Pain Research and Management

Novel Advances in the Clinical Assessment and Management of Painful Musculoskeletal Conditions

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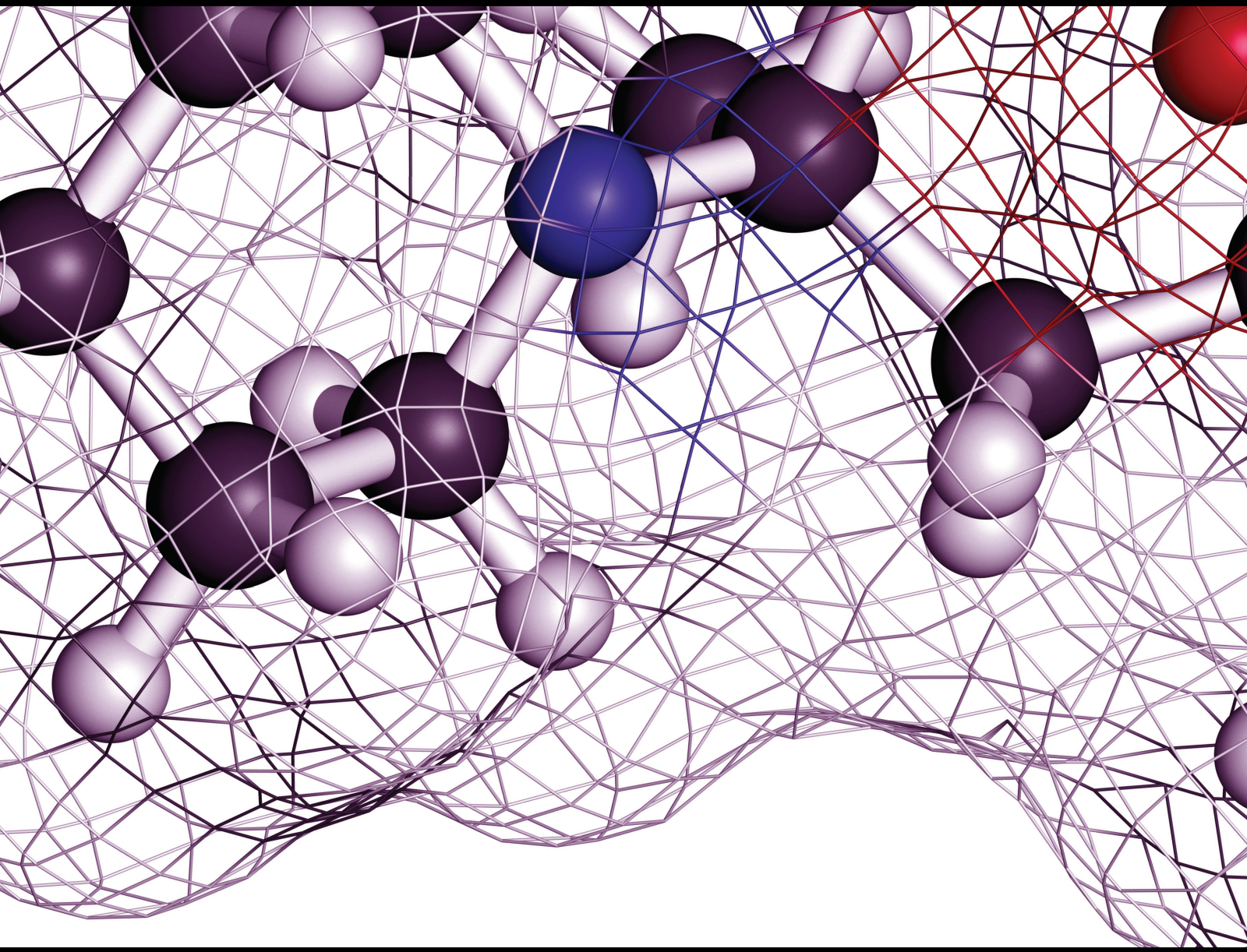

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Research Article

Clinical Effects and Safety of Auricular Acupressure as an Adjunct Therapy on Postoperative Pain among Patients with Hip Fracture: A Meta-Analysis

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Objectives. To evaluate the short-term outcome of treatment by auricular acupressure (AA) on postoperative pain among hip fracture (HF) patients. *Methods*. A systematic search for randomized controlled trials on this topic was conducted through May 2022 by searching multiple English and Chinese databases. The methodological quality of the included trails was assessed by the Cochrane Handbook tool, and relevant data were extracted and statistically analyzed by RevMan 5.4.1 software. The quality of the evidence supporting each outcome was evaluated by GRADEpro GDT. *Results*. Fourteen trials with a total of 1390 participants were included in this study. Compared with conventional treatment (CT) alone, the combination of AA and CT had a significantly greater effect on the visual analog scale at 12 h (MD −0.53, 95% CI −0.77 to −0.30), 24 h (MD −0.59, 95% CI −0.92 to −0.25), 36 h (MD −0.07, 95% CI −0.13 to −0.02), 48 h (MD −0.52, 95% CI −0.97 to −0.08), and 72 h (MD −0.72, 95% CI −1.02 to −0.42), amount of analgesics used (MD −12.35, 95% CI −14.21 to −10.48), Harris Hip Score (MD 6.58, 95% CI 3.60 to 9.56), effective rate (OR 6.37, 95% CI 2.68 to 15.15), and adverse events (OR 0.35, 95% CI 0.17 to 0.71). *Conclusions*. Compared with CT alone, the combination of AA and CRT had a significantly greater effect on postoperative pain in HF patients. However, trails with a rigorous methodology, including standard protocols for AA and multiethnic subjects, are still needed.

1. Introduction

As the aging process of the population continues to accelerate, the proportion of the elderly (>60 years) will continue to increase [1]. It is estimated that by 2050, the proportion of the elderly population will reach 21.1% worldwide [2, 3]. Hip fracture is a common type of fracture in the elderly and ranks among the top 10 of disability [4]. It is estimated that the absolute number of hip fractures is expected to increase from 1.6 million in 2000 to 6.3 million by the year 2050 [5]. Hip fracture (HF) has become a worldwide health problem, it is estimated that the annual cost of HF treatment has increased from approximately 10.3 to 15.2 billion dollars in 1990 to 17 billion in 2002 [6].

Timely surgery for hip fractures remains the mainstay of treatment, including internal fixation, total hip arthroplasty, and hemiarthroplasty [7]. Many official clinical societies recommend postoperative multi-modal analgesia [8] because elderly patients with inadequate postoperative pain control are reluctant to mobilize, thus increasing the potential risk of complications and slowing recovery [9]. Adequate analgesia is of great significance. Current strategies for pain management include oral and parenteral systemic analgesia, and systematic administration of opioids remains the most commonly used analgesia protocol [10]. While opioids are effective in relieving static pain, they may not be sufficient for dynamic pain [11]. Furthermore, the use of opioids may bring side effects, such as delirium, drowsiness, and even respiratory

depression, which may affect the prognosis of patients [12]. Thus, to lower the risk of adverse events and also guarantee treatment efficacy, complementary and alternative therapies have been investigated and compared.

Acupuncture is a traditional nonpharmacological treatment in China and has been widely recognized worldwide [13]. Available evidence suggests that acupuncture is effective for pain relief, thus the World Health Organization recommends the use of acupuncture for a variety of pains, including postoperative pain [13]. As an important component of acupuncture [14], auricular acupressure (AA) has also been deemed effective for pain management by the National Institutes of Health [15]. A literature search yielded many published clinical randomized controlled trials (RCTs) of AA for postoperative pain among HF patients. Consequently, the aim of this study was to evaluate the short-term outcome of treatment by AA on postoperative pain among HF patients by conducting a systematic literature review and meta-analysis of RCTs.

2. Methods

The protocol of this study was registered in PROSPERO (https://www.crd.york.ac.uk/prospero). This work was performed following criteria in the Cochrane Handbook [16] and reported in line with preferred reporting items for systematic reviews and meta-analyses (PRISMA) [17].

2.1. Search Strategy. Eight databases (Pubmed, EMBASE, Cochrane Library, Web of Science, China National Knowledge, and Wan Fang Database, China National Knowledge Infrastructure, Chongqing VIP, and Sino-Med) were searched on May 18, 2022, using the following keywords: auricular acupressure, hip fracture, randomized clinical trials. The detailed search strategy for PubMed is given in supplementary file A.

2.2. Criteria for Considering Studies. Included criteria were as follows: (i) type of study: published randomized controlled trial (RCT) in English and Chinese; (ii) intervention: AA with conventional treatment (CT); (iii) comparison: CT; (iv) population: diagnosed as having a hip fracture confirmed by imaging, regardless of race, sex, or age; and (v) outcome: pain intensity (visual analog scale (VAS)) at 12, 24, 36, 48, and 72 h after surgery the amount of analgesics used, the Harris Hip Score (HPS), the effective rate (ER), and adverse events (AE). In general, ER is defined by the formula: ER = ("total number of patients" – "number of patients without response")/total number of patients; "no response" is defined as no significant change in VAS score after treatment. Trails of AA with more than one Traditional Chinese medicine treatment technique as an intervention were also excluded.

2.3. Study Identification. Search results were imported into Endnote and duplicates were removed. Two research studies independently screen the titles and abstracts of the retrieved articles, evaluate the potential full texts, and determine the eligibility of the reviews. Any discrepancies were solved by introducing a third researcher for judgment.

Data were extracted by two independent research studies using a predefined form, including: first author, year, country, simple size, characteristics of patients, course of disease, treatment protocol, outcome indicators, and consequences of and outcomes. Resolve any discrepancies through consultation.

2.4. Quality Assessment. Two research studies independently assessed the risk of bias by using the Cochrane Collaboration tool [18]. Each trail could be judged to be at "low," "high," or "unclear" risk of bias according to the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete dataset, selective reporting, and other bias. If more than half of the domains were assessed as having a low risk of bias, the trial was assessed as having a low overall risk of bias; if more than half of the domains were assessed as having a high risk of bias or an unclear risk of bias, the trial was assessed as having a high overall risk of bias. Resolve any discrepancies through consultation.

2.5. Data Synthesis. The odds ratio (OR) with 95% of CIs for dichotomous outcomes and the mean difference (MD) for continuous variables. The heterogeneity of the studies was assessed using the I^2. If $I^2 < 50\%$, there was no significant heterogeneity among studies, and a fixed effect model was used to analyze the data. If $I^2 \geq 50\%$ of the heterogeneity among the studies was significant and a random effect model was used to provide the evaluations of the intervention. Subgroup analyses were determined by whether the obtained data were sufficient. A funnel plot was used to assess publication bias.

2.6. Level of Evidence. Two research studies independently assessed the certainty of evidence for each outcome using a grading of recommendations assessment, development, and evaluation (GRADE) system [19]. The GRADE guideline consists of seven domains, namely, risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of the evidence was rated as high, moderate, low, and very low. The summary of findings table was created by the GRADEpro GDT (https://gradepro.org/). Resolve any discrepancies through consultation.

3. Results

3.1. Literature Screening. Literature screening flowchart is shown in Figure 1. A total of 460 trails were identified. After removing duplications, the titles and abstracts of 267 trails were further evaluated. Next, the full texts of the remaining 21 records were assessed, and 14 trails were finalized for inclusion in our meta-analysis [20–33].

