in the general population [6]. The literature reports great variability in the prevalence of the clinical symptoms (6–93%) and signs (0–93%), probably as a result of the different clinical criteria employed. Between 3–7% of the population seek treatment for pain and dysfunction of the TMJ or related structures [7].

In the sample population recruited for our study, the number of female subjects was more than the number of male subjects. There is a statistically significant prevalence of TMDS among females in our patient population. Cairns in 2010 proposed that psychosocial stressors contribute to the development of TMD-related pain, particularly masticatory muscle pain, and hence more women suffer from TMD than men. Although there are arguably multiple reasons for sex-related differences in the prevalence of TMD, one potential trouble shooter for the increased occurrence of this disorder in women has been suggested to be the female sex hormone oestrogen [8].

Among the 60 patients, 50% (30 patients) were affected with pain on the left side, and this finding was statistically significant. We could not attribute this to any of the factors like missing teeth, wear facets, or prosthesis. This was contradictory to the findings of a study undertaken by

Table 3: Improvement in mouth opening in the study period between the TENS and MENS group (post hoc analysis by Bonferroni test; measure: MEASURE_1; parameter: MOUTH OPENING (MM)).

Type	Mean difference	Std. error	Change (%)	P value	
MENS: day 0 to day1	−0.133	0.142	0.45	1.000	
Day 2	−1.233	0.278	4.19	0.003	HS
Day 3	−3.400	0.409	11.55	0.000	HS
Day 4	−5.267	0.452	17.89	0.000	HS
Day 5	−6.800	0.535	23.10	0.000	HS
At 1 month	−7.167	0.601	24.35	0.000	HS
TENS: day 0 to day1	−0.600	0.195	2.02	0.097	
Day2	−1.733	0.442	5.83	0.010	Sig
Day3	−3.200	0.602	10.76	0.000	HS
Day4	−4.000	0.625	13.45	0.000	HS
Day5	−5.000	0.690	16.82	0.000	HS
At 1 month	−5.333	0.914	17.94	0.000	HS

Table 4: Improvement in VAS in the study period between the TENS and MENS group (post hoc analysis by Bonferroni test; measure: MEASURE_1; parameter: VAS).

Type	Mean difference	Std. error	Change (%)	P value	
MENS: day 0 to day1	0.600	0.163	10.78	0.020	Sig
Day2	1.933	0.197	34.73	0.000	HS
Day3	3.400	0.252	61.08	0.000	HS
Day4	4.733	0.262	85.03	0.000	HS
Day5	5.067	0.262	91.02	0.000	HS
At 1 month	5.067	0.318	91.02	0.000	HS
TENS: day 0 to day1	0.200	0.074	3.68	0.245	
Day2	1.333	0.154	24.54	0.000	HS
Day3	2.333	0.188	42.94	0.000	HS
Day4	3.733	0.271	68.71	0.000	HS
Day5	4.533	0.295	83.44	0.000	HS
At 1 month	4.700	0.319	86.50	0.000	HS

Diemberger who observed that the right side was the commonly affected side. Their study revealed that women reported more frequently of a preferred chewing side (PCS), and in 64% of the recorded cases, it was observed that the right side (64%) was the preferred chewing side. PCS was found in almost half of the study population and was associated with unilateral signs of TMD, TMJ pain, and asymmetrical loss of antagonist contact [9]. One probable cause for our contradictory finding could be the prevalence of PCS in the left side.

MENS had a statistically significant increase in mouth opening as compared with TENS at the end of the fifth day of the treatment regimen and also at one month recall. However, TENS showed a faster increase in mouth opening compared with MENS. To our knowledge, there are no documented studies comparing improvement in mouth opening between TENS and MENS.

TENS group revealed an acceptable improvement in pain scale by day two, and patients obtained a 43% improvement in pain score by day three of treatment. There was an improvement of pain by 91.02% from the day of initiation of treatment to one month recall. MENS group showed acceptable pain relief from day one itself, and a 60% reduction in pain was obtained in patients by day three. The decrease in pain was seen to be more marked in the MENS group especially after day four of the treatment. Patients in the MENS group showed a significant immediate response to treatment in comparison with the TENS group.

A study by Rajpurohit et al. showed a significant improvement in VAS in the MENS group than patients in the TENS group, in patients with masticatory muscle pain secondary to bruxism, which was in accordance with the findings of our study [10]. Their study, however, does not measure the functional mouth opening. Our study is also the first to consider patients with two different degrees of pain in VAS,mild to moderate and moderate to severe.

5. Conclusion and Summary

Physical therapies have been used as an adjunct in the management of chronic and acute masticatory muscle pain of various etiologies. They have various advantages: noninvasive, negligible side effects, not technique sensitive, and easy to use. They form an alternative modality to medicinal management of masticatory muscle pain. However, the efficacy of one physical therapy with another has not been compared in a randomized controlled trial. The present study aims to compare the effectiveness of two physical therapy modalities, namely, TENS & MENS.

In the present study, it was found that TENS and MENS are equally effective in improving the functional mouth opening. However, MENS showed better and immediate

effect in relief of pain. Microcurrent also has the advantage of being subthreshold, and hence the side effects such as tingling sensation and paresthesia which are seen to occur in a few patients following TENS are absent in MENS therapy. TENS and MENS can be considered as the first line of treatment in patients with acute and chronic masticatory muscle pain and also as an effective treatment option in cases of functional mouth opening.

The following aspects need to be considered in any future research:

(1) TMDs are usually chronic and are seen to recur following periods of remissions, and hence long term follow-ups should be considered.

(2) It is important to consider the psychological tangent to TMDs, and hence future studies could include a questionnaire on the patient's anxiety and stress scale, pre- and posttreatment effect on quality of life.

Data Availability

The data used to support the findings of this article are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Clinical Study

Microdecompression versus Open Laminectomy and Posterior Stabilization for Multilevel Lumbar Spine Stenosis: A Randomized Controlled Trial

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Background. Lumbar spinal stenosis most often results from a gradual, degenerative ageing process. Open or wide decompressive laminectomy was formerly the standard treatment. However, in recent years, a growing tendency towards less invasive decompressive procedures has emerged. The purpose of this study was to compare the results of microdecompression with those of open wide laminectomy and posterior stabilization for patients with symptomatic multilevel lumbar spinal stenosis who failed to respond to conservative treatment. *Methods*. This randomized controlled study was conducted between January 2016 and October 2018. One hundred patients were involved in this study. All these patients suffered from radicular leg pain with MRI features of multilevel lumbar spinal stenosis and were treated by conservative treatment of medical treatment and physiotherapy without benefit for 6 months. Those patients were divided into two groups: Group A, 50 microdecompression, and Group B, 50 patients who were treated by open wide laminectomy and posterior stabilization. Both groups of patients were followed up with ODI (Oswestry disability index) and VAS (visual analogue score) for the back and leg pain for one year. *Results*. The results showed that both groups got significant improvement regarding the Oswestry disability index. Regarding back pain, there was a significant improvement in both groups with better results in group A due to minimal tissue injury as the advantage of the minimal invasive technique. In both groups, there was marked improvement of radicular leg pain postoperatively. *Conclusions*. Both microdecompression and wide open laminectomy with posterior stabilization were effective in treatment of multilevel lumbar spinal stenosis with superior results of microdecompression regarding less back pain postoperatively with less blood loss and soft tissue dissection. Clinical trial number: NCT04087694.

1. Introduction

Stenosis of the lumbar spine is an extremely widespread disorder that frequently arises from a gradual degenerative ageing progression [1]. The clinical condition of the stenosis is characterized by low back pain and pain and numbness in the legs, and it is a common cause of weakened walking and inability in elderly people (≥60 years). It is the most frequent indication for spinal surgery in the elderly [2]. Management of spinal stenosis can be challenging and needs the incorporation of patients' symptoms, clinical results, and diagnostic imaging. There is rising evidence that decompressive surgery offers a priority over nonsurgical management for particular patients with continual severe signs [3]. Presently, it is normally accepted that surgery is designated if conservative or nonsurgical management fails. Development in radiating pain, neurogenic claudication, functional position, and quality of life are the major treatment aims. Open laminectomy, often combined with medial facetectomy and foraminotomy, has conventionally been the

typical therapy in patients without instability [4, 5]. In recent years, less invasive measures have developed [6, 7] and microdecompression through smaller incisions is often achieved. Decompressive laminectomy is widely used to treat LSS. Although satisfactory surgical outcomes have been reported using this technique, instability following the procedure is one of the greatest concerns amongst surgeons as it may cause deterioration of symptoms [4] In a research conducted in 2005, unilateral microdecompression for bilateral decompression and bilateral microdecompression were found to be hopeful therapy alternatives when compared with open decompressive laminectomy [4]. Subsequently, unilateral and bilateral microdecompression have been adopted by several spine surgeons, and as is the case in Norway, often among neurosurgeons than orthopaedic surgeons. However, there is still a necessity to assess the benefits and risks of different decompressive surgical measures for lumbar spinal stenosis [8, 9].