3.2. General Characteristics. Characteristics of the included trails are presented in Table 1. 1390 participants were included from the 14 RCTs, which were published between 2012 and

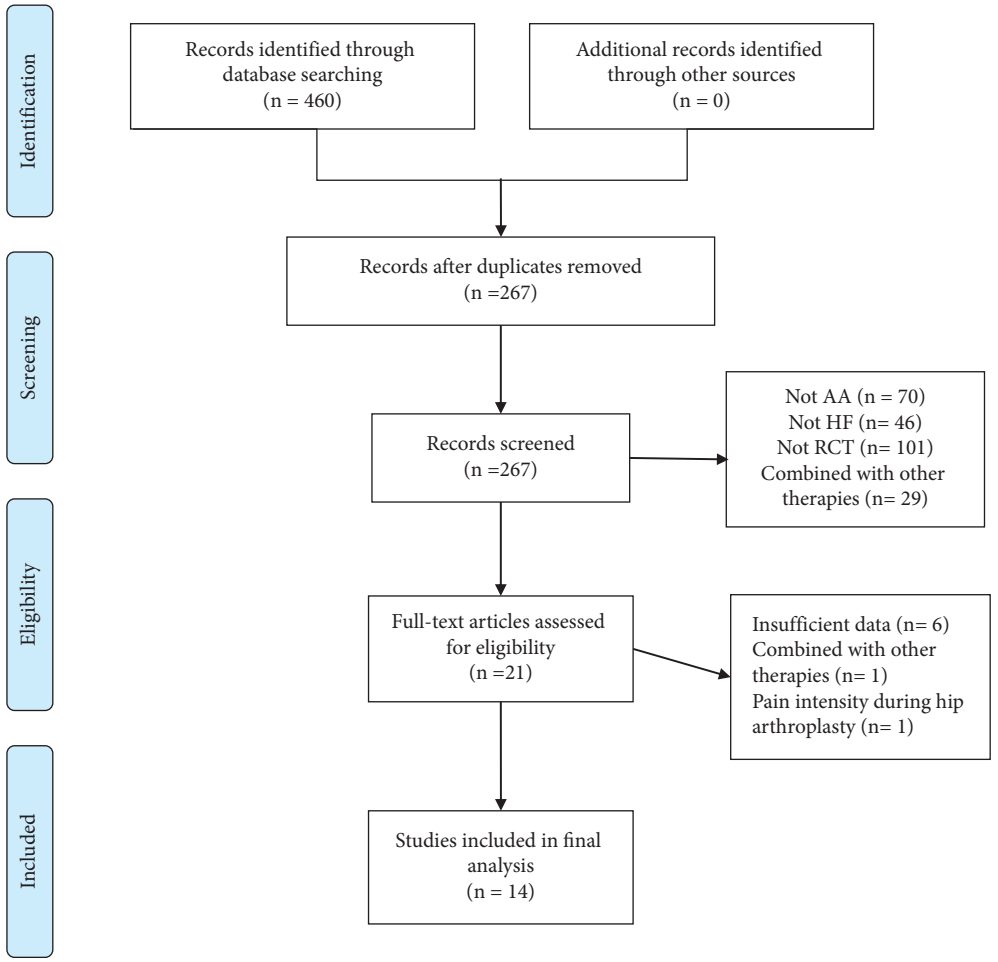

Figure 1: Literature screening flowchart.

Table 1: Characteristics of the included trails.

Study	Simple size	Age		Intervention		Therapy duration	Outcomes
		I	*C*	*I*	*C*		
Li et al. [20]	35/35	68.94 ± 5.66	69.67 ± 5.52	AA + CT	CT	3~5 t/d, 3 d	VAS, HHS, AAS
Xu and Li [21]	38/38	66.80 ± 3.73	66.88 ± 3.79	AA + CT	CT	3~5 t/d, 2 d	VAS, AAS
Sun [22]	48/48	N/A	N/A	AA + CT	CT	3~5 t/d, 3 d	ER
Wu and Wang [23]	35/33	39.5 ± 7.1	41.3 ± 7.2	AA + CT	CT	4~6 t/d, 3 d	VAS, AAS, AE
Wang et al. [24]	40/40	N/A	N/A	AA + CT	CT	3~5 t/d	HHS, AE
Yang [25]	60/60	54.6 ± 8.1	53.4 ± 8.3	AA + CT	CT	3~4 t/d	VAS, ER
Chen [26]	30/30	73.56 ± 7.09	73.48 ± 6.82	AA + CT	CT	4 t/d	VAS
Lv [27]	49/49	59.8 ± 8.6	59.5 ± 8.7	AA + CT	CT	3~5 t/d, 3 d	VAS
Zhu [28]	235/183	59.84 ± 6.13	60.19 ± 5.74	AA + CT	CT	4 t/d	VAS, HHS, AAS, AE
Shen and Zhou [29]	40/40	N/A	N/A	AA + CT	CT	3~5 t/d, 3 d	VAS, HHS
Tian et al. [30]	36/36	N/A	N/A	AA + CT	CT	3~5 t/d, 3 d	VAS
Xu [31]	19/19	60.74 ± 8.76	59.32 ± 7.68	AA + CT	CT	3~5 t/d, 3 d	VAS, AE
Wang et al. [32]	30/30	60.93 ± 5.90	59.87 ± 6.21	AA + CT	CT	4 t/d	VAS, HHS, AAS, AE
Usichenko et al. [33]	29/25	68 ± 10	66 ± 11	AA + CT	CT	3 d	VAS, AAS, AE

C: control group; *I*: intervention group; N/A: not applicable AA: auricular acupressure; CT: conventional treatment; VAS: visual analog scale; AAS: amount of analgesics used; HHS: Harris Hip Score; ER: effective rate; AE: adverse events.

2022. All of them were conducted in China and reported nonsignificant differences in their patient baseline characteristics. The main assessment tools were the VAS and the amount of analgesics used, HPS: Harris Hip Score, ER, and AE.

3.3. Methodological Quality Assessment. As shown in Figures 2 and 3, the risk of bias in the included studies was mainly derived from random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Finally, 8 of the 14 RCTs were assessed as having a low overall risk of bias, and the rest had a high overall risk of bias.

3.4. Results of Meta-Analyses

3.4.1. Visual Analog Scale

(1) Visual Analog Scale at 12 h. VAS was used to score the pain degree of patients, which the score was in direct proportion to the pain degree. Eight trials with a total of 886 participants recorded VAS at 12 h of the intervention. The random effect model was applied, and pool results showed that AA could reduce VAS significantly in the experimental group than control group (MD −0.53, 95% CI −0.77 to −0.30) as shown in Figure 4. In addition, the data provided by the included studies were insufficient to support subgroup analyses, and therefore no further subgroup analyses were performed in subsequent analyses. The funnel plot was given in supplementary file B.

(2) Visual Analog Scale at 24 h. Eight trials with a total of 960 participants recorded VAS at 24 h of the intervention. The random effect model was applied, and pool results showed that AA could reduce VAS significantly in the experimental group than the control group (MD −0.59, 95% CI −0.92 to −0.25) as shown in Figure 5. Funnel plot was given in supplementary file B.

(3) Visual Analog Scale at 36 h. Three trials with a total of 532 participants recorded VAS at 36 h of the intervention. The fixed effect model was applied, and pool results showed that AA could reduce VAS significantly in experimental group than the control group (MD −0.07, 95% CI −0.13 to −0.02) as shown in Figure 6. Funnel plot was given in supplementary file B.

(4) Visual Analog Scale at 48 h. Nine trials with a total of 1002 participants recorded VAS at 48 h of the intervention. The random effect model was applied, and pool results showed that AA could reduce VAS significantly in the experimental group than control group (MD −0.52, 95% CI −0.97 to −0.08) as shown in Figure 7. The funnel plot was given in supplementary file B.

(5) Visual Analog Scale at 72 h. Six trials with a total of 826 participants recorded VAS at 72 h of the intervention. The random effect model was applied, pool results showed that AA could reduce VAS significantly in the experimental group than control group (MD −0.72, 95% CI −1.02 to −0.42), as shown in Figure 8. The funnel plot was given in supplementary file B.

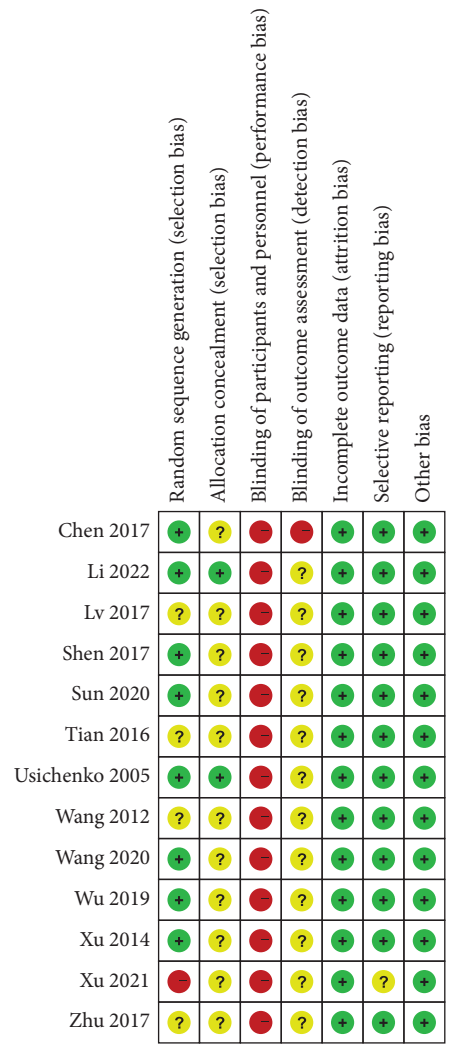

Figure 2: Risk of bias summary.

3.4.2. Harris Hip Score. Five trials with a total of 688 participants recorded HHS at the end of the intervention. The random effect model was applied and the pool results showed that AA could improve HHS significantly in the experimental group than control group (MD 6.58, 95% CI 3.60 to 9.56), as shown in Figure 9. The funnel plot was given in supplementary file B.

3.4.3. Amount of Analgesics Used. Five trials with a total of 682 participants recorded the amount of analgesics used at the end of the intervention. The random effects model was applied, and pool results showed that AA could reduce the amount of analgesics used significantly more in the experimental group than the control group (MD −12.35, 95% CI −14.21 to −10.48), as shown in Figure 10. The funnel plot was given in supplementary file B.

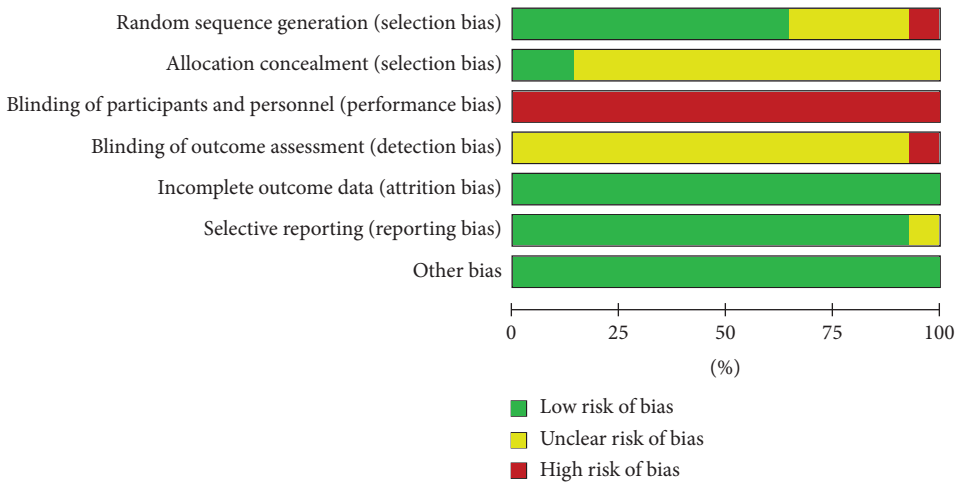

Figure 3: Risk of bias graph.

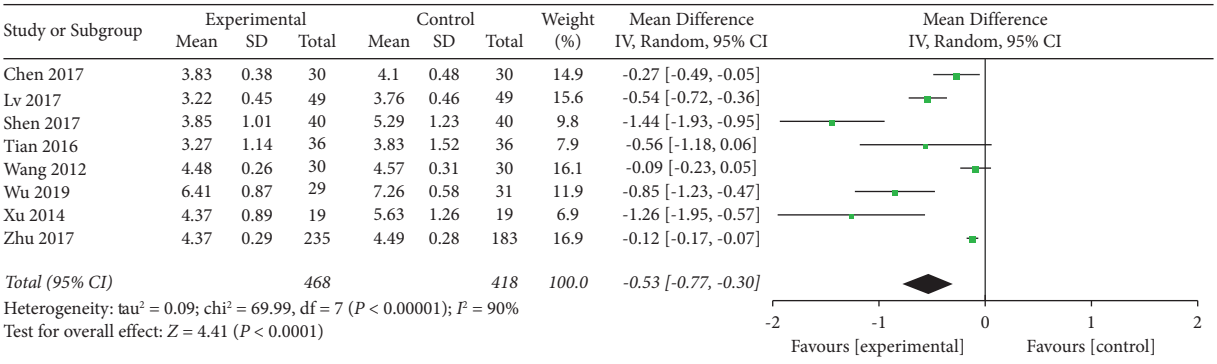

Figure 4: Comparison of the VAS at 12 h between the AA group and the control group.