The present study aimed to compare the results of microdecompression for multilevel lumbar spine stenosis with those of open laminectomy and posterior stabilization regarding the Oswestry disability index and visual analogue score for back pain and leg pain.

2. Methods

The protocol of this study was reviewed and approved by the research ethics committee in our university. Written informed consents were obtained from all patients. This study is a randomized controlled trial. One hundred patients were involved in this study from January 2016 to October 2018. All these patients suffered from back pain of different degrees with spinal claudication and were treated by conservative treatment of medical treatment and physiotherapy without benefit for 6 months at least. MRI of the lumbosacral spine showed multilevel spinal stenosis L3-S1, and all patients were assessed clinically and radiologically. All patients underwent dynamic flexion and extension lumbosacral plain x-ray to exclude any instability.

The patients were divided into two groups according to the ODD and EVEN number on receiving of the patients: Group A, 50 patients who were treated by microdecompression, and Group B, 50 patients who were treated by open laminectomy and posterior stabilization with pedicle screws from L3 to S1 levels.

The two groups of patients were operated by one team which consisted of one orthopaedic surgeon and one neurosurgeon. The instability was assessed by dynamic X-ray, and those cases with instability were excluded. Cases with decreased disc height and disc degeneration of significant degrees were not involved in this study. All patients in this study suffered from radiculopathy as the primary complain, and those cases with only back pain (discogenic pain) are not involved in this study.

All these patients were assessed and followed up by ODI preoperatively and 1 month postoperatively and VAS for back pain and leg pain preoperatively, in addition to 1, 6, and 12 months postoperatively.

2.1. Exclusion Criteria. Exclusion criteria of the present study include smoking, diabetic patients, previous spinal surgery, any neuromuscular disorder like poliomyelitis, vertebral instability proved by dynamic plain radiographs, and patients with significant loss of disc height and degeneration.

2.2. Data Analysis. Statistical analysis was carried out using SPSS version 21 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and percentages. Continuous variables were presented as Mean ± SD. The student's *t*-test was used to compare means between two groups. The Mann–Whitney *U* test was used to compare two groups when the variable was not normally distributed. The paired *t*-test was used to compare means for paired reading. The Pearson's chi-square test (χ^2) was used to find the association between categorical variables. A *P* value of ≤0.05 was considered as significant.

2.3. Surgical Procedures

2.3.1. Group A. Under general anesthesia, with supine position and flexion of both hips and knees by pillows, and with the aid of a microscope, midline incision was done after determination of the spinal levels by fluoroscopy with cautery. The deep fascia was opened, and paravertebral muscles were retracted laterally to expose the lamina of L5 on the symptomatic side. Then, by high speed drill the lamina was thinned by passing a hook under the lamina and retracting the ligamentum flavum; then, by using tenotome the ligamentum falvum was incised over the hook; then, by karyson the ligamentum flavum was removed to expose the dura and the nerve root on that side; foraminotomy was performed; and then, the microscope was tilted 15 degrees, and the bed of the patient was tilted 15 degrees. Therefore, we directed the microscope on the contralateral side to remove a part of the lamina and the ligementum flavum to decompress the contralateral nerve root; then, hemostasis was performed starting with proximal level (L4) and then (L3) with the same technique but on the alternating way. After securing hemostasis, the surgical wound was closed in layers with no drain. The patients are mobilized after 6–8 hours after operation.

2.3.2. Group B. Under general anesthesia, with supine position and flexion of both hips and knees by pillows, midline incision was performed after determination of the target levels from L3 to S1. By cautery, the deep fascia was opened, and the paravertebral muscles were retracted to expose the laminae from L3 to L5. Insertion of pedicle screws from L3 to S1 (the stenosed levels) and wide laminectomy were performed to the stenosed levels with decompression of the nerve roots and then hemostasis secured. The rodes were inserted with consideration of lumbosacral lordosis; decortication was performed, and the bone grafts were put posterolaterally from the removed spinous processes and laminae. The surgical wound was closed in layers with drain which was removed the next day, and the patient started mobilization the next day postoperatively.

3. Results

Table 1 shows the distribution of patients according to sociodemographic characteristics (including age and gender).

Table 2 shows the mean differences of age between study groups including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There were no significant differences between means of age between these two groups.

Table 3 shows the association between gender and study group including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There was no significant association between gender and study group.

Figure 1 shows the mean differences of the postoperative Oswestry disability index (ODI) between study groups including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There were significant differences between means of the ODI between these two groups after one month ($P = 0.001^*$), while there were nonsignificant differences between two groups after six and twelve months of operation ($P = 0.421$ and $P = 0.57$).

Figure 2 shows the mean differences of the postoperative visual analogue score (VAS) for back pain between study groups including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There were significant differences between means of VAS for back pain between these two groups after one month and six months ($P < 0.001^*$, $P < 0.001^*$), while there were no significant differences between means of VAS for back pain between these two groups after 12 months ($P = 0.524$).

Figure 3 shows the mean differences of the postoperative visual analogue score (VAS) for leg pain between study groups including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There were no significant differences between means of VAS for leg pain between these two groups after 1, 6, and 12 months ($P = 0.618$, $P = 0.604$, and $P = 0.23$, respectively).

Table 4 shows the mean differences of ODI, VAS for back pain, and VAS for leg pain between preoperative and postoperative assessments three times after 1, 6, and 12 months for group A patients who underwent microdecompression surgery.

Table 5 shows the mean differences of ODI, VAS for back pain, and VAS for leg pain between preoperative and postoperative assessments three times after 1, 6, and 12 months for group B patients who underwent open decompression and spine fixation.

Table 6 shows the mean differences of operation time (in minutes) and amount of blood lost (in ml) between study groups including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There were significant differences between means of operation time and amount of blood lost between these two groups.

Table 7 shows the association between the cost of operation and study group including Group A patients who underwent microdecompression surgery and Group B patients who underwent open decompression and spine fixation. There was significant association between the cost of operation and study groups.

Table 1: The distribution of patients according to sociodemographic characteristics.

Sociodemographic variables		
Age (years)	(55.9 ± 8.03)	(37.0 – 74.0)
Gender		
Male	35	35%
Female	65	65%
Total	100	100.0%

Table 2: The mean differences of age between study groups.

Study variables	Study groups	N	Mean	SD	t-test	P value
Age (years)	Group A	50	56.60	7.79	0.87	0.386
	Group B	50	55.20	8.28		

Table 3: The association between gender and study group.

Study variables	Study group		$\chi 2$	P value
	Group A	Group B		
Gender				
Male	16 (32.0)	19 (38.0)		
Female	34 (68.0)	31 (62.0)	**0.396**	**0.529**
Total	50 (100.0)	50 (100.0)		

$^*P$ value ≤0.05 was significant.

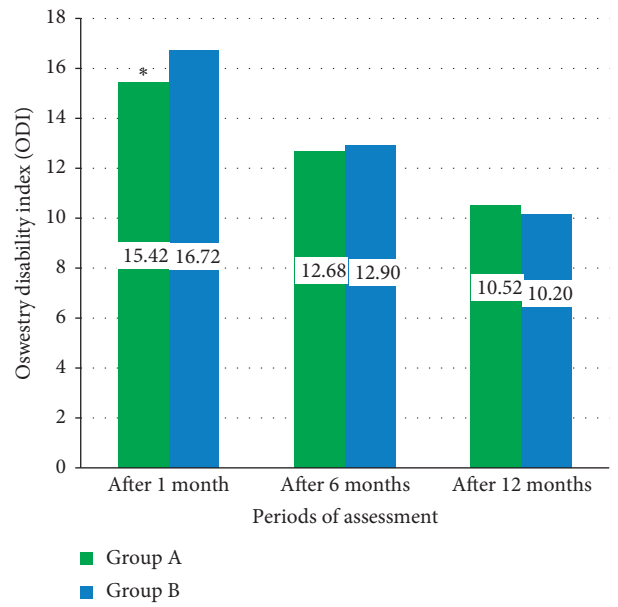

Figure 1: The mean differences of the postoperative Oswestry disability index (ODI) between study groups.