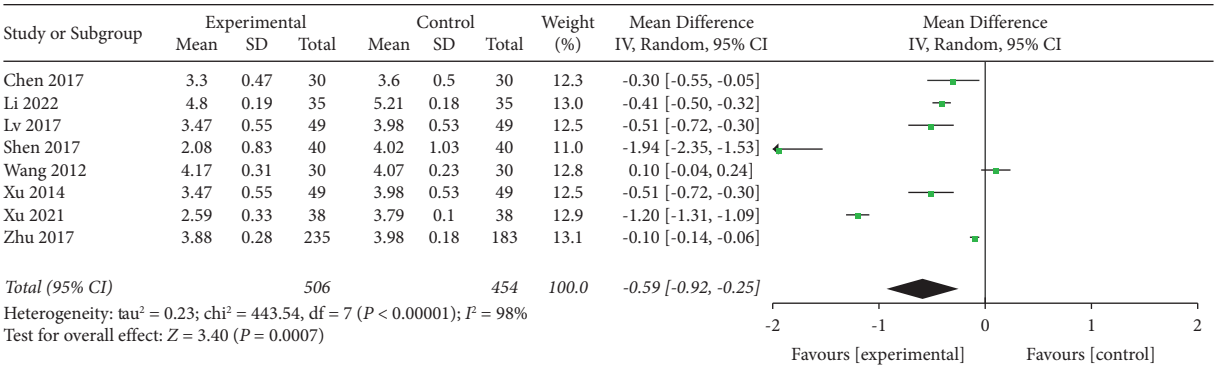

Figure 5: Comparison of the VAS at 24 h between the AA group and the control group.

3.4.4. Effective Rate. Two trials, with a total of 176 participants, recorded an effective rate at the end of the intervention. The fixed effect model was applied, and pool results showed that AA could increase the effective rate significantly in the experimental group than control group (OR 6.37, 95% CI 2.68 to 15.15), as shown in Figure 11. The funnel plot was given in supplementary file B.

3.4.5. Adverse Events. Four trials with a total of 232 participants recorded adverse events at the end of the intervention. The fixed effect model was applied, pool results showed that AA could reduce adverse events significantly in experimental group than control group (OR 0.35, 95% CI 0.17 to 0.71), as shown in Figure 12. Funnel plot was given in supplementary file B.

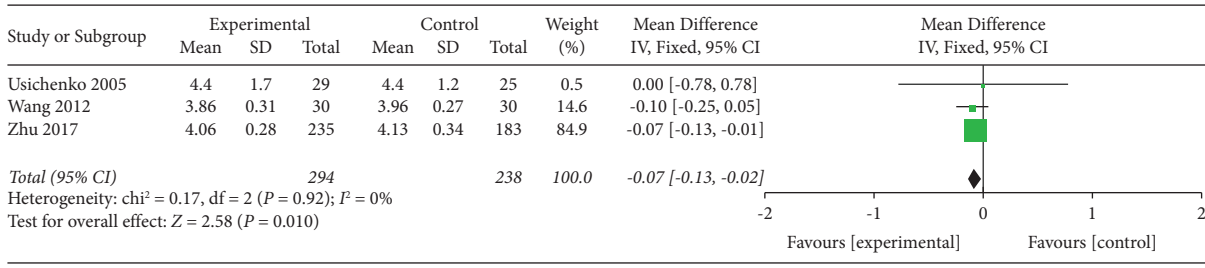

Figure 6: Comparison of the VAS at 36 h between the AA group and the control group.

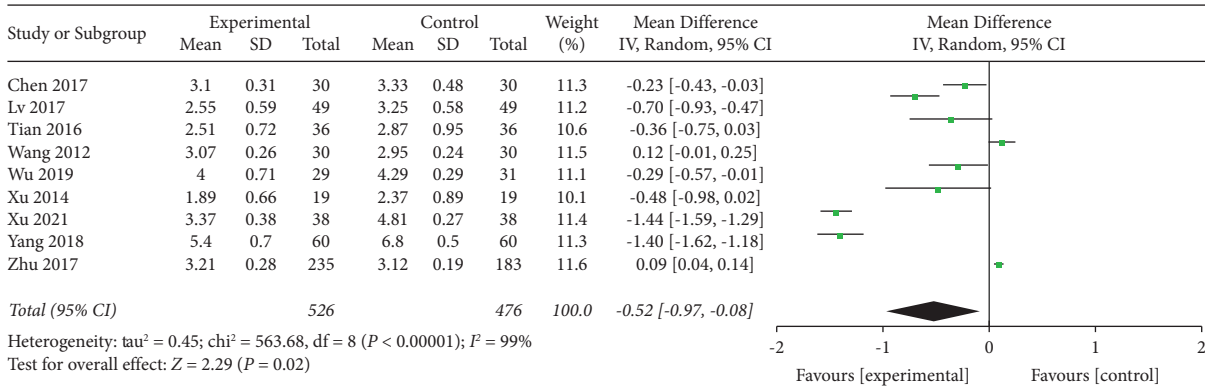

Figure 7: Comparison of the VAS at 48 h between the AA group and the control group.

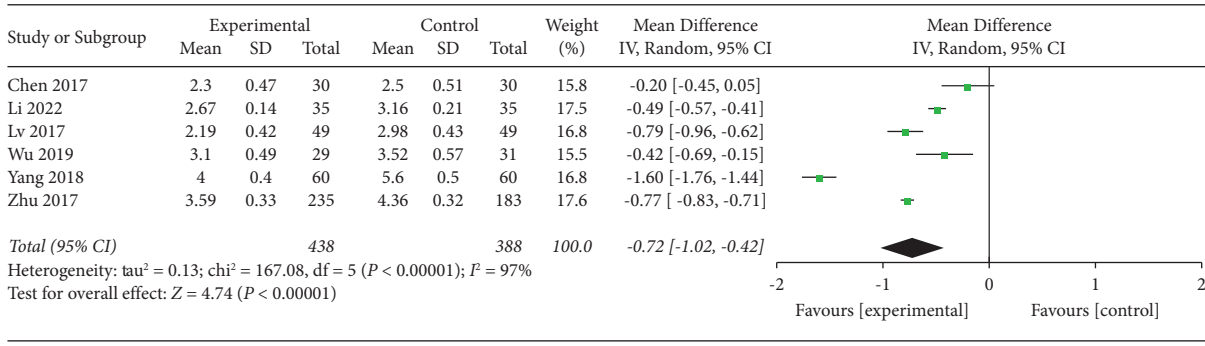

Figure 8: Comparison of the VAS at 72 h between the AA group and the control group.

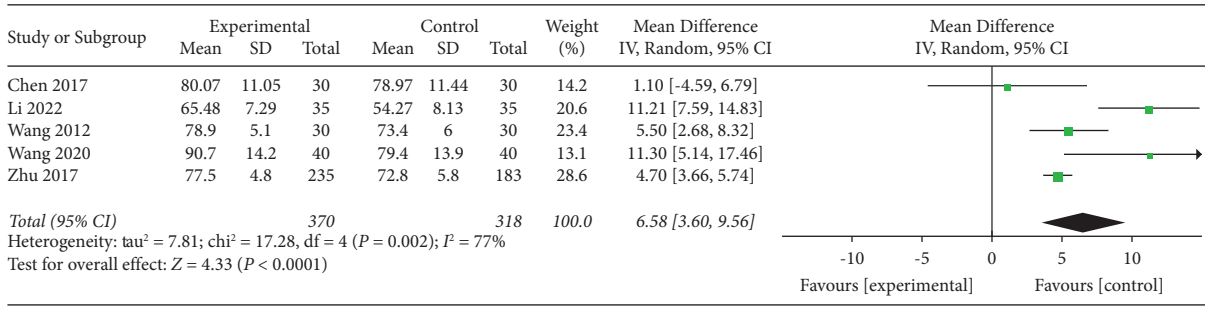

Figure 9: Comparison of the HHS between the AA group and the control group.

3.5. Evidence Quality Assessment. Due to limitations of the enrolled trails, the strength of the evidence was weakened for all outcomes. Inconsistency, imprecision, and publication bias also limited the strength of the evidence for some outcomes.

Finally, one of the outcomes was assessed as low moderate quality, and the rest were of low or very low quality. Funnel graphs for these outcomes are given in Appendix B. Details are outlined in Table 2.

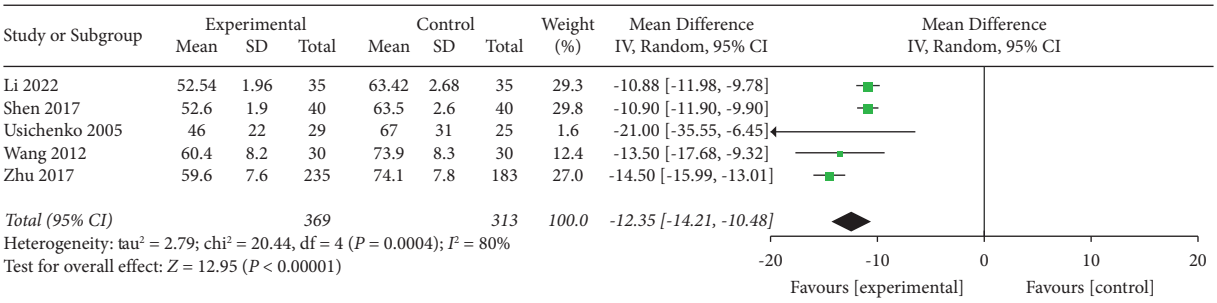

Figure 10: Comparison of the amount of analgesics used between the AA group and the control group.

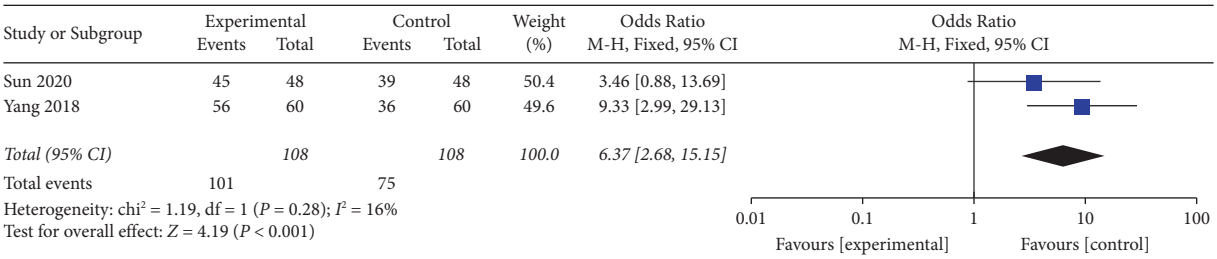

Figure 11: Comparison of the effective rate between the AA group and the control group.

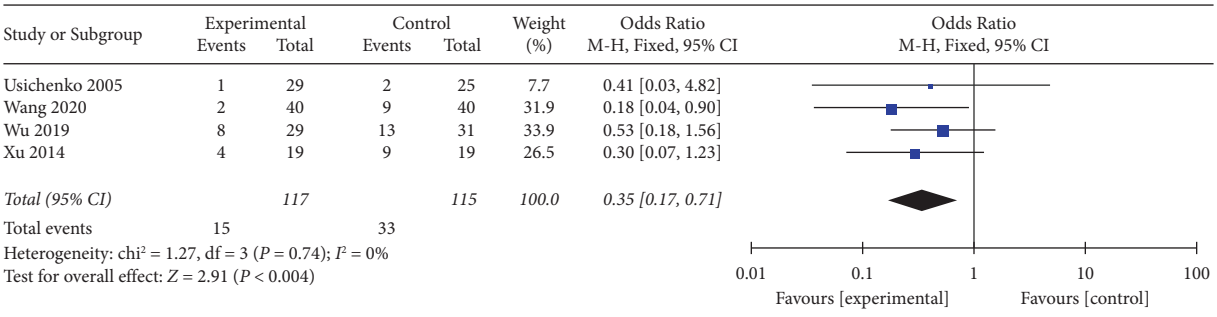

Figure 12: Comparison of the adverse events between the AA group and the control group.

4. Discussion

In recent years, there have been more publications on AA for postoperative pain among patients with HF. However, interpretation of this evidence from these studies is difficult. We conducted this study to systematically evaluate the clinical effect of AA on postoperative pain in HF patients.

4.1. Summary of Main Results. In this study, 14 trails involving 1390 patients were included for meta-analysis. First, the pooled results suggested that AA combined with CT was significantly superior to CT alone in terms of VAS at 12, 24, 48, 36 h, and 72 h, HHS, amount of analgesics used, ER, and AE. These results indicated that AA can help reduce postoperative pain degree, reduce the amount of analgesics, improve hip function, and reduce the incidence of AE among HF patients. Second, it should be emphasized that methodological flaws are prevalent in existing RCTs. Most RCTs did not report proper allocation concealment or blinding procedures for outcome assessments. Furthermore, no study was blinded to participants and personnel, suggesting potential performance bias. Of the 7 bias items, only one study met the requirement for low risk of bias. Third, the evidence quality was generally evaluated as "moderate" "low" or "very low" by the GRADE system. No study was rated as having a high level of evidence. Although AA has been widely used in China, and the pooled analysis of this study has yielded that AA combined with CT was likely to have potential therapeutic benefits in postoperative pain among HF patients, but the level of evidence was not high. There may still be gaps between the evidence supporting the efficacy of AA and its clinical implementation. Further trials with rigorous methodology, including standard protocols for AA and multiethnic subjects, are still warranted to provide stronger evidence. Fourth, limited by insufficient data, this study was unable to evaluate the long-term effects of AA. The included studies only evaluated the use of AA for several days and assessed outcomes before and immediately after treatment, therefore, the long-term effects of AA on postoperative pain could not be revealed.

Table 2: Level of evidence.

Outcomes		No of participants (studies)	Certainty assessment					Mean difference (95% CI)	Certainty of the evidence (GRADE)
			Limitations	Inconsistency	Indirectness	Imprecision	Publication bias		
VAS	12 h	886 (8)	Serious①	Serious②	No	No	Serious④	MD−0.53, 95% CI −0.77 to −0.30	⊕⊕◯◯◯ very low
	24 h	960 (8)	Serious①	Serious②	No	No	Serious④	MD−0.59, 95% CI −0.92 to −0.25	⊕⊕◯◯◯ very low
	36 h	532 (3)	Serious①	No	No	No	No	MD −0.07, 95% CI −0.13 to −0.02	⊕⊕⊕⊕◯ Moderate
	48 h	9 (1002)	Serious①	Serious②	No	No	Serious④	MD −0.52, 95% CI −0.97 to −0.08	⊕⊕◯◯◯ very low
	72 h	6 (826)	Serious①	Serious②	No	No	Serious④	MD −0.72, 95% CI −1.02 to −0.42	⊕⊕◯◯◯ very low
AAS		4 (682)	Serious①	Serious②	No	No	Serious④	MD −12.35, 95% CI−14.21 to −10.48	⊕⊕◯◯◯ very low
HHS		5 (688)	Serious①	Serious②	No	No	Serious④	MD 6.58, 95% CI 3.60 to 9.56	⊕⊕◯◯◯ Very low
ER		2 (176)	Serious①	No	No	Serious③	Serious④	OR 6.37, 95% CI 2.68 to 15.15	⊕⊕⊕◯◯ Low
AE		4 (232)	Serious①	No	No	No	Serious④	OR 0.35, 95% CI 0.17 to 0.71	⊕⊕⊕◯◯ Low

OR: odds ratio; MD: MD: mean difference; VAS: visual analog scale; AAS: amount of analgesics used; HHS: Harris Hip Score; ER: effective rate; AE: adverse events; ①the experimental design had a large bias in its random, distributive findings or was blinded; ②the confidence interval overlapped less, the P value of the heterogeneity test was very small, and the I^2 was larger; ③the confidence interval was not narrow enough, or the simple size was small; ④funnel graph asymmetry.

4.2. Agreements and Disagreements with Other Studies or Reviews. This review agrees with the results of the other study [34] in the aspect that AA as a complement to conventional drugs reduces postoperative pain, though with uncertainty. A systematic review [34] reported that in postoperative patients with fractures treated with AA, the degree of pain significantly improved 24 hours after surgery and was also significantly lower than in the control group in terms of ER. These results agree with our study. However, this review [34] focused only on pain at one time point and did not address the question of duration of action, and this study included patients with all types of fractures. The difference in our review is that we focused on patients with HF and observed pain at multiple time points after surgery and also on HHS, amount of analgesics used, and AE, making the assessment more comprehensive. In addition, as in the previous review, this study was also limited by the high risk of bias in the included trials, so the level of evidence obtained was not high. More well-designed, rigorous, and large trials are needed in this field.

4.3. Implications for Practice. In addition to shorter hospital stays and reduced morbidity and mortality, effective relief of acute postoperative pain is associated with increased patient satisfaction [33]. AA is an ancient Chinese non-pharmacological treatment that has been reported to be effective and safe in improving multiple factors in fracture patients and has the potential to promote postoperative recovery in combination with CT. Although the current review did not provide the best evidence, the results suggested that the combination of AA with CT postoperative pain degree, reduce the amount of analgesics, improve hip function, and reduce the incidence of AE among HF patients.

AA has been used to treat various types of pain, including postoperative, musculoskeletal pain, and pain associated with anesthesia [35]. The analgesic effect of AA has been preliminarily revealed. Research studies have found that AA stimulation can activate the descending pain inhibitory pathway in the brainstem-spinal cord and inhibit the ascending pain pathway, which in turn exerts analgesic effects [36]. It has been found that acupoint stimulation of one or both ears can increase the pain threshold [37], and this effect peaks 5–10 minutes after stimulation and lasts for hours to days [38]. Furthermore, it has been suggested that the analgesic effect of AA is also associated with the endogenous opioid system [39].

4.4. Limitations. Considering that all included trails were conducted in China, it should be noted that publication bias was also observed in this meta-analysis, which indicates that the results of this review may be challenging to generalize, especially in countries other than China. As a country that has practiced AA for a long time, Chinese attitudes towards AA may be more favorable than those of other ethnic groups, which may contribute to the placebo effect. Therefore, further studies in countries other than China are still needed. Furthermore, the diversity of the AA protocol used in the included trails may contribute to the heterogeneity of the findings [40]. While complementary and alternative therapies, such as AA, may emphasize tailoring treatments to individual patient characteristics, developing basic treatment standards that allow for some modifications can improve the quality of clinical evidence in this field.

5. Conclusion

Compared with CT alone, the combination of AA and CRT had a significantly greater effect on postoperative pain in HF patients. However, trails with a rigorous methodology, including standard protocols for AA and multiethnic subjects, are still needed.

Abbreviations

AA: Auricular acupressure
HF: Hip fracture
N/A: Not applicable
AA: Auricular acupressure
CT: Conventional treatment
VAS: Visual analog scale
AAS: Amount of analgesics used
HHS: Harris Hip Score
ER: Effective rate
AE: Adverse events
GRADE: Grading of recommendations, assessment, development, and evaluation
RCTs: Randomized clinical trials
PRISMA: Preferred reporting items for systematic reviews and meta-analyses
OR: Odds ratio
SMD: Standardized mean difference.

Data Availability

The detailed search strategy is given in Appendix A. All analyses were based on previously published studies.

Conflicts of Interest

The authors declare that they have no conflicts of interest in the publication of this study.

Authors' Contributions

Xiaohi Qin and Pin Li designed the study and drafted the manuscript. Xiuzhen Fu, Haili Zhou, and Fan Lai contributed to the literature search, figures, data collection, and data analysis. Hongyun Chen provided guidance on the methodology. All authors have read and approved the final manuscript.

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Supplementary Materials

The detailed search strategy for the PubMed is given in supplementary file A. Funnel plot for outcomes was given in supplementary file B. (*Supplementary Materials*)

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Research Article

Do Temporomandibular Disorder Patients with Joint Pain Exhibit Forward Head Posture? A Cephalometric Study

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Purpose. To evaluate head and cervical posture in individuals with or without temporomandibular disorders (TMDs) and to assess the correlations between pain, severity of symptoms, and posture. *Methods*. A total of 384 patients (129 males and 255 females) was included. The Fonseca Anamnestic Index (FAI) was used to assess the severity and prevalence of TMD and the presence of temporomandibular joint (TMJ) pain. Patients were divided into three groups: the TMD-free group, TMD without TMJ pain group, and TMD with TMJ pain group. Subsequently, the patients with TMJ pain were further divided into mild TMD and moderate/severe TMD groups. Nine parameters were traced on cephalograms to characterize the head and cervical posture. *Results*. TMD patients with TMJ pain showed increased forward head posture (FHP) than patients without TMJ pain and TMD-free subjects. No significant difference was observed between the TMD patients without TMJ pain and TMD-free subjects. In the TMD patients with the TMJ pain group, the moderate/severe TMD patients demonstrated increased FHP compared to mild TMD patients. TMD patients with joint pain had greater CVT/RL ($B = 3.099$), OPT/RL ($B = 2.117$), and NSL/C2' ($B = 4.646$) than the patients without joint pain after adjusting for confounding variables ($P < 0.05$). *Conclusion*. TMD patients with TMJ pain showed increased FHP compared to other groups, and FHP became more significant as TMD severity increased in male patients, indicating the FHP might play an important role in the development of TMJ pain. In the clinical assessment of TMD, the patients' abnormal head and cervical posture might be considered.

1. Introduction

Temporomandibular disorders (TMDs), with a reporting prevalence between 28% and 88%, are common in young people aged 20 to 40 years and in female [1]. TMD is a comprehensive disease involving joints, muscles, and nerves, which is mainly characterized by the restriction, deviation, and deflection of mandibular movement, clicking sound of temporomandibular joint (TMJ), and pain in masticatory muscles, anterior ear, and the TMJ region [2–4].

TMD might be caused by a variety of factors, including trauma, mental pressure, mandibular dysfunction, and malocclusion [5]. Among those, abnormal head and cervical posture has been reported to be associated with TMDs. Studies found that TMD patients had a higher cervical anteversion and an increased craniocervical angle [6]. Significant increases in craniovertebral, odontoid plane, and individual vertebral angles were also noted in TMD patients [7], while others did not identify association between head and cervical posture and TMD [8, 9]. Therefore, the

relationship between the head and cervical posture and TMD remains controversial and needs further investigation.

Based on the biopsychosocial model, diagnostic criteria for temporomandibular disorders (DC/TMD) enable researchers to understand the relationship between physical and psychological factors and the development of TMD cases, which is a commonly used method for the diagnosis of TMD at present [10]. However, the use of DC/TMD is time-consuming and impractical in TMD fast screening. Currently, a number of simplified screening questionnaires for TMD have been proposed, and one of them is the Fonseca Anamnestic Index (FAI). FAI composed of only 10 questions has been widely used in many studies for its convenience and ease of use, which can quickly screen TMD patients in a large population [11, 12]. The FAI scale has been shown to be consistent with other tools for diagnosing TMD like Helkimo Index and the American Academy of Orofacial Pain questionnaire [13]. Zhang et al. [14] used DC/TMD as a criterion measure, and the Chinese version of the FAI has demonstrated good sensitivity (0.959) and specificity (0.719) and can be used to screen for TMD in Chinese population. In addition, FAI could compensate for the inability of DC/TMD to quantify TMD severity, allowing the researchers to evaluate patients based on the severity of TMD symptoms [11, 14].

Although TMD-related pain is not a life-threatening problem, it can affect oral health-related quality of life, and symptoms might transform into a chronic state and be difficult to control [15]. Like many other chronic pain syndromes, the biological mechanism of pain caused by TMD needs to be further studied. Using the FAI scale to diagnose TMD and identify pain in the TMJ area, our previous study has found that patients with TMJ pain had specific craniofacial features [16]. Nevertheless, the investigation about the relationship between head and cervical posture and TMJ pain is limited. The purpose of this study is to evaluate the head and cervical posture in patients with or without TMD, and furtherly explore the relationships between TMJ pain, severity of TMD, and the head and cervical posture. The null hypothesis is that there is no significant difference in the head and cervical posture between the TMD patients with and without TMJ pain.

2. Materials and Methods

2.1. Subjects. This study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of the West China Hospital of Stomatology in Sichuan University (Approval no. WCHSIRB-D-2021-431). After obtaining oral informed consent before the procedure, the participants provided written informed consent when filling the questionnaires. Parents or legal guardians of juvenile patients provided oral informed consent and written informed consent as well.