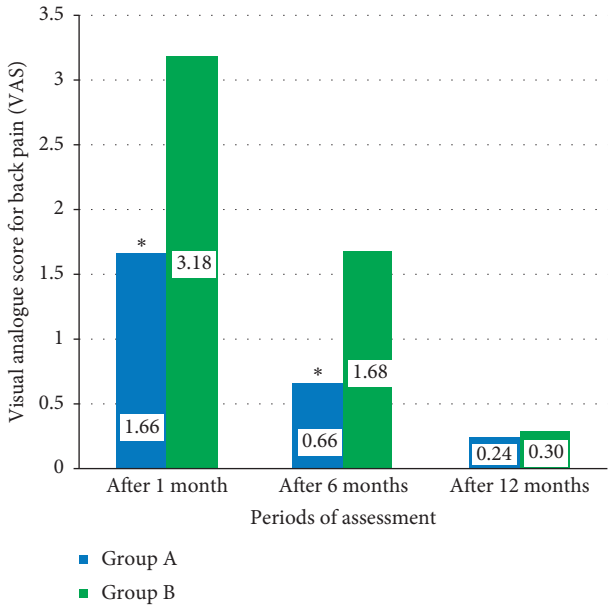

Figure 2: The mean differences of the postoperative visual analogue index (VAS) for back pain between study groups.

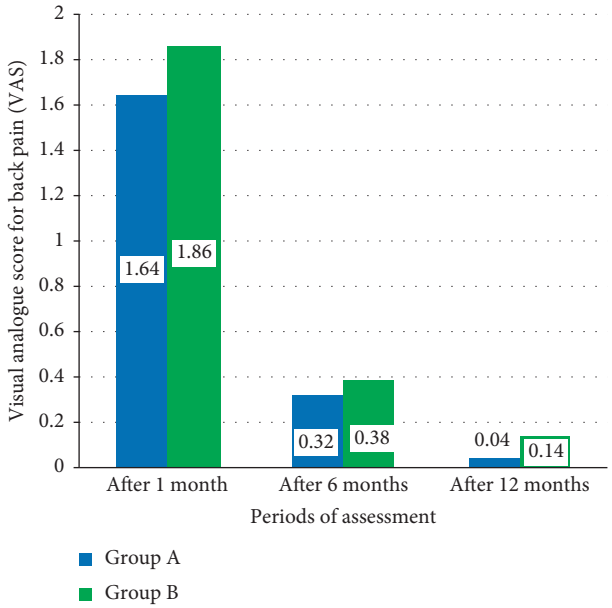

Figure 3: The mean differences of the postoperative visual analogue index (VAS) for leg pain between study groups.

4. Discussion

In our study, we found that both groups got significant improvement regarding the Oswestry disability index (Table 1). Regarding back pain, there was a significant improvement in both groups with better results in group A due to minimal tissue injury as the advantage of minimal invasive technique (Table 2). In both groups, there was a marked improvement of radicular leg pain postoperatively (Table 3). In comparison with previous observational studies [4, 6, 7], secondary outcome analyses showed a major improvement in health-related quality of life in both treatment groups. Although results at one year were extremely similar, patients in the microdecompression group had shorter hospital stays than patients who went through laminectomy.

This result was reliable using various policies for analyzing data. A possible clarification is that microdecompression decreases surgical trauma, permitting early mobiliation after surgery. Nevertheless, it is also probable that surgical units adapting to least invasive procedures will be prone towards shorter hospital stays, taking different practices for postoperative mobilization, pain management, and hospital discharge. Conventional laminectomy with removal of posterior bony and ligamentous structures has been the gold standard of surgical treatment for decades. Although postoperative development of segmental

Table 4: The mean differences of ODI, VAS for back pain, and VAS for leg pain between preoperative and postoperative assessments three times.

Study variables	Periods of assessment	*N*	Mean	SD	Paired *t*-test	*P* value
ODI	Preoperative ODI	50	71.30	1.69	**94.57**	**<0.001***
	1 month postoperative ODI	50	15.42	3.59		
	Preoperative ODI	50	71.30	1.69	**177.31**	**<0.001***
	6 months postoperative ODI	50	12.68	1.44		
	Preoperative ODI	50	71.30	1.69	**237.4**	**<0.001***
	12 months postoperative ODI	50	10.52	0.88		
VAS for back pain	Preoperative VAS for back pain	50	5.22	0.70	**19.66**	**<0.001***
	1 month postoperative VAS for back pain	50	1.66	1.08		
	Preoperative VAS for back pain	50	5.22	0.70	**42.41**	**<0.001***
	6 month postoperative VAS for back pain	50	0.66	0.55		
	Preoperative VAS for back pain	50	5.22	0.70	**56.58**	**<0.001***
	12 month postoperative VAS for back pain	50	0.24	0.43		
VAS for leg pain	Preoperative VAS for leg pain	50	9.86	0.35	**71.28**	**<0.001***
	1 month postoperative VAS for leg pain	50	1.64	0.80		
	Preoperative VAS for leg pain	50	9.86	0.35	**99.72**	**<0.001***
	6 month postoperative VAS for leg pain	50	0.32	0.55		
	Preoperative VAS for leg pain	50	9.86	0.35	**178.92**	**<0.001***
	12 month postoperative VAS for leg pain	50	0.04	0.19		

Table 5: The mean differences of ODI, VAS for back pain, and VAS for leg pain between preoperative and postoperative assessments three times.

Study variables	Periods of assessment	*N*	Mean	SD	Paired *t*-test	*P* value
ODI	Preoperative ODI	50	72.24	2.38	**84.07**	**<0.001***
	1 month postoperative ODI	50	16.72	4.07		
	Preoperative ODI	50	72.24	2.38	**155.4**	**<0.001***
	6 months postoperative ODI	50	12.90	1.26		
	Preoperative ODI	50	72.24	2.38	**179.73**	**<0.001***
	12 months postoperative ODI	50	10.20	1.62		
VAS for back pain	Preoperative VAS for back pain	50	5.14	0.90	**11.28**	**<0.001***
	1 month postoperative VAS for back pain	50	3.18	1.15		
	Preoperative VAS for back pain	50	5.14	0.90	**23.21**	**<0.001***
	6 month postoperative VAS for back pain	50	1.68	0.84		
	Preoperative VAS for back pain	50	5.14	0.90	**32.99**	**<0.001***
	12 month postoperative VAS for back pain	50	0.30	0.50		
VAS for leg pain	Preoperative VAS for leg pain	50	9.86	0.35	**77.65**	**<0.001***
	1 month postoperative VAS for leg pain	50	1.86	0.78		
	Preoperative VAS for leg pain	50	9.86	0.35	**103.68**	**<0.001***
	6 month postoperative VAS for leg pain	50	0.38	0.60		
	Preoperative VAS for leg pain	50	9.86	0.35	**128.21**	**<0.001***
	12 month postoperative VAS for leg pain	50	0.14	0.45		

Table 6: The mean differences of operation time and amount of blood lost between study groups.

Study variables	Study groups	*N*	Mean	SD	*t*-test	*P* value
Operation time (minutes)	Group A	50	118.10	9.30	−38.78	<0.001*
	Group B	50	178.00	5.71		
Blood lost (ml)	Group A	50	77.50	9.54	−64.03	<0.001*
	Group B	50	308.20	23.62		

instability is a multifactorial problem, unnecessary damage to anatomic structures, which stabilize the functional spinal unit, has always been a problem with this technique [8–11]. Moreover, the fact that the spinal canal is exposed more than what would be necessary just for a decompression increases the contact surface between paravertebral muscles and the dura is one of the reasons for extensive scar tissue formation and epidural fibrosis following conventional laminectomy, which may lead to tethering of the cauda equina and radicular symptoms [9, 12, 13]. Microsurgical crossover decompression through a unilateral approach significantly minimizes these problems [14–18]. The muscles are retracted

Table 7: The association between the cost of operation and study groups.

Study variables	Study group		Total	χ^2	P value
	Group A	Group B			
Cost of operation					
4500$	33 (100.0)	0 (0.0)	33 (100.0)		
6000$	0 (0.0)	32 (100.0)	32 (100.0)	**65.02**	**<0.001***
Performed in a governmental hospital (free)	17 (48.6)	18 (51.4)	35 (100.0)		
Total	50 (100.0)	50 (100.0)	100 (100.0)		

*P value ≤0.05 was significant.

only on one side, and the area of the spinal canal, which is exposed to the surrounding tissue, remains small. This reduces the area of potential scar formation. Moreover, the integrity of the contralateral facet joint remains nearly completely intact.

All cases in group A (who underwent microdecompression) had no instability as instability was considered as an exclusion criterion (the patients with vertebral instability are not included in our study, whether group A or group B).

5. Conclusion

Both microdecompression and open laminectomy with posterior stabilization were effective treatment methods for lumbar spinal stenosis regarding leg pain with less postoperative back pain in the group of microdecompression with less operative time, less blood loss, and less cost.

Data Availability

The datasets supporting the conclusions of this article are included within the article.

Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Research Article

A Prospective Six-Month Study of Chronic Pain Sufferers: A Novel OTC Neuromodulation Therapy

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Objective. To assess the durability of treatment over various chronic pain conditions of an emerging, nonprescription electromagnetic neuromodulation device that uses pulsed shortwave therapy. *Methods*. A 6-month prospective study, involving 240 chronic pain sufferers, 94% of whom reported using pain pills and 98% reported using pain therapies prior to entering the study. Their average baseline pain was 8.2 VAS points before treatment; they had a pain duration of 6.5 years, and they were positive responders to pulsed shortwave therapy in an initial 7-day trial. Prospective assessments were obtained at intervals of 3, 4, and 6 months following a retrospective 7-day assessment. Longitudinal analyses were conducted to determine pain relief trends after the initial 7-day device use. *Results*. Seven days after initial treatment, the average pain was reduced to 2.9, a 65% pain reduction for the study subjects. At the 6-month measurement, the average pain was 3.3, a 60% pain reduction from baseline. Only 17% of the subjects saw their pain level increase although this new level was still lower than baseline pain. Pain relief translated into improved quality of life and reduced medication use for the majority of the subjects. There were no significant adverse side effects reported over the 6 months of use. *Conclusion*. Ninety-seven percent of the recruited subjects, all of whom had previously reported clinically significant pain relief using the 7-day PSWT device, sustained this relief for 6 months by using the device on an as-needed basis.

1. Introduction

Developing long-term effective treatments for chronic pain sufferers has proved to be elusive. Evidence from clinical trials and systematic reviews indicate that many interventions for chronic pain provide only mild-to-moderate short-term benefits, with a lack of evidence for long-term effectiveness [1]. The challenge with treating chronic pain is reflected in the lack of correlation between pain level and severity of tissue damage [2] due to complex changes in immuno, sensory, hormonal, and inflammatory processes in the peripheral and central nervous system. Repetitive nociceptive stimulation induces pathophysiological changes in the pain pathways leading to a persistent state of high reactivity and a lowering of the pain threshold. Such a condition is referred to as central sensitization (CS) [3, 4]. Often this occurs after the onset of persistent acute pain which then transitions to chronic pain and is marked by CS-associated neuroplasticity. CS has been linked to the etiologies of osteoarthritis [2, 5], chronic lower back pain [6], plantar fasciitis [7], fibromyalgia [8, 9], neuropathy [10], migraine [11], and many other chronic conditions [6, 12, 13].

Recent guidelines on treating chronic pain recommend a multimodal treatment approach, with an emphasis on nonpharmacologic therapies prior to using pharmacological treatments [14]. Bioelectronic medicine is one such treatment approach aimed at providing therapeutic benefits and involves the use of electrical, magnetic, optical, and ultrasound pulses to modulate nervous system activity (*neuromodulation*) [15]. Those devices that use electrical impulses to achieve targeted neuromodulation are referred to as "*Electroceuticals*." They do this through at least three methods: invasive (implanted), semi-invasive (surface electrodes, such as in transcutaneous electrical nerve

stimulation (TENS) devices), or noninvasive (using electromagnetic fields (EMF)). Modalities based on the first two approaches, i.e., spinal cord stimulators (SCS) and TENS, are routinely employed for pain management [16]. However, these invasive and semi-invasive electroceuticals present risks such as skin damage, postsurgical complications, and cost, factors which have largely tempered recurring use of these electroceuticals for chronic pain management.

The third electroceutical approach relies on EMF. This has the unique advantage of not requiring direct skin contact and thus can be used over clothing/bandaged skin, etc. In addition, the use of radiofrequency (RF) EMF (MHz range) potentially allows battery-operated electroceuticals with long lifetimes. Although classic bioelectromagnetic theory indicates that beyond 10 MHz, RF fields are incapable of producing biological effects other than simple heating [17], Koneru et al. have demonstrated that when low-power RF transmitters are operated adjacent to biological tissue and at maximum output (saturation), modulation of peripheral nerve activity (neuromodulation) can occur [18]. This indicates that RF EMF electroceuticals can achieve neuromodulation.

Pulsed shortwave therapy (PSWT) is a low-power RF electroceutical technology that operates at saturation and relies on tissue absorption of EMF to achieve neuromodulation of peripheral nerves [19, 20]. Recently, a wearable version of PSWT, sold under the brand name ActiPatch®, has become available for nonprescription use in the United States for treating knee osteoarthritis and plantar fasciitis, both of which have been linked to CS. At the time of this study, it was available as a 7-day unit (with no on/off switch) or a 30-day unit with an on/off switch. Although this device does not provide any sensory feedback when topically placed over the area of pain, the PSWT device has been shown to reduce chronic pain and improve quality of life for several chronic pain conditions over treatment periods ranging from 7 days [21–23] to 28 days [24].

At least 3 studies have investigated treatment effectiveness of this device over 7 days. One is a randomized controlled trial (RCT) conducted in the US on plantar fasciitis [21], and two are large registry studies of UK pain sufferers, most of whom reported suffering from pain for at least 6 months prior to using the device. Each study assessed pain using a 0–10 point visual analog scale (VAS). In the plantar fasciitis study, which consisted of 70 subjects, the active treatment group reported a 40% reduction in morning pain (1.7 VAS points) following 7 days of PSWT use, compared to only 7% in the placebo group (0.3 VAS points). The first of the registry studies reported on 5000 subjects suffering with chronic pain of varying etiologies [22]. The study population consisted of individuals with severe pain levels (average VAS ≈ 8) who had independently purchased and used a trial unit (the 7 day unit) of the medical device. Sixty-five percent (65%) reported a clinically meaningful reduction in pain (defined herewithin to be ≥ 2 VAS points) [22]. In this subgroup of clinically significant responders, the mean reduction in pain was 57% (4.7 VAS points). The second registry study involved 1394 chronic back pain sufferers, who reported baseline measures that were very similar to the first registry study [23]. In this back pain study, 52% reported at least a 40% reduction in pain, resulting in an average pain reduction of 5.4 VAS points after 7 days of treatment [23].

A second RCT study, consisting of 60 subjects, investigated treatment efficacy over 28 days of daily PSWT device use, in reducing chronic knee osteoarthritis pain and changes in function. Subjects receiving active treatment reported a 25% decrease in VAS compared to only 3% in the placebo device group [24]. Additionally, active treatment subjects reported a 16% improvement in functionality when compared to 1.6% in the placebo group. More importantly, subjects in the active treatment group demonstrated a significantly greater improvement in pain tolerance thresholds, via a technique known as quantitative sensory testing (QST). This approach is widely considered to be a gold standard in quantifying nerve hyperactivity associated with CS [25].

The above-discussed literature indicates that daily PSWT use is effective in reducing chronic pain levels for a majority of pain sufferers with varying etiologies (many of which are associated with CS) and for up to 28 days. However, evaluating treatment durability for longer periods is crucial in determining the durability of treatment effectiveness. A decline in treatment effectiveness is commonly associated with long-term use of pharmacological treatments, for example, with NSAIDS [26] and opioids, owing to tolerance [27]. The goal of this prospective study is to assess the durability of treatment effectiveness for the PSWT medical device over a 6-month period. Specifically, we investigate whether subjects who reported clinically significant pain relief following 7-day use of the medical device were able to maintain longer-term relief over 6 months, and if so, were any factors predictive of the magnitude of pain relief. The study sample was composed of 240 chronic pain sufferers who had previously indicated that they had been suffering with pain for at least six months, had already started using the 7-day PSWT device, had lowered their pain level by a minimum of 2 VAS points over the course of this 7-day treatment, and had intended to continue treatment using the longer-lasting device. These subjects were then assessed over six months of treatment, evaluating changes in pain level, functionality (sleep and physical activity), quality of life, and medication use compared to baseline.

2. Materials and Methods

This study is a prospective study and was carried out over 6 months. Subjects provided consent, and data analysis was approved by the Institutional Review Board of Duke University (2019-0285).

2.1. Population and Study Sample Characteristics. The sample for this prospective study came from a population of 1841 UK/Ireland chronic pain sufferers who independently purchased a 7-day trial version of the focal PSWT medical device between April and October of 2015 and who also responded to a follow-up marketing and assessment e-mail sent out by the manufacturer. This initial assessment

determined, among other measures, the individual's baseline pain level, the duration of this pain, the pain level after 7 days of PSWT, current treatment therapies, and the degree of their intention to continue treatment with the medical device. The average baseline pain for this population before using the medical device was 8.0 VAS points. They also reported being in pain for an average of 6.4 years and prior to using the medical device were using an average of 1.8 therapies that included pain pills (85%), TENS (16%), heat wraps (27%), topicals (33%), and physical therapy (20%). Of these users, 1143 (62%) reported clinically significant pain reduction over the course of 7 days of PSWT and of this clinically responsive subset, 682 (60%) indicated a definite intent to continue therapy by purchasing the retail (longer lasting) PSWT device. This latter subset was contacted via e-mail with a request to consent in participating in a 6-month study and complete three further assessments. No restrictions were placed in terms of them using or discontinuing other therapies during the study period or the degree to which they needed to use the medical device. The only requirement was that they were asked to fill out the three assessments, which were measured among other things, their use of other therapies, and the degree to which they used the medical device. Of the 682 subjects contacted, 240 (35%) agreed to participate in the study, provided written consent via e-mail, and completed at least one additional assessment. Subjects who completed the six-month assessment were compensated with a free 720-hour retail version of the device (retail price £19.95) given at the end of the study.