Patients visiting the Department of Orthodontics in the West China Hospital of Stomatology in Sichuan University from August to December in 2021 were consecutively included in this study. The patients were requested to fill out a questionnaire including demographic information and the FAI scale and were asked orally if they had a clinical history related to the exclusion criteria. Then, the lateral cephalograms of the patients performed at the Department of Medical Imaging in our hospital were collected. The inclusion criteria were as follows: (1) patients participating in this study voluntarily; (2) patients visiting our department for the first time; (3) patients filling out the questionnaire clearly; (4) patients aged 12 years or above; and (5) patients with clear cephalogram and in natural head position. The exclusion criteria were as follows: (1) patients with history of orthodontic or orthognathic treatment; (2) patients with head and neck trauma or tumour; (3) patients with congenital deformities of the head and the neck, such as cleft lip; (4) patients with systemic diseases, such as rheumatoid arthritis; (5) patients with severe dental, periodontal, and oral mucosal diseases; (6) patients with psychological disorders; (7) patients with the history of TMD treatment; (8) patients with the history of treatment for cervical; (9) patients with primary headaches; and (10) patients with severe malocclusion and craniofacial abnormalities.

2.2. Questionnaire

2.2.1. Demographic Information. The demographic information of the patients included name, age, gender, educational level ("senior high school or lower", "university," or "graduate school or higher"), residence ("urban" or "rural"), and family per capita monthly income ("<3000 yuan," "3000–6000 yuan," or ">6000 yuan").

2.2.2. TMD and TMJ Pain Assessment. The FAI scale was used to assess the presence and severity of TMD in each patient [14, 17]. As described in our previous study [16], the total score of 10 questions reflected the presence and severity of TMD. Patients with a score of 0–15 were considered TMD-free patients, while patients with a score of 20 or higher were considered TMD patients. TMD patients could be further categorized based on TMD severity: a score of 20–40 = mild TMD, a score of 45–65 = moderate TMD, and a score of 70–100 = severe TMD [18].

The TMJ pain assessment was performed according to our previously reported method [16]. For TMD patients, if the answer of item 6 in FAI "Do you have ear pain or pain in the TMJ area?" was "sometimes" or "yes," the patient was considered to be a TMD patient with TMJ pain. If the question was answered with a "no," the patient was considered to be a TMD patient without TMJ pain.

2.3. Cephalometric Analysis. The lateral cephalograms of the patients were performed at the Department of Medical Imaging. The patients were required to maintain the natural head position with the mandible in the maximum intercuspal position, remain still, and not to swallow [19]. The cephalograms were collected from the database in the Department of Medical Imaging. Uceph software (version780, Yacent, Chengdu, Sichuan, China) was used for cephalometric analysis. Figure 1 and Supplement Table 1 show the

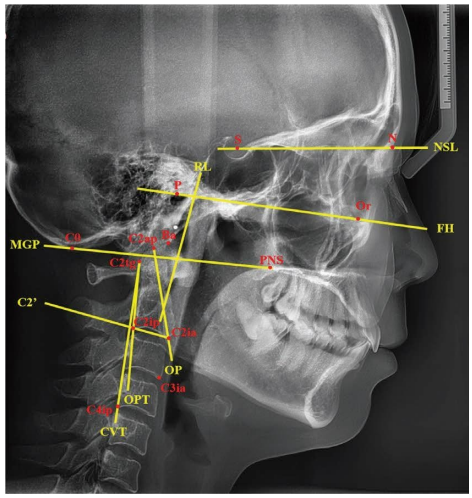


Figure 1: Cephalometric reference points and lines used in this study.

cephalometric reference points and lines used in this study. Table 1 shows the 9 head and cervical posture parameters, including 2 linear measurements and 7 angular measurements [9, 20, 21].

Two blinded researchers performed the cephalometric analysis, and the intra- and interobserver reliability on cephalogram tracing was tested as previous described [16, 22]. No statistical differences between the two measurements of each researcher and between the measurements of two researchers were observed, and all intraclass correlation coefficients were >0.80 [23, 24].

2.4. Statistical Analysis. The sample size was computed by using G ∗ power (version 3.1.9, Germany). Kang [25] reported that the mean value for OPT/CVT in patients with painful TMD was $-12.8^{\circ} \pm 1.3^{\circ}$ compared with $-11.7^{\circ} \pm 1.2^{\circ}$ in the control group. Based on the previous cross-sectional studies, the prevalence of TMD was reported to be about 50% among the orthodontic patients [16], and we assumed that half of these patients have painful TMD. Keeping the power of the study as 90% and α as 0.05, the estimated minimum sample size was 108 subjects (54 in TMD-free group, 27 in TMD without TMJ pain group, and 27 in TMD with TMJ pain group) for this study. Considering that it may be beneficial to analyse the genders separately, a total of 384 subjects were included in this study.

All statistical analysis was conducted using IBM SPSS Statistics (version 20.0, IBM Corp, Armonk, NY, USA). $P < 0.05$ was considered to have a statistically significant difference. The quantitative data were expressed as mean and standard deviation, and the qualitative data were expressed by quantity and frequency. The Shapiro–Wilk test was used to judge the normality of data distribution. In order to compare the quantitative data of the patients in each group, independent sample *t*-test and one-way analysis of variance (ANOVA) were used when the data showed a normal distribution, and the Student-Newman-Keuls hoc test was used after ANOVA. The Mann–Whitney U-test or the Kruskal–Wallis H-test was used when the data did not show a normal distribution. In order to compare the qualitative data of the patients in each group, a chi-squared test was used. Spearman correlation analysis was used to correlate the FAI score and head and cervical posture parameters. Correlations were interpreted as follows: weak correlation, $r < 0.30$ and moderate or strong correlation, $r > 0.30$. Also, the results of correlation analysis were visualized by scatterplots.

Multivariate linear regression was used to explore the correlation between TMJ pain in TMD patients and head and cervical posture parameters. The independent variable was TMJ pain, with "TMD patients without TMJ pain" as the reference group. The dependent variables were all head and cervical posture parameters. The other covariables including gender, age, educational level, residence, and family per capita monthly income were adjusted in the regression model.

3. Results

A total of 384 patients were included in this study, including 169 TMD-free patients (44.01%), 147 TMD patients without TMJ pain (38.28%), and 68 TMD patients with TMJ pain (17.71%). In terms of demographic characteristics, no significant difference in gender distribution was noted among the three groups ($P = 0.265$). TMD patients without TMJ pain were significantly older than TMD-free patients, with no difference in the age between the TMD patients with TMJ pain and the other groups ($P < 0.001$). Concerning the educational level, the proportion of senior high school or lower in the TMD patients with TMJ pain was significantly higher than that in the other two groups ($P < 0.001$). No significant difference in residence and family per capita monthly income was observed among the three groups ($P > 0.05$). In the FAI survey, the score of FAI in the TMD group with TMJ pain was significantly higher than that in the other two groups ($P < 0.001$), and the proportion of moderate/severe TMD patients was significantly higher than that in the TMD group without TMJ pain ($P < 0.001$) (Table 2).

In all the male patients, the CVT/FH of TMD patients with TMJ pain was significantly larger than those of the TMD patients without TMJ pain and TMD-free patients ($P = 0.033$). In all the female patients, the CVT/RL and NSL/C2' of TMD patients with TMJ pain were significantly larger than those of the other two groups ($P < 0.05$) (Table 3).

In adult population, no significant difference in the gender distribution among the three groups was noticed ($P = 0.276$). In adult male patients, the CVT/RL, OPT/RL, and NSL/C2' of the TMD patients with TMJ pain were significantly larger than those of the other two groups ($P < 0.05$). In adult female patients, the CVT/RL and NSL/C2' of the TMD patients with TMJ pain were significantly larger than those of the other two groups ($P < 0.05$) (Table 4). Meanwhile, no significant differences in head and neck posture parameters were observed in the minor population ($P > 0.05$) (Supplement Table 2).

In the TMD patients with TMJ pain, stratified analysis based on the severity of TMD was performed (Table 5). No significant difference in gender distribution between mild

Table 1: Cephalometric parameters used in this study.

Cephalometric parameters	Definition
Ba-C3ia (mm)	The distance between basion and the most inferior-anterior point on the body of the third cervical vertebra. Higher values of Ba-C3ai represent more severe FHP.
C2ap-C4ip (mm)	The distance between the apex of the odontoid process of the second cervical vertebra and the most inferior-posterior point on the body of the fourth cervical vertebra (C4ip). C2ap-C4ip represents the length of the upper segment of the cervical column.
Cranio cervical angle (°)	The posterior-inferior angle of the intersection of the McGregor's plane (MGP) and odontoid plane (OP). Higher values of cranio cervical angle represent a flexion position of the head and in an FHP position.
CVT/OPT (°)	The anterior-inferior angle between the posterior tangent to the odontoid process through C4ip (CVT) and the posterior tangent to the odontoid process through C2ip (OPT). Higher values of CVT/OPT represent a larger cervical curvature and more severe FHP.
CVT/FH (°)	The anterior-inferior angle between CVT and Frankfort horizontal line (FH). Higher values of CVT/FH represent more severe FHP.
CVT/NSL (°)	The anterior-inferior angle between a line that goes from the sella turcica to the nasion and the tangent that goes posterior to the odontoid process through the most posterior and inferior aspect of the fourth cervical vertebra body. Higher values of CVT/NSL represent more severe FHP.
CVT/RL (°)	The anterior-inferior angle between a tangent line to the posterior border of the mandibular ramus and the tangent that goes posterior to the odontoid process through the most posterior and inferior aspect of the fourth cervical vertebra body. Higher values of CVT/RL represent more severe FHP.
OPT/RL (°)	The anterior-inferior angle between a tangent line to the posterior border of the mandibular ramus and the tangent that goes posterior to the odontoid process through the most posterior and inferior aspect of the second cervical vertebra body. Higher values of OPT/RL represent more severe FHP.
NSL/C2' (°)	The anterior-superior angle between a line that goes from the sella turcica to the nasion and the tangent line to the inferior edge of the second cervical vertebra. Higher values of NSL/C2' represent increase in cervical forward flexion in the second cervical segment and more severe FHP.

TMD patients and moderate/severe TMD patients with TMJ pain existed ($P = 0.209$). Among male, the craniocervical angle of moderate/severe TMD patients with TMJ pain was significantly smaller than that of the mild TMD patients, and the CVT/NSL, CVT/RL, OPT/NSL, and OPT/RL were significantly larger than those of the mild TMD patients ($P < 0.05$). However, no significant differences in head and neck posture parameters were observed between the two groups in female ($P > 0.05$).

In the overall study sample, the FAI score was weakly and positively correlated with CVT/NSL ($r = 0.162$, $P = 0.018$), CVT/RL ($r = 0.208$, $P = 0.002$), and NSL/C2' ($r = 0.233$, $P = 0.001$). For male and female TMD patients, the FAI score was also weakly and positively correlated with several head and cervical posture parameters ($P < 0.05$) (Table 6). The correlations between the FAI score and CVT/NSL, CVT/RL, and NSL/C2' in overall patients were demonstrated using scatter plots (Figure 2).

The nonadjusted model showed that C2ap-C4ip, CVT/RL, OPT/RL, and NSL/C2' were positively correlated with the possibility of presenting TMJ pain in multivariate linear regression analysis. After adjustment for possible confounding factors, C2ap-C4ip became insignificant, and the possibility of presenting TMJ pain in the TMD patients were correlated with three head and neck posture parameters, including CVT/RL ($B = 3.099$, 95% CI: 1.172~5.026, and $P = 0.002$), OPT/RL ($B = 2.117$, 95% CI: 0.002~4.232, and $P = 0.048$), and NSL/C2' ($B = 4.646$, 95% CI: 2.209~7.083, and $P < 0.001$) (Table 7).

4. Discussion

The main finding of this study was that there were significant differences in head and cervical posture between the TMD patients with and without TMJ pain, and the patients with TMJ pain have a significant trend of forward head posture (FHP). In the multivariate linear regression analysis, after adjustment for potential confounders, the increased in CVT/RL, OPT/RL, and NSL/C2' were independently associated with the TMJ pain risk. Thus, the null hypothesis was rejected.

The CVT/FH of male patients with TMJ pain and the CVT/RL and NSL/C2' of female patients with TMJ pain were significantly larger than those of the patients in other groups. Cephalometric results showed that the TMD patients with TMJ pain of both genders had a forward inclination of the upper segment of the cervical column and cervical hyperflexion. We then analysed head and cervical posture in adult patients. Adult TMD patients with TMJ pain for both genders also showed increased FHP when compared to TMD-free patients and TMD patients without TMJ pain.