In summary, the prospective sample consisted of long-term pain sufferers who, prior to using the medical device, had not found (or at least were not using) therapies that reduced their high levels of pain, but who after using the device for 7 days, reported clinically significant short-term pain relief, who continued use after purchasing the commercially available 30-day device and who provided consent and participated in the prospective study.

The PSWT medical device used in the study is commercially available (ActiPatch®, BioElectronics Corporation, Frederick, Maryland USA). It is regulated as a class II device (special controls) by the US FDA and indicated for over-the-counter use in treating chronic musculoskeletal pain related to knee osteoarthritis and plantar fasciitis in the US. It is also available for broader use in Canada, EU, Australia, and many other countries where it is regulated as a class II(a) device. The device operates at a carrier frequency of 27.12 MHz and has a pulse frequency of 1 kHz, each pulse sustained for a duration of 100 microseconds. The device has a peak incident power of 73 μW/cm^2 (as measured into a 50-ohm load) and a treatment area of 110 cm^2 (See Figure 1).

2.2. Primary Outcome Measures. The goal of this study was to determine if initial pain relief, measured in terms of pain reduction over the 7-day treatment period, was maintained over a period of 6 months. This longer-term pain relief was measured not only by the six-month pain level and changes in pain level from baseline pain but also by changes over time in function (sleep quality and physical activity), quality of life (QoL), and medication use. Using multiple outcome measures reflects the belief that pain relief is a multidimensional construct. Consequently, all of these change measures were viewed to be primary measures of longer-term pain relief.

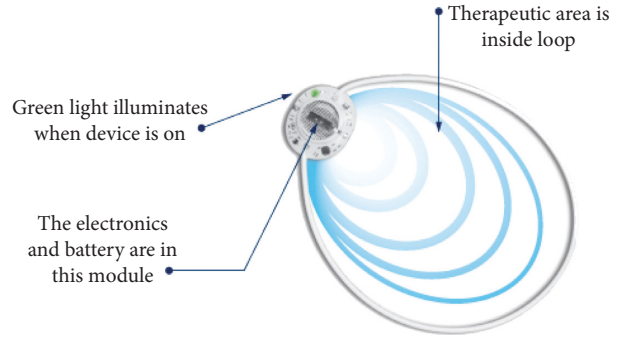

Figure 1: ActiPatch® is a commercially available, topically applied, over-the-counter medical device used for treating chronic pain. The device provides stimulation that relies on tissue energy absorption of high-frequency electromagnetic waves to influence nerve activity in the exposed tissue, a process known as neuromodulation (reproduced with the permission of BioElectronics Corp).

2.3. Description of Assessments. Subjects were sent an assessment at 3, 4, and 6 months following their initiation of PSWT. As a result, four data sets were potentially available for each of the 240 subjects that participated in the prospective study. In the first assessment, subjects' demographics were collected, as well as the location of device use (back, knee, etc.), the underlying etiology, the location of their pain, the baseline pain level, the pain level after 7 days of treatment, the use of analgesic medications, the use of alternate pain therapies (TENS, heat wraps, topicals, physical therapy, and other), and the intent to purchase the longer-lasting medical device. There were no data collected on the stage and/or classification of the chronic pain condition other than pain level, duration, and location of pain. In the three follow-up assessments, data were collected on current pain level, how often they used the medical device, and the degree of change (if any) from baseline in sleep quality, physical activity, quality of life, medication use, and other pain therapies. The levels of available responses and the coding for each response for many of the questions asked are given in Table 1. Higher numbers indicated a more positive change, i.e., an increase in sleep, physical activity, and quality of life and a decrease in medication use and the use of other therapies.

2.4. Data Preparation and Statistical Analyses. Raw data were collected using the Constant Contact e-mail application (*Constant Contact Inc., Waltham, Massachusetts USA*) and exported into a comma-delimited (CSV) file and analyzed with Excel 2016 (*Microsoft Corporation, Redmond, Washington USA*). Data from the 4 assessments times (day 7, 3 months, 4 months, and 6 months) were merged to yield one longitudinal database from which subject identification

Table 1: Available responses and coding for assessment queries.

Assessment queries	Response options
How often do you use ActiPatch?	(i) Every day = 1 (ii) A few times a week = 0.5 (iii) only when needed = 0.3
Pain level (11-point VAS scale)	(i) No pain = 0, ..., worst pain = 10 (ii) *Mild pain is defined as scores of 0-3, moderate as pain scores of 4–6, and severe as pain scores of 7–10*
Changes in sleep and physical activity relative to prior use of ActiPatch	(i) No change = 0 (ii) Increased a little = 1 (iii) Increased a fair amount = 2 (iv) Increased a lot = 3
Changes in medication use relative to prior use of ActiPatch	(i) No change = 0 (ii) Decreased a little = 1 (iii) Decreased a fair amount = 2 (iv) Decreased a lot = 3 (v) Stopped using medications = 4
Patient global impressions of change with PSWT treatment	(i) No change or got worse = 0 (ii) Almost the same, but hardly any change at all = 1 (iii) A little better,but no noticeable difference = 2 (iv) Somewhat better, but the change has not made any real difference-3 (v) Moderately better, a slight but noticeable change = 4 (vi) Better, a definite improvement that has made a real and worthwhile difference = 5 (vii) A great deal of better and considerable improvement that has made all the differences in the world = 6

information (e-mail address) was removed. The Institutional Review Board of Duke University provided protocol approval under Analysis of Existing Data for this database along with the sample of 1841 trial device users.

Temporal changes in outcome measures were analyzed two ways: (1) changes in pain levels (VAS), which were determined by calculating the difference between a subject's baseline pain (day 0, prior to using the trial device) and their reported current pain; (2) Changes in the other measures (i.e., sleep quality, physical activity, medication use, and overall quality of life), which were determined by the subject's responses to questions concerning the extent of change over the specified assessment period, relative to the person's baseline (Table 1). The basic assumption in making these temporal comparisons is that although there is no comparison group not using the medical device for six months, each individual acts as his or her own control since subjects had been treating their pain beforehand, had been suffering from this pain for a long time (average 6.5 years), and their high baseline pain levels implied they had not obtained any substantial long-term temporal relief in pain level from the other tried therapies. We later control for therapy use and duration of prior pain when assessing changes in pain relief after using the medical device during the study period.

Any missing data during the six-month period for an individual were imputed using the last-observed carried forward (LOCF) approach. Factors associated with each of the different multidimensional change measures (including medication use) were determined via OLS regression analyses using Regressit, an Excel add-on statistical package. A p value of 0.05 was set as the threshold for determining statistical significance. Analyses were also conducted to see if there was any selection bias or bias due to subjects dropping out of the study. This was done by comparing the characteristics and distributions of pain levels across three different subsamples of the population of 1841 chronic pain sufferers, these groups being the retrospective population of 1841 users of the 7-day device, the sample of subjects who completed the six-month assessment, and the sample of subjects that dropped out of the study before completion.

3. Results

3.1. Description of Study Sample. The study sample had an average age of 57.9 years, were primarily women (70%), and predominantly (91%) had pain for more than 6 months at the beginning of the study (average 6.5 years). These demographics are nearly identical to the demographics for the sampled population (Table 2 comparing columns 1 and 6). The etiologies most commonly reported by subjects in both the study sample and the sampled population were arthritis and fibromyalgia. However, the study sample reported a higher incidence of fibromyalgia (20%), when compared to the sampled population (10%). While baseline pain levels (VAS) were similar in both groups, the VAS pain levels following 7-day treatment with the PSWT were markedly different (5.0 for the sampled population vs. 2.8 for the study sample). No major differences were observed between the two groups in terms of demographics except by gender (Table 2). This difference is due to the fact that the subsample

Table 2: Baseline demographics/etiologies between total sample and study sample.