Table 2: Demographic characteristics and the FAI survey results of TMD-free patients, TMD patients without TMJ pain, and TMD patients with TMJ pain.

		TMD-free	TMD without TMJ pain	TMD with TMJ pain	*P*
Number (*n* (%))		169 (44.01%)	147 (38.28%)	68 (17.71%)	
Gender (*n* (%))	Male	62 (48.06%)	42 (32.56%)	25 (19.38%)	0.265
	Female	107 (41.96%)	105 (41.18%)	43 (16.86%)	
Age	Mean ± SD	21.82 ± 8.09	25.02 ± 6.67	23.29 ± 6.74	< 0.001*
	Median (IQR)	20.08 (14.58, 27.71)[a]	24.83 (19.75, 29.02)[b]	22.71 (18.35, 27.03)[a,b]	
Educational level (*n* (%))	Senior high school or lower	25 (22.94%)[a]	19 (17.43%)[a,b]	65 (59.63%)[b]	< 0.001*
	Undergraduate	98 (44.14%)[a]	36 (16.22%)[a,b]	88 (39.64%)[b]	
	Graduate or higher	24 (45.28%)[a]	13 (24.53%)[a]	16 (30.19%)[a]	
Residence (*n* (%))	Urban	14 (35.90%)	9 (23.08%)	16 (41.02%)	0.677
	Rural	133 (38.55%)	59 (17.10%)	153 (44.35%)	
Family per capita monthly income (*n* (%))	<3000 yuan	15 (50.00%)	4 (13.33%)	11 (36.67%)	0.448
	3000–6000	53 (40.77%)	25 (19.23%)	52 (40.00%)	
	>6000 yuan	79 (35.27%)	39 (17.41%)	106 (47.32%)	
FAI scores	Mean ± SD	7.25 ± 5.69	29.90 ± 9.80	46.18 ± 14.82	< 0.001*
	Median (IQR)	5 (0, 15)[a]	25 (20, 35)[b]	45 (35, 55)[c]	
TMD severity (*n* (%))	Mild TMD	—	127 (82.47%)	27 (15.73%)	< 0.001*
	Moderate/severe TMD	—	20 (32.79%)	41 (67.21%)	

Notes: The chi-squared test and the Kruskal–Wallis H-test were used. Different superscript letters indicate significant differences, and $^{*}P < 0.05$. TMD, temporomandibular disorders; TMJ, temporomandibular joint; FAI, the Fonseca Anamnestic Index; SD, standard deviation; IQR, interquartile range.

Table 3: Head and cervical posture parameters of TMD-free patients, TMD patients without TMJ pain, and TMD patients with TMJ pain.

Head and cervical posture parameters		TMD-free	TMD without TMJ pain	TMD with TMJ pain	P	Post hoc test
Number (n(%))	Male	62 (48.06%)	42 (32.56%)	25 (19.38%)	0.265	
	Female	107 (41.96%)	105 (41.18%)	43 (16.86%)		
Ba-C3ia (mm)	Male	60.78 ± 4.97	59.36 ± 4.59	61.15 ± 4.85	0.235	
	Female	54.32 ± 3.86	54.99 ± 3.61	55.36 ± 3.72	0.522	
C2ap-C4ip (mm)	Male	70.14 ± 5.59	68.69 ± 4.32	70.71 ± 5.67	0.080	
	Female	62.75 ± 4.65	63.65 ± 3.69	64.33 ± 4.28	0.084	
Craniocervical angle (°)	Male	101.88 ± 8.04	102.57 ± 7.83	99.41 ± 6.60	0.327	
	Female	103.58 ± 7.44	102.55 ± 8.44	102.13 ± 7.20	0.488	
CVT/OPT (°)	Male	3.75 ± 2.61	3.26 ± 3.41	3.06 ± 2.56	0.528	
	Female	4.41 ± 2.95	4.27 ± 2.74	4.32 ± 2.55	0.930	
CVT/FH (°)	Male	87.33 ± 9.05	86.18 ± 7.76	91.79 ± 9.05	0.033*	3 > 2, 3 > 1
	Female	87.90 ± 7.26	87.85 ± 8.48	87.52 ± 7.72	0.964	
CVT/NSL (°)	Male	103.59 ± 7.30	103.85 ± 6.68	104.53 ± 6.04	0.800	
	Female	101.40 ± 6.93	102.31 ± 8.01	104.2 ± 8.58	0.121	
CVT/RL (°)	Male	11.25 ± 7.16	10.17 ± 5.86	12.58 ± 7.45	0.374	
	Female	8.14 ± 6.12	8.21 ± 6.96	11.33 ± 5.78	0.015*	3 > 2, 3 > 1
OPT/RL (°)	Male	7.50 ± 7.65	6.91 ± 7.10	9.52 ± 7.75	0.373	
	Female	3.73 ± 6.89	4.04 ± 7.57	5.59 ± 6.28	0.337	
NSL/C2' (°)	Male	23.80 ± 9.11	22.02 ± 8.34	26.93 ± 6.9	0.076	
	Female	22.27 ± 9.13	22.57 ± 8.44	26.8 ± 8.51	0.007*	3 > 2, 3 > 1

Notes: The chi-squared test, one-way analysis of variance, and the Kruskal–Wallis H-test were used. In the post hoc test column, numbers "1", "2," and "3" represent TMD-free, TMD without TMJ pain, and TMD with TMJ pain groups of the subjects, respectively, $^*P < 0.05$. TMD, temporomandibular disorders; TMJ, temporomandibular joint.

Table 4: Head and cervical posture parameters of TMD-free patients, TMD patients without TMJ pain, and TMD patients with TMJ pain in the adult population.

Head and cervical posture parameters		TMD-free	TMD without TMJ pain	TMD with TMJ pain	P	Post hoc test
Number (n (%))	Male	41 (43.16%)	36 (37.89%)	18 (18.95%)	0.276	
	Female	68 (34.52%)	93 (47.21%)	36 (18.27%)		
Ba-C3ia (mm)	Male	61.66 ± 3.93	59.27 ± 4.81	61.62 ± 3.72	0.035*	1 > 2
	Female	54.39 ± 3.76	54.87 ± 3.65	55.25 ± 3.85	0.510	
C2ap-C4ip (mm)	Male	71.46 ± 4.89	68.84 ± 4.60	71.91 ± 4.38	0.023*	1 > 2, 3 > 2
	Female	62.98 ± 4.22	63.70 ± 3.82	64.34 ± 4.21	0.376	
Cranio cervical angle (°)	Male	102.24 ± 8.70	102.80 ± 7.01	98.01 ± 7.18	0.092	
	Female	103.76 ± 6.88	102.45 ± 8.42	101.55 ± 7.38	0.340	
CVT/OPT (°)	Male	3.81 ± 2.82	2.91 ± 3.37	2.36 ± 2.29	0.174	
	Female	4.31 ± 2.68	4.22 ± 2.63	4.24 ± 2.62	0.978	
CVT/FH (°)	Male	86.53 ± 9.12	86.50 ± 7.80	91.62 ± 10.28	0.095	
	Female	86.74 ± 6.29	87.93 ± 8.61	86.74 ± 8.05	0.561	
CVT/NSL (°)	Male	103.78 ± 7.00	103.87 ± 6.16	105.65 ± 6.38	0.436	
	Female	101.34 ± 6.51	102.40 ± 8.04	104.98 ± 8.97	0.065	
CVT/RL (°)	Male	11.10 ± 6.95	10.08 ± 5.51	14.67 ± 5.97	0.041*	3 > 2, 3 > 1
	Female	8.12 ± 5.06	8.13 ± 6.49	11.94 ± 5.64	0.002*	3 > 2, 3 > 1
OPT/RL (°)	Male	7.29 ± 7.56	7.16 ± 6.51	12.31 ± 5.70	0.021*	3 > 2, 3 > 1
	Female	3.81 ± 5.59	4.02 ± 7.02	6.00 ± 6.35	0.214	
NSL/C2' (°)	Male	23.66 ± 8.24	21.91 ± 7.75	28.16 ± 7.52	0.027*	3 > 2, 3 > 1
	Female	22.26 ± 8.11	22.75 ± 8.39	27.85 ± 8.50	0.002*	3 > 2, 3 > 1

Notes: The chi-squared test, one-way analysis of variance, and the Kruskal–Wallis H-test were used. In the post hoc test column, numbers "1", "2," and "3" represent TMD-free, TMD without TMJ pain and TMD with TMJ pain groups of the subjects, respectively, $^*P < 0.05$. TMD, temporomandibular disorders; TMJ, temporomandibular joint.

Table 5: Head and cervical posture parameters of mild TMD patients with TMJ pain and moderate/severe TMD patients with TMJ pain.

Head and cervical posture parameters		Mild TMD with TMJ pain	Moderate/severe TMD with TMJ pain	P
Number (n(%))	Male	12 (48.00%)	13 (52.00%)	0.209
	Female	15 (34.88%)	28 (65.12%)	
Ba-C3ia (mm)	Male	60.80 ± 6.09	61.47 ± 3.59	0.738
	Female	54.84 ± 4.17	55.65 ± 3.50	0.504
C2ap-C4ip (mm)	Male	69.94 ± 6.99	71.42 ± 4.27	1.000
	Female	63.63 ± 5.17	64.70 ± 3.77	0.486
Cranio cervical angle (°)	Male	102.49 ± 4.56	96.56 ± 7.05	0.020*
	Female	102.87 ± 6.31	101.73 ± 7.71	0.625
CVT/OPT (°)	Male	3.56 ± 2.30	2.60 ± 2.79	0.359
	Female	4.37 ± 2.47	4.29 ± 2.64	0.916
CVT/FH (°)	Male	90.75 ± 5.68	92.75 ± 11.50	0.584
	Female	87.59 ± 6.65	87.48 ± 8.36	0.967
CVT/NSL (°)	Male	101.75 ± 5.47	107.10 ± 5.53	0.019*
	Female	103.45 ± 8.32	104.61 ± 8.83	0.678
CVT/RL (°)	Male	8.65 ± 7.15	16.21 ± 5.87	0.008*
	Female	10.75 ± 5.34	11.64 ± 6.07	0.635
OPT/RL (°)	Male	5.09 ± 7.44	13.61 ± 5.62	0.004*
	Female	5.57 ± 5.00	5.60 ± 6.95	0.989
NSL/C2' (°)	Male	24.4 ± 7.22	29.27 ± 5.94	0.077
	Female	25.06 ± 9.85	27.73 ± 7.73	0.386

Notes: The chi-squared test, the independent sample t-test, and the Mann–Whitney test were used, $^*P < 0.05$. TMD, temporomandibular disorders; TMJ, temporomandibular joint.

Table 6: Correlation between the FAI score and head and cervical posture parameters in TMD patients.

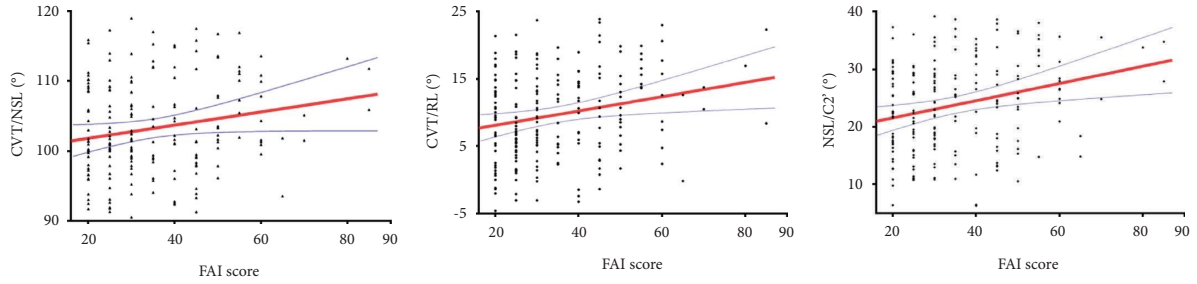
Head and cervical posture parameters	Overall ($N = 215$)		Male ($N = 67$)		Female ($N = 148$)	
	P	r	P	r	P	r
Ba-C3ia (mm)	0.216	0.085	0.038	0.254*	0.952	0.005
C2ap-C4ip (mm)	0.423	0.055	0.045	0.246*	0.872	−0.013
Cranio cervical angle (°)	0.110	−0.109	0.127	−0.188	0.343	−0.079
CVT/OPT (°)	0.647	0.031	0.645	0.057	0.711	0.031
CVT/FH (°)	0.602	0.036	0.065	0.227	0.547	−0.050
CVT/NSL (°)	0.018	0.162*	0.308	0.126	0.033	0.175*
CVT/RL (°)	0.002	0.208*	0.042	0.250*	0.010	0.212*
OPT/RL (°)	0.051	0.134	0.127	0.188	0.136	0.123
NSL/C2' (°)	0.001	0.233*	0.052	0.238	0.005	0.228*

Notes: Spearman correlation analysis is used. $^*P < 0.05$.