	Sample population ($n = 1841$)	Sample with ≥2 VAS reduction at 7 days ($n = 1143$)	Sample with <2 VAS reduction at 7 days ($n = 698$)	Sample with ≥2 VAS reduction at 7 days + "definitely purchase" ($n = 682$)	Sample with ≥2 VAS reduction at 7-days + "not definitely purchase" ($n = 461$)	Study sample ($n = 240$)
Demographics						
Age (years)	55.6	54.4	54.3	56.4	56.3	57.9
Duration of pain (years)	6.4	6.5	6.2	6.4	6.6	6.5
Women	66%	70%	61%	71%	69%	70%
Pain > than 6 months	89%	89%	88%	90%	88%	91%
Baseline VAS	8.02	8.17	7.77	8.26	8.02	8.23
7-day treatment VAS	5.03	3.38	7.72	2.97	3.97	2.82
% pain reduction	33%	59%	0%	64%	51%	66%
VAS ≥2 reduction	62%	100%	0%	100%	100%	100%
VAS ≥3 reduction	54%	87%	0%	94%	77%	97%
% "definitely purchase" intent	38%	60%	3%	100%	0%	100%
Pain etiology						
Osteoarthritis	30%	31%	28%	33%	26%	25%
Rheumatoid arthritis	15%	15%	14%	15%	15%	7%
Fibromyalgia	10%	10%	9%	10%	11%	20%
Sports injury	8%	8%	7%	8%	8%	12%
Neuropathy	5%	5%	5%	5%	5%	8%
Surgery	6%	6%	5%	6%	6%	6%
Tendinitis	3%	3%	3%	3%	2%	4%
Other	23%	22%	29%	20%	27%	18%

Subjects often reported pain in multiple areas of the body, but this designation was predominantly for the back (49%), followed by knee (27%), shoulder (17%), hip (16%), neck (8%), and others (11%). The rank ordering of the locations where the PSWT medical device was applied mirrored the rank order of reported locations of pain.

indicating clinically significant reduction in 7-day pain contained 70% women, compared to only 61% for the subsample not reporting a minimum 2 VAS pain reduction after 7 days (see columns 2 and 3.) This latter subsample also reported lower baseline pain (7.77 vs. 8.17) and a much smaller intent to "definitely buy" a retail device (60% vs. 3%).

3.2. Prior Medication Use in Study Sample. Initial assessment of medication at baseline shows that 94% of subjects in the study sample were using pain pills and 98% were using some pain therapy. A subsample of size 172 of the study sample provided more detail on the variety of analgesic medications they used to help with their severe pain level (Table 3). Ninety-five percent (95%) reported using at least one OTC or prescription analgesic and 43% indicated using at least one opioid or morphine medication.

3.3. Missing Data. Of the 240 subjects, 31 did not complete all follow-up assessments. Of these 31, 15 subjects completed only the 3-month assessment, while the remaining 16 completed both the 3-month and 4-month but not the 6-month assessment. Subgroup analysis for these 31 subjects indicated that 15 last reported having mild pain (0–3 VAS) and their quality of life had improved "a great deal" or shown "a definite improvement." In contrast, the remaining 16 last-reported VAS scores ≥4 before being lost to follow-up and many of these 16 subjects reported little or no improvement in their quality of life.

Table 3: Analgesic medications used by the study sample.

Analgesics	Fraction of users (%)
NSAIDS (e.g., ibuprofen)	43
Paracetamol	61
Weak opioids (e.g., codeine)	25
Strong opioids (e.g., hydrocodone)	11
Tramadol or equivalent	8
Pregabalin (e.g., Lyrica)	8
Amitriptyline	17
Topical opioid (e.g., morphine)	8
Topical NSAIDS (e.g., Voltarol)	21
Gabapentin	2
Other	4
No analgesics	5

Note: medication use data were available for only 172 out of the 240 subjects.

3.4. Temporal Trends in Pain Reduction. The distribution of subjects, partitioned by three pain categories for the different points in time, is shown in Table 4, while the full distribution of pain scores for these same time periods is shown in Figure 2.

Ninety-one percent of the study sample reported being in severe pain prior to using the medical device (baseline), but only 3% continued to be in severe pain after the 7-day PSWT treatment period. In contrast, the subsample of the population who did not indicate clinically significant initial reduction reported almost no average pain reduction over this time period (see Table 2). By the end of the 6-month intervention period, using data for 209 subjects who completed the assessment in month 6, 58% reported being in mild pain, 36% reported moderate pain, and 6% reported severe pain. Importantly, 9% reported no pain. These lower levels of pain (and thus large pain reductions) are in stark contrast to the high pain levels these subjects reported having for extended periods of time (average duration of 6.5 years) prior to using the medical device.

Comparing the breakdown of scores for the 209 subjects with that of the 31 subjects who did not complete the study, we found 52% of the latter group reported mild pain on their last assessment, 42% moderate pain, and 6% severe pain. These percentages are very similar to the percentages in each of the pain categories for the 209 subjects that completed the six-month assessment. Consequently, the distributions for all 240 subjects used in the study are very similar to the 209 who completed the last assessment.

The vast majority (72%) of the subjects, who reported mild pain levels after 7 days of treatment, reported mild levels of pain at the end of the six-month study period, and the remaining 28% reported moderate pain levels (Table 5). For the other two 7-day pain levels (i.e., moderate and severe), the general trend for the duration of the study was towards lower pain levels (i.e., pain reduction). For example, all but 9% of those few who reported severe levels of pain after 7 days reported mild (36%) or moderate (55%) levels of pain by the end of the study.

3.5. Additional Outcome Measures. Subjects also provided other measures of pain relief, i.e., improvements in function (sleep quality and physical activity) and overall quality of life, any decrease in their medication use, and stopping medication use or other therapies (Table 6).

These additional outcome measures show strong associations with the initial 7-day pain level and the final pain level. The 57% of subjects in the study sample who reported being in the mild pain category by the end of the study also reported an average QoL score greater than 5 ("=*definite improvement, one that made a real difference*") and average scores greater than 2 for sleep and physical activity ("=*improving a fair amount*"). Approximately 28% of the study sample indicated that they were no longer using any analgesic medications and 16% stopped using other therapies; unsurprisingly, subjects with the lowest final pain levels more likely belonged to these groups. Even the 15% of subjects in the study sample who reported final VAS≥6 reported functional improvements: ≥3.5 for QoL ("=*a slight but noticeable difference*") and ≥1.00 for sleep quality ("=*little improvement*") although all these individuals continued to use pain medication.

Usage of the medical device monotonically decreased over time, from 100% using the device every day during the first 7-day period, to only 36% using the device every day after 6 months. Forty-one percent (41%) reported using the device only as needed or stopped using it completely by the end of the study (Figure 3).

In terms of overall improvements for the study sample, 62% reported a "*great deal*" or "*definite improvement*" in their QoL. For sleep, 60% reported a "*great deal*" or a "*fair amount*" of improvement, while for physical improvement, 53% reported a "*lot more*" or a "*fair amount*" of improvement. For medication, 52% reported a "*lot*" or a "*fair amount*" of reduction. These four percentages of people reporting meaningful improvements were compatible with the 57% of the sample who reported having mild levels of final pain (defined as having pain levels of 3 VAS points or less). They are also in line with the 73% who reported at least a 50% reduction in pain and the 52% who reported at least a 60% reduction in pain by the end of six months of treatment.

3.6. Likeliness of Long-Term Pain Relief. Linear regression analyses were used to identify the observable variables that could best predict which subjects were most likely to receive long-term pain relief. Pain relief (dependent variable) was defined in terms of seven different measures: the first three were in terms of VAS scores, i.e., final pain level, change in pain, and percent improvement, while the remaining four were based on the two function measures, sleep and physical activity, the one being change in QoL measure and the other being measure of change in medication use. As a result, there was a total of 7 independent regression analyses conducted, each tapping the underlying construct of pain relief. In all cases, the same 13 independent variables were used. Variables are categorized in terms of five subsets: demographics, etiology and location of pain, baseline pain intensity, baseline treatments, and the 7-day pain level (Table 7).

This selection of variables was done for three reasons. First, all these variables are available after the subject used the PSWT device for the initial 7-day treatment. Second, by including a broad set of predictors, it is possible to control for the diverse set of etiologies, baseline conditions, and use of other therapies in determining long-term pain relief. Third, by including all the variables in each analysis, it is possible to better assess if any discovered association is possibly spurious or consistent across the multiple dimensions of pain relief.

The regression coefficients and the statistical significance of factors that reached at least 0.05 level of significance are shown in Table 7. Consistent with Table 5 results, the VAS score following the 7-day treatment is a statistically significant predictor for all seven pain relief measures. Higher 7-day VAS scores are indicative of lower long-term treatment effectiveness, regardless of which of the seven pain relief measures were used. No other observable variable

Table 4: VAS scores of the study sample categorized by mild, moderate, and severe levels at baseline and at the four assessment periods.