After adjusting for potential confounding factors, increased in CVT/RL, OPT/RL, and NSL/C2' remained significant risk factors for TMJ pain in the TMD patients. It demonstrated that the TMD patients with TMJ pain exhibited more pronounced FHP. Also, the increased in the length of the upper segment of the cervical column (C2ap-C4ip) might also be associated with the possibility of presenting TMJ pain. The significance was not statistical, but it was very close to the $P = 0.05$ threshold.

In this study, the TMD patients with TMJ pain showed a significant FHP compared to the TMD-free patients and the TMD patients without TMJ pain. It is worth noting that there was no significant difference in head and cervical posture between the latter two groups. Therefore, a hypothesis was developed that a close relationship may exist between the FHP and the specific type of TMD with TMJ pain.

Previous studies have found that abnormal head and cervical posture was significantly associated with head and neck pain [26, 27]. This might be attributed to the complex anatomical structure and muscle connection between the functional unit formed by the cranium, mandible, and cervical spine, i.e., the craniocervical-mandibular system [28, 29]. From an anatomical point of view, when the FHP occurs, the postural misalignment could lengthen the anterior cervical muscles as well as shorten the posterior cervical muscles, and the increased pressure is exerted on the cervical facet joints and neck muscles [30, 31]. At the same time, a greater electromyographic activity in the temporal and masseter muscles could be observed in the TMD subjects [32, 33]. Increased pain sensitivity in the neck muscles and masticatory muscles in patients with TMD has also been detected [34–36]. Researchers reported that changes in cervical curvature could influence the muscle tension of the neck, subsequently affect the mandible movement and the muscle function in the TMJ area and eventually induce TMD [37, 38]. As for TMJ pain and headache related to TMD, they were also found to be associated with the dysfunction of the masticatory muscles [39, 40]. In conclusion, there is a tight relationship among head and cervical posture, muscle function, and TMD-related pain. It is very likely that FHP



(a) (b) (c)

Figure 2: Scatterplot for the correlations between the FAI score and (a) CVT/NSL, (b) CVT/RL, and (c) NSL/C2' in overall patients. Scatterplot is fitted with the regression line (red line). The blue bands represent the 95% confidence interval.

Table 7: Multivariate linear regression analysis between the possibility of presenting TMJ pain and head and cervical posture parameters, adjusted for gender, age, educational level, residence, and family per capita monthly income.

Head and cervical posture parameters	Nonadjusted				Adjusted model			
	B	*P*	95% CI		*B*	*P*	95% CI	
Ba-C3ia (mm)	1.249	0.064	−0.075	2.573				
C2ap-C4ip (mm)	1.579	0.029*	0.161	2.997	1.092	0.083	−0.146	2.329
Cranio cervical angle (°)	−1.426	0.219	−3.707	0.855				
CVT/OPT (°)	−0.125	0.766	−0.953	0.703				
CVT/FH (°)	1.719	0.161	−0.690	4.128				
CVT/NSL (°)	1.579	0.162	−0.639	3.797				
CVT/RL (°)	3.018	0.002*	1.106	4.930	3.099	0.002*	1.172	5.026
OPT/RL (°)	2.179	0.046*	0.044	4.315	2.117	0.048*	0.002	4.232
NSL/C2' (°)	4.432	0.000*	2.051	6.813	4.646	0.000*	2.209	7.083

Notes: Adjusted model adjusts for gender, age, educational level, residence, and family per capita monthly income. *$P < 0.05$. TMD, temporomandibular disorder; TMJ, temporomandibular joint; CI, confidence interval.

contributes to the development of TMJ pain, but the direct causal relationship between the two has not been determined because of the missing longitudinal studies.

Similarly, the FHP was found in patients with back pain, migraine, and chronic headache. Researchers also suggested that excessive stretch of muscles, soft tissues, and capsular ligaments beyond biological limitations from FHP may reduce the threshold of pain sensation in nerve endings and irritate proprioceptors in the joint capsules, which may contribute to these pain symptoms [26, 41–44].

Meanwhile, a severe FHP might not simply be a matter of the presence or absence of TMJ pain. We then further explored the relationship between TMD severity and head and cervical posture in the TMD patients with TMJ pain. Limited by the sample size, we had to combine patients with moderate and severe TMD into one group for statistical analysis, which inevitably overlooked some detailed information. We observed that the FHP appeared to become more significant in male patients with moderate/severe TMD than patients with mild TMD. Similarly, TMD severity in the TMD patients was weakly positively correlated with FHP in correlation analysis for both males and females. This finding suggested a possible "dose effect" could exist between the FHP and the signs and symptoms of TMD, and this requires further investigation based on a large sample size. Few studies have focused on the relationship between the head and cervical posture and TMD severity or the frequency of TMD-related symptoms, and the findings observed in this study in the TMD patients may provide some useful insights for subsequent research studies.

TMJ region pain and ear pain are common complaints in TMD patients [45]. To the best of our knowledge, there are few studies evaluating head and cervical posture in the TMD patients with TMJ pain. In this study, the findings of the specific head and cervical posture in these patients could contribute to our understanding of the underlying mechanisms of the development of TMD-related TMJ pain. So far, noninvasive, minimally invasive, and invasive treatments for TMJ pain usually focus on local pain conditions [46], while less attention has been given to the role of the head and cervical spine as a functional unit on the development of joint pain. In the clinical treatment for TMJ pain in the TMD patients, the effect of abnormal head and cervical posture might be considered. Although the previous studies have found that cognitive behavioral treatment [47, 48] and posture training [49, 50] can significantly relieve TMD symptoms including pain, treatments vary greatly among these studies, and the role of psychological factors and conventional treatments cannot be adequately adjusted [51]. This study identified organic changes in the head and neck posture in the TMD patients with joint pain, which provided the basic evidence of physiotherapy for pain-related TMD. In addition, the examination and intervention of abnormal head and neck postures are rarely included in the routine clinical practice. When treating TMD patients with main complaints of pain, it

is necessary for physicians to pay attention to the relative position of their head and shoulders and to provide necessary explicit reminders and suggestions for posture training.

There are some limitations in this study. First, this study was a cross-sectional study and cannot establish a causal relationship between TMJ pain and head and cervical posture, and longitudinal investigations are necessary in the future. Second, this study only stratified patients based on the presence or absence of TMJ pain and did not quantify pain duration and pain intensity. Third, this study did not strictly distinguish between adults and adolescents. Adolescents at different growth stages may have specific cervical spine morphologies and head and neck posture characteristics due to their growth potential. Since this study included only a small number of adolescent TMD patients, the analysis of adolescent subjects alone may not meet the sample size requirement. It would be meaningful to increase the sample size of adolescents and analyse differences in their head and neck postures in further studies. Fourth, this study only used FAI to assess the severity and prevalence of TMD in patients without further verification of the diagnosis, which may result in grouping error and mislead the final conclusion. The use of DC/TMD could perform an accurate diagnosis of TMD and more detailed clinical subtypes of TMD patients in the follow-up studies.

5. Conclusion

TMD patients with TMJ pain showed abnormal head and cervical posture and increased FHP compared with TMD-free patients and TMD patients without TMJ pain. In male patients experiencing TMJ pain, the FHP appeared to become more significant in moderate/severe TMD patients compared to mild TMD patients. The FHP may play an important role in the development of TMJ pain in TMD. In the clinical treatment for TMD-related TMJ pain, the effect of abnormal head and cervical posture might be considered. Longitudinal investigations are necessary to define the causal relationship between the FHP and TMJ pain in the TMD 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 that there are no conflicts of interest.

Authors' Contributions

Chu-Qiao Xiao and Yi-Dan Wan contributed equally to this work.

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Supplementary Materials

Supplement Table 1: cephalometric reference points and lines used in this study and their definition. Supplement Table 2: head and cervical posture parameters of TMD-free patients, TMD patients without TMJ pain, and TMD patients with TMJ pain in the minor population. (*Supplementary Materials*)

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Research Article

The Effect of Spinal Muscle Fatigue and Psychosocial Factors on Pressure-Pain Threshold in Healthy Adults

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Objective. Pain sensitivity decreases following isometric exercise. It is not clear whether this exercise-induced hypoalgesia (EIH) occurs to the same extent in men and women. It is also unclear if the effect is systemic or local to the exercised musculature. The aim of our study was to investigate whether fatiguing isometric exercise of the spinal and hip extensors would result in increased pressure pain threshold (PPT) at sites local to and remote from the exercised muscles in healthy men and women and whether there is a relationship between central sensitization, psychosocial factors, and PPT. *Subjects*. 35 healthy adults (age 27.1 ± 4.5 years, 22 women). *Methods*. This was a within-subjects cohort study. Participants completed questionnaires quantifying central sensitization, pain catastrophizing, sleepiness/insomnia, anxiety, and depression. PPT was assessed at the lumbar and thoracic paraspinals, hamstrings, gastrocnemius, wrist, and third digit before and immediately after participants performed the Biering–Sorensen test to failure. *Results*. PPT increased postexercise in the thoracic paraspinals, hamstrings, and gastrocnemius in men and women and in the lumbar paraspinals in men only but did not change at the wrist and digit sites. A lower average PPT at baseline was associated with a higher central sensitization scores. A greater increase in average PPT postfatigue was significantly associated with higher average PPT at baseline. *Conclusions*. Exercise-induced hypoalgesia occurs at sites overlying the muscles involved in fatiguing exercise, but not at remote sites, and is more evident in males than females. The magnitude of EIH depends upon baseline PPT. Even in healthy individuals, greater central sensitization is associated with lower baseline PPT.

1. Introduction

An individual's pain sensitivity is affected in the short term and long term by multiple factors. Pain sensitivity can be assessed using the measurement of pressure-pain threshold (PPT). This is a simple quantitative sensory test of pain that is often used in research and clinical practice [1–4]. The PPT is defined as the minimum pressure applied to anatomical site that results in an individual perceiving the mechanical stimulus as pain [5]. The measurement of PPT is accurate, valid, and reproducible [6, 7]. Women typically display a lower PPT than men [8]. Individuals with persistent musculoskeletal pain disorders such as recurrent or chronic low back pain also demonstrate reduced pain thresholds when measured using PPT [9–11]. This reduced PPT may occur at the location of the clinical symptoms, suggestive of peripheral sensitization mechanisms, and also at locations that are not anatomically or neurophysiologically related to the symptoms, suggestive of supraspinal mechanisms [2, 10–12]. To understand the contribution of short- and long-term factors to localize and widespread pain sensitivity in individuals with persistent pain disorders, it is critical to first examine potential contributing factors in asymptomatic men and women.

Pain sensitivity is modulated in response to exercise [13]. In the short term, isometric muscle exercise appears to decrease pain sensitivity [3, 9, 14, 15]. This is called exercise-induced hypoalgesia (EIH). The greatest change in pain threshold occurs in response to long-duration, low-intensity isometric contraction that is maintained until failure [16]. However, it is unclear if the reduction in pain sensitivity following muscle fatigue is local to the affected muscle or if it

is a generalized response that also occurs at sites remote to the fatiguing exercise [3]. The Biering–Sorensen test is a long-duration, low-intensity isometric task that is often used to quantify the endurance of the spinal and hip extensor musculature in individuals with and without low back pain [17, 18]. Previous preliminary work investigating the effect of the Sorensen test on PPT in the spinal extensors and remote sites suggested that the extent of EIH at remote locations is greater in women [3]. However, in this previous study, the Sorensen test was held for a standardized duration, and so the muscles may not have been fatigued to failure. Sex differences in the local and systemic hypoalgesic response to fatiguing exercise may depend on testing location as conflicting results across studies suggest that these differences are muscle specific [3, 19].