Pain score (VAS)	Fraction of study sample					
	Baseline ($N = 240$)	7 days ($N = 240$)	3 months ($N = 222$)	4 months ($N = 208$)	6 months ($N = 209$)	Last reported ($N = 240$)
0–3 (mild pain) (%)	0	70	67	61	58	57
4–6 (moderate pain) (%)	9	27	30	35%	36	37
7–10 (severe pain) (%)	91	3	3	4	6	6
Average sample VAS	8.23	2.86	2.96	3.13′	3.25	3.31

The last column is data from the last-observed value of all subjects.

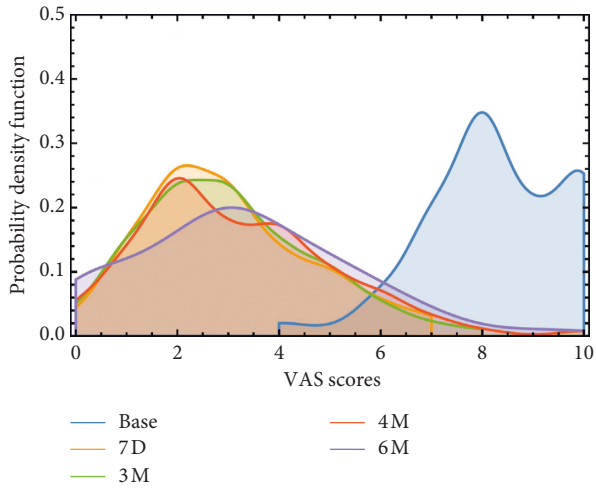

Figure 2: Distribution of pain levels (VAS) in the study sample at the various time points during which data were collected: baseline, 7days, and 3, 4, and 6 months. A shift in distribution from baseline, following initial 7-day PSWT treatment, indicates that most of the pain relief obtained in the first 7 days is maintained over a 6-month period, with continued device use.

following the 7-day treatment had a strong predictive value across all the multiple pain relief measures. Higher baseline VAS levels were associated with a greater reduction in pain (VAS change both in absolute and percent), greater improvements in sleep quality, and overall QoL by the end of the study, all else equal. The longer a subject suffered with a pain condition (duration), the higher their VAS scores tended to be after the 6-month intervention. Longer pain durations were also found to have a negative impact on changes in medication use, as does the use of other different treatment therapies. In contrast, reduction in medication use tends to be greater for subjects who initially (at baseline) used more OTC medications and/or were less likely to use other therapies prior to using the PSWT device. The only demographic variable to reach significance was the age of the subject which was negatively correlated with the person's change in QoL. Other than fibromyalgia, which is negatively associated with change in sleep quality, none of the seven pain relief measures were found to be related to the location or etiology of the pain.

4. Discussion

There is inadequate evidence to ascertain whether over-the-counter electroceutical technologies, such as TENS, are effective in relieving chronic pain [28]. Pulsed shortwave therapy (PSWT) is an OTC electroceutical technology that uses electromagnetic fields (EMFs) to achieve nonsensory neuromodulation without skin contact, thus allowing continuous and recurring use. In this study, we investigated the durability of PSWT treatment in relieving chronic pain.

The PSWT device that was used in the present study was previously evaluated for treatment effectiveness in two large registry studies [22, 23]. In both studies, it was found that about 2/3rd of the users obtained clinically significant reductions in pain (VAS reduction ≥ 2). In addition, it was also shown that this pain reduction was obtained for multiple etiologies and anatomical locations. However, these registry studies did not evaluate whether the pain reduction reported by these subjects was durable, and if so, whether it was possible to predict which subset of subjects were most likely to experience treatment durability. Evaluating treatment durability is important for any medical intervention, since a vast body of clinical research indicates that many pharmacological treatments show a decline in effectiveness over time [26, 27]. This lack of efficacy from a wide range of existing treatments was evident among subjects in the two discussed registry studies as well as the present study, as witnessed by the fact that subjects reported high baseline pain levels (VAS ≥ 7) despite actively using one or more analgesic therapies [22, 23]. The present prospective study examines the durability of treatment effectiveness for a PSWT neuromodulation device in a cohort of 240 subjects who had indicated clinically significant pain reduction after using the PSWT device for 7 days.

The 240-subject sample recruited for this study did not present with any significant differences in age, duration of pain, and baseline pain level from the sampled population of 1841 UK/Ireland chronic pain sufferers. Both groups had a high incidence of women participants, with 66% in the sampled population and 70% in the study sample classifying themselves as women. The slightly larger percentage in the study sample was due to the fact that 66% of all the women in the total population indicated a clinically significant reduction in pain after 7 days of treatment compared to only 55% for men and thus were more likely to be asked to participate in the study. This finding of women being more likely to report clinically significant reduction in pain is in line with the prior literature that indicates differences in responses to pain between men and women [29, 30] and merits further exploration for why such differences might occur. Both the sampled population and study samples

Table 5: Transition matrix for VAS score.

VAS score after initial PSWT treatment (7 days)	VAS score at end of study (6 months)		
	0–3 (mild pain) (%)	4–6 (moderate pain) (%)	7–10 (severe pain) (%)
0–3 (mild pain)	72	28	0
4–6 (moderate pain)	31	52	17
7–10 (severe pain)	36	55	9

A majority of subjects who are experiencing only mild pain after the initial 7-day PSWT treatment continue to maintain relief over 6 months. The same is true for individuals with mild pain although there is more of a tendency to see a reduction in pain versus an increase. The majority of subjects still in severe pain after 7 days of PSWT treatment reduced their pain over 6 months.

Table 6: Average outcome measures for the different levels of final pain.

Last reported VAS	% study sample ($N = 240$)	7-day VAS (after 7-day treatment)	Δ VAS (baseline: last reported)	Δ QoL (baseline: last reported)	Δ sleep (baseline: last reported)	Δ medications (baseline: last reported)	Δ physical activity (baseline: last reported)	% stopped medication use	% stopped nondrug pain therapies
0–1	18%	1.43	7.41	+5.48	+2.22	+3.02	+2.18	34	23
2–3	39%	2.71	5.54	+5.07	+1.99	+2.5	+1.86	16.5	17
4–5	28%	3.59	3.91	+4.6	+1.76	+2.02	+1.4	13.5	14
6–7	12%	4.31	2.58	+3.95	+1.23	+0.57	+0.98	0	13
8–10	3%	5.00	−0.33	+3.50	+1.00	+0.50	+0.83	0	0

Numerical values for the change measures can be found in Table 1.

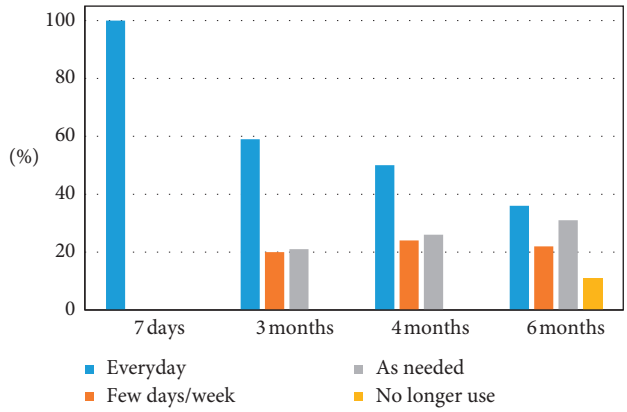

Figure 3: Device usage patterns among study sample cohorts over the 6-month period. Pain relief was maintained over the 6-month period despite decreasing device use. The number of subjects using the device daily decreased from 100% in the first 7-days, to only 36% at 6-months. Additionally, 11% of users no longer needed to use the device after 6 months.

reported a wide range of etiologies and pain locations although arthritis and fibromyalgia were the most common pain etiologies and back was the most common location. The study sample of 240 subjects reported a higher incidence of fibromyalgia (20%), when compared to 10% for the population of 1841 chronic pain sufferers. We cannot ascertain at this time why the study group had a higher incidence of fibromyalgia participants. There were only minor differences in average age and pain duration between subjects reporting a clinically significant reduction in pain after the 7-day treatment and those that did not. The implication is that these variables are not good predictors of who are most likely to report 7-day pain relief from the focal medical device.

The range of pain etiologies and other demographic information measured within the study sample allowed investigation of factors that could be highly associated with both initial pain relief and the durability of this relief. The initial pain relief attributed to treatment from the focal medical device is not highly associated with any etiology of pain or demographic factor, other than gender (Table 2). The regression analyses revealed that the only statistically significant factor in predicting the seven six-month pain relief measures was an individual's 7-day pain score. This is noteworthy, since it highlights that if this 7-day treatment is successful, the individual is highly likely to continue to get long-term pain relief, not only in terms of reduced pain levels but also in terms of increased function and decreased medication use. Pain duration at baseline was also a good predictor for assessing final pain levels, level of pain reduction (percent), and change in medication use—the longer the pain duration, the lower the reported pain relief. Thus, it appears that the longer a subject was suffering from pain, the less relief the person was able to obtain. Interestingly, no gender effects were noted, and the only pain etiology found to predict six-month pain relief was fibromyalgia, which negatively impacted improvements in sleep quality. Thus, neither etiology nor location of pain appears to have any major influence in determining who will get pain relief (either short term or long term), with gender only affecting the probability of getting initial pain relief (women more so, than men). Conditional on getting this relief, no gender differences were found in terms of long-term relief.

The consistency of the treatment effectiveness over the six-month period is reflected in the trend of the mean VAS reduction, which after the 7-day treatment was 5.3 points (65% reduction) and 4.9 points (60% reduction) after six months. In terms of pain reduction, the majority (73%) of the study sample reported at least 50% VAS reduction compared to baseline at the end of the 6-month period and more than half the sample (52%) reported pain reduction of

Table 7: Variables used in the regression analyses to determine if the variable is useful in explaining a particular outcome measure and the coefficients and significance level of those which reached the 0.05 significance level.

Independent variable	Final pain score	Change in pain	% improvement	Change in sleep	Change in physical activity	Change in QoL	Change in meds
Demographics							
Gender (women)							
Age						−0.013 (0.1)	
Etiology/location							
Arthritis							
Fibromyalgia				−0.364 (0.03)			
Back							
Knee							
Other location							
Pain intensity							
Baseline		1.10 (00)	0.058 (00)			0.112 (0.04)	0.153 (0.02)
Duration	0.045 (00)	−0.044 (00)	−0.005 (02)				−0.038 (0.00)
Current treatment							
OTC meds							0.356 (00)
Use of opiate meds							
Other therapies							−0.186 (0.01)
7-day pain level	0.613 (00)	−0.633 (00)	−0.074 (00)	−0.079 (0.04)	−0.080 (0.04)	−1.87 (00)	−0.264 (00)
R^2	0.36	0.48	0.32	0.10	0.08	0.18	0.27

at least 60%. When categorized by VAS scores at the end of the 6-month intervention, 57% of the sample previously suffering with severe chronic pain reported they were only in mild pain, while 29% reported moderate pain levels. These results were found to be independent of the pain etiology and pain location.

When tracking the consistency of an individual's pain relief over time, we found that 72% of subjects who report their pain after the 7-day treatment as mild will continue to experience this level of pain relief even at the end of the 6-month period. The same pattern was observed for subjects reporting moderate pain after 7-day treatment, with 83% of these subjects reporting mild-moderate pain after 6 months. Interestingly, 91% of the few subjects in our sample who reported severe pain even after the 7-day treatment were no longer in severe pain by the end of 6 months, with 36% experiencing only mild pain and 55% experiencing moderate pain. This indicates that a majority of individuals who reported still being in severe pain even after reducing their baseline pain by 2 or 3 VAS points after the initial 7-day treatment still benefited from longer-term PSWT use. However, this latter group was composed of only 14 subjects, and thus, we caution the reader not to generalize from these findings. Further study is needed to determine if longer use of the medical device is needed for some subjects who did not get initial significant pain relief to get subsequent long-term functional improvements. With this noted, the overarching finding is that the long-term benefits of PSWT for chronic pain patients in terms of pain reduction can be quickly assessed after a relatively short trial period of 7 days. Once assessed, patients who report clinically significant pain relief with the 7-day initial treatment have a high likelihood of maintaining the pain relief for at least six months.

Unsurprisingly, pain reduction was accompanied with functional improvements in sleep quality, physical activity, patient global impressions of life changes, and a reduction in medication use—all of which are strong indicators of QoL improvements. This decrease in analgesic medication use over the 6-month period is a significant outcome, since long-term use of many analgesics results in adverse side effects that can impact patient quality of life [23, 31]. These include the highly significant and often multiple adverse side effects from opiate-based analgesics that are correlated with higher doses and long-term use [32].

The PSWT device used in this study was a low-power RF electroceutical that provided therapeutic benefits through peripheral neuromodulation [19, 20]. This is in line with Brook et al. [21] who demonstrated that neuromodulation can occur when low-power RF transmitters, such as the one used in the PSWT study device, are operated adjacent to biological tissue and at maximum output [18]. It is also compatible with clinical evidence showing that PSWT stimulation increases proximal and distal pain tolerance thresholds in subjects with knee osteoarthritis [24] and is consistent with the premise that mitigation of nerve hypersensitivity plays a critical role in treating chronic, intractable pain. Additionally, PSWT treatment has also been shown to reduce pain for patients presenting with various levels of nerve hypersensitivity (central sensitization), as measured by a standardized, central sensitization inventory assessment (CSI) [33–35], an evaluation tool developed to determine the extent of CS in chronic pain patients [34, 35].

The durability results reported from the current study indicate that subjects do not appear to habituate to continuous/recurring PSWT stimulation. This may be a reflection of the mechanism of action associated with PSWT, i.e., the *stochastic* (i.e., nondeterministic) nature of the stimulation. Moreover, subjects continued to maintain lower pain levels over the study period despite gradually reducing the duration of device use. This may be due to an increase in pain tolerance thresholds, indicating a possible mitigation of underlying nerve hypersensitivity associated with the

chronic pain etiology. Whether PSWT treatment can mitigate central sensitization itself needs to be further evaluated in future randomized, double-blinded, placebo-controlled studies by utilizing CSI as an outcome measure.

4.1. Possible Limitations. This study has several limitations. First, the study utilized self-reported data and some of the measures required the subject to recall levels of pain, sleep, etc., prior to using the PSWT device. Consequently, these measures are subject to recall bias. However, it is the authors' belief that since chronic pain is salient to the respondents, recalling pain levels is not a cognitively difficult task. Perhaps of more concern is the reliability of responses, especially for pain. However, the average responses for subjects were consistent with findings from the large-scale registry studies discussed earlier. Likewise, many of the measures used in the study recorded changes over time, e.g., the difference in baseline and final pain (6 month) levels. By utilizing differences, any individual level bias associated with the person over/under reporting pain levels was removed. Other change measures were taken relative to the person's long-term baseline. These function and medication measures trended in the same direction as the person's pain reduction, thereby increasing confidence that the study captured true therapeutic responses to the PSWT treatment.

Another possible limitation is the lack of a control arm. Placebo effects associated with analgesics have been reported to range from 19% to 30% [36] and result in an average reduction of about 1.5 VAS points [37]. Furthermore, prior placebo-controlled studies using the same PWST device have shown only modest placebo responses [21, 24]. The observed reduction in pain over the six-month study was 59% (4.9 VAS points), which is far greater than the reduction associated with analgesic placebo effects reported in the literature. Moreover, the authors are unaware of any clinical research indicating that placebo effects associated with an active analgesic intervention can persist for 6 months, in the majority of subjects under study. While the decrease in pain level and an increase in functionality/QoL over the 6-month period could be attributed to causes other than the medical device, it is to be noted that these subjects had experienced persistent pain for several years and tried multiple interventions—without obtaining substantial and/or sustained pain relief. Thus, there is little reason to expect that this pain relief fortuitously occurred in the study period.

5. Conclusion

Electroceuticals offer immense potential as a non-pharmacological intervention for chronic pain management. Current over-the-counter electroceuticals, such as TENS devices, rely on skin contact to achieve neuromodulation. However, continuous/recurring use of TENS is limited due to the potential for skin damage, need for short use duration (typically, less than 30 mins, twice a day), and unpleasant sensations (shocks, tingling). PSWT electroceuticals, on the other hand, use electromagnetic fields (EMF), which easily pass through skin/bandaging, can be incorporated into wraps/braces and are well tolerated by patients owing to a lack of any sensation during use. This prospective study involved a 6-month assessment of 240 chronic pain subjects, who at the time of enrollment had obtained pain relief after 7 days of treatment with a commercially available PSWT electroceutical device. The results indicate that pain relief was sustained for 6 months in over 85% of subjects. In addition, subjects reported a substantial improvement in functionality through measures such as physical activity, sleep quality, and overall quality of life. They also decreased consumption of pain medication, including prescription and opioid-based pain medications.

A major objective of any electroceutical is to serve as an effective adjunct for multimodal pain management. PSWT was found to be consistently effective in providing pain relief for varying pain etiologies and in multiple anatomical locations. Given the lack of adverse effects and ability of patients to tolerate long-term PSWT use, it is the authors' conclusion that PSWT is an effective, over-the-counter electroceutical therapy for a substantial portion of the chronic pain population.

Data Availability

The data are the property of BioElectronics Corp but can be viewed on request.

Conflicts of Interest

Richard Staelin is an investor in and consultant for BioElectronics Corporation. Sree Koneru is a paid employee of BioElectronics Corporation. Ian Rawe is a paid employee of BioElectronics Corporation. The authors declare that they have no conflicts of interest.

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