In the short and long terms, pain sensitivity can increase because of the heightened responsiveness of nociceptive neurons to normal or subthreshold afferent input. This phenomenon is known as central sensitization [20]. While central sensitization is a neurophysiological mechanism that cannot be directly measured in vivo, signs and symptoms such as widespread increased pain sensitivity suggest its presence [21]. Central sensitization is known to contribute to many persistent pain disorders [22]. Recently, it has been recognized that central sensitization may also be elevated in individuals who do not have persistent pain. Elevated central sensitization may in fact be a precursor to the development of clinical pain [22, 23]. It is not known if central sensitization influences pain sensitivity in nonclinical populations or if it alters the extent of hypoalgesia following isometric exercise. Clinically, central sensitization can be assessed using a combination of quantitative sensory testing and self-report measures. One such self-report measure is the Central Sensitization Inventory (CSI) [24], which quantifies the presence of biological and psychological symptoms and characteristics that are associated with central sensitization syndromes [24]. It is not clear, however, how quantitative measures such as PPT and self-report measures such as the CSI are related [25, 26].

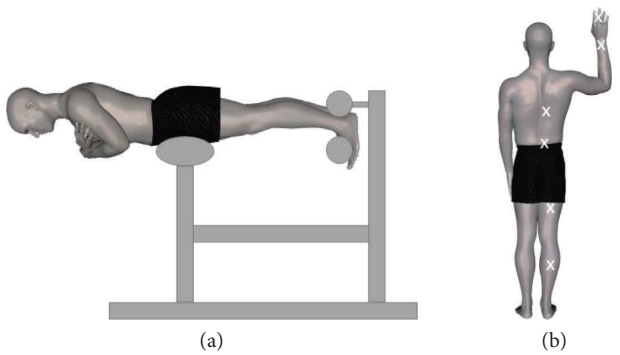
Multiple psychosocial factors are associated with pain sensitivity. These include depression, anxiety, pain catastrophizing, and sleep quality. Depression and increased pain sensitivity frequently occur together [27], but the mechanism underlying this relationship is unclear [28]. Evidence also suggests that in individuals with and without persistent pain, elevated anxiety is associated with decreased PPT [1, 12]. Pain catastrophizing has been associated with a number of indicators of pain sensitivity in the context of experimental pain testing paradigms, both among healthy, pain-free participants and individuals with persistent pain disorders [29–32]. There is also increasing evidence of a relationship between sleep quality and an individual's pain experience [33]. In the short term, healthy individuals have increased pain sensitivity following experimentally-induced sleep deprivation [34, 35]. Long-term sleep disruption is also associated with increased pain sensitivity in individuals with and without persistent pain disorders [36]. However, it is unclear if any of these psychosocial factors influence EIH.

The aim of our study was to investigate whether performing a long-duration, low-intensity fatiguing exercise to failure would result in increased PPT at local and remote sites in healthy men and women and whether there is a relationship between central sensitization, psychosocial factors, and PPT in healthy individuals. It was hypothesized that (1) the fatiguing isometric exercise would produce an increase in PPT at both local and remote sites; (2) the increase in PPT in response to fatiguing exercise would be more pronounced in women than in men; and (3) impaired sleep quality, and increased anxiety, pain catastrophizing, and central sensitization would be associated with lower PPT in healthy adults at baseline and would be associated with a smaller extent of change in PPT in response to fatiguing exercise.

2. Materials and Methods

2.1. Participants. Thirty-five healthy adults (mean age of 27.1 ± 4.5 years, 22 women and 13 men) participated in the study. Sample size exceeded the minimum necessary to detect a main effect of fatigue and the interaction effect of fatigue and sex with a power of 0.90 and an alpha of 0.05 ($n = 22$, G*Power version 3.1.9.7 [3, 37]). Participants were recruited via word of mouth and study flyers at an academic institution and included faculty members, staff, and students. Participants were eligible for inclusion if they were aged between 18 and 60 years. Participants were excluded if they were currently experiencing any back or leg pain, had any history of back pain requiring treatment, or a change in activity for more than one week, if they were currently using any form of analgesic medication and if they had any history of neurological or cardiovascular diseases. Participants gave written consent prior to participating. Chapman University's Institutional Review Board approved this study prior to its commencement.

2.2. Psychosocial Factors. All testing was conducted in the same teaching laboratory space on a consistent day of the week/time of day. Participants completed the Central Sensitization Inventory (CSI), the Pain Catastrophizing Scale (PCS), the Karolinska Sleepiness Scale (KSS), the Insomnia Severity Index (ISI), and the Hospital Anxiety and Depression Scale (HADS) prior to PPT assessment. The CSI is a widely used questionnaire that is valid and reliable for assessing central sensitization [24, 38]. Part A of the CSI contains 25 questions identifying symptoms associated with central sensitization and has a maximum score of 100. Part B assesses if the individual experiences any disorders associated with central sensitivity, such as fibromyalgia and temporomandibular disorder. The PCS is a reliable and valid measure of pain catastrophizing and includes the domains of pain magnification, rumination, and helplessness, with a maximum score of 52 [39]. The KSS is used to estimate the state-sleepiness of participants, with a score range from 1 to 9 [40]. It has high validity and correlates with EEG and behavioral indicators of sleepiness [41]. The ISI is a valid and reliable tool to assess perceived insomnia, with scores



(a) (b)

Figure 1: (a) Performance of the isometric fatiguing exercise (Sorensen test) on a roman chair. (b) Location of pressure-pain threshold assessment sites (note that the digit site was on the palmar surface of the finger).

ranging from 0 to 28 [42]. The HADS is a validated self-report measure of psychological status, encompassing depression and anxiety subscales (HADS-D and HADS-A, maximum scores of 21 for each subscale [43]).

2.3. Assessment of Pressure-Pain Thresholds. Prior to the PPT assessment, participants warmed up by walking on a treadmill at a speed of 2.8 mph for 5 minutes. Upon completion of the warm-up, participants quantified their perceived exertion during the walk on the 0–10 Rating of Perceived Exertion (RPE) scale [44, 45]. Participants also rated any pain/discomfort from 0 to 10 after the warm-up on a numeric pain rating scale.

The sites for PPT assessment were palpated and marked with an indelible pen so that the location of each site was identical prefatigue and postfatigue. Pressure-pain threshold was assessed at the following sites on the participants' dominant sides (Figure 1): the erector spinae at the level of T9, 3 cm lateral to the spinous process (thoracic site); erector spinae at the level of L4, 2 cm lateral to the spinous process (lumbar site); the hamstrings halfway between the ischial tuberosity and the popliteal crease (hamstring site); the gastrocnemius one third of the distance between the calcaneus and the popliteal crease (calf site); the palmar aspect of the middle phalanx of the third digit (digit site); and the dorsal wrist at the midpoint between the ulnar and radial styloid processes (wrist site).

Pressure-pain threshold was measured utilizing a handheld pressure algometer with a 1 cm diameter circular application area (FDX Digital Force Gauge, Wagner Instruments, and CT). Increasing pressure was applied at a rate of approximately 0.5 kg/s. The same male experimenter performed all PPT assessments for the study and was blinded to the results. Participants were instructed on the testing procedure and were told to verbally indicate immediately when the sensation of pressure changed to pain. A practice trial at the dorsal wrist was administered to the participant while seated. Following this, PPT was assessed while the participant was prone on a plinth. Two PPT measurements were taken at each site, with 20 seconds between each measurement [3]. The order in which the sites were assessed was randomized across participants, but for each participant the order was the same before and after exercise.

2.4. Isometric Fatiguing Exercise. Following the baseline PPT measurements, participants completed the Biering–Sorensen test (Figure 1(a)). The Sorensen test fatigues the spinal extensor, latissimus dorsi, gluteus maximus, and hamstring muscles [46, 47]. Participants were positioned on a Roman chair, with the anterior superior iliac spines aligned with the edge of a pelvic pad. Participants were instructed to hold their body parallel to the ground with the arms crossed across their chest for as long as possible. To assist in monitoring the performance of the test, a plumb bob at the end of a lanyard was placed around the neck of each subject during the test. The researchers adjusted the lanyard so that the plumb bob was one inch above the seat of a standard-height chair placed in front of the participant. The test was concluded when the participant placed their hands back down onto the chair or if the plumb bob dropped to the chair, indicating failure to maintain the test position [48], and the duration of the test was noted. Immediately following completion of the Sorensen test, participants rated the intensity of exertion during the test using the same RPE scale and rated the intensity of any pain/discomfort during the test on the numeric pain rating scale. The PPT measurement was then repeated using identical methods to the prefatigue testing. Postfatigue PPT assessment for all sites was completed within 5 minutes of the end of the fatiguing exercise. This ensured that the postfatigue testing was applied during the window of time when the muscles were still measurably fatigued [49].

2.5. Statistics. Variables were checked for assumptions of normality and homoscedasticity. Variables that did not meet the assumptions of normality were log-transformed. Psychosocial characteristics were compared between males and females using independent *t*-tests and the chi-square test of independence. The effect of fatigue at each assessment site, and averaged across all assessment sites, was tested using a mixed model ANOVA with the main effect of fatigue (within subject effect), main effect of sex (between subject effect), and interaction effect of fatigue*sex. In the case of a significant interaction, pairwise comparisons were made using paired or two sample *t*-tests with Bonferroni correction for multiple comparisons.

Linear relationships between psychological variables and (a) the average PPT at baseline and (b) average change in PPT were examined using Pearson correlation coefficients. Statistical analyses were conducted in IBM® SPSS® statistical software (Version 26, IBM, Armonk, NY, USA). Level of significance was set at 0.05 for all tests.

3. Results

Participant demographic characteristics are shown in Table 1. The duration of the Sorensen test did not differ between sexes (female duration 126.6 ± 52.8 s; male duration 126.3 ± 64.8 s). There was also no difference between sexes for the rating of

Table 1: Participant demographic characteristics, psychosocial characteristics, and the Sorensen test outcomes.

	Females ($n = 22$)	Males ($n = 13$)	p
Age (years)	27.3 (5.2)	26.3 (3.2)	0.547
BMI (kg/m^2)	23.2 (4.2)	25.3 (2.1)	0.096
Race, frequency			
American Indian/Alaska native	0	0	
Asian	8	8	
Black/African America	0	0	
Native Hawaiian/other Pacific Islander	0	0	0.473
White	10	4	
Mixed	3	0	
Unknown/not reported	1	1	
Anxiety, HADS-A	8.5 (2.5)	6.4 (3.3)	0.035*
Depression, HADS-D	3.8 (2.5)	3.0 (1.4)	0.304
Central sensitization, CSI	25.5 (10.3)	18.6 (8.6)	0.052
Pain catastrophizing, PCS	9.1 (7.2)	8.5 (10.1)	0.851
Sleepiness, KSS	3.7 (1.7)	3.9 (1.3)	0.668
Insomnia, ISI	6.8 (4.6)	5.1 (3.7)	0.267
Sorensen duration (seconds)	126.6 (52.8)	126.3 (64.8)	0.989
Perceived exertion, 0–10	5.3 (1.7)	5.3 (1.5)	0.941
Pain/discomfort, 0–10	0.5 (1.3)	0.5 (1.2)	0.959

*Statistically significant difference between males and females.

perceived exertion at the end of the test or discomfort reported at the end of the test (see Table 1, $p > 0.05$ for all comparisons). Female participants scored higher on the HADS (anxiety subscale) and tended to score higher on the CSI than males (see Table 1, $p = 0.035$ and 0.052, respectively). Eight individuals (22% of the cohort) reported at least one disorder in Part B of the CSI. Six individuals reported one disorder. These were most commonly headache ($n = 2$), neck injury ($n = 2$), and anxiety ($n = 2$). Two individuals reported two disorders (chronic fatigue/temporomandibular joint disorder and headache/irritable bowel syndrome, respectively).

3.1. Baseline PPT and Change in PPT in Response to Fatigue. Data from one male participant were excluded due to his PPT exceeding the maximum possible pressure for the device at several sites. Group data from three sites were log-transformed to meet assumptions of normality (calf, wrist, and digit). Group data for all sites, prefatigue and postfatigue, are shown in Figure 2.

For pressure-pain threshold averaged across all sites, there was a significant main effect of fatigue ($F = 22.276$; $p = 0.001$), as well as a main effect of sex ($F = 6.002$; $p = 0.020$) and fatigue by sex interaction ($F = 6.622$; $p = 0.015$). Bonferroni-corrected post hoc comparisons indicated that average PPT increased significantly postfatigue in males ($p = 0.012$) but not in females. None of the other pairwise comparisons were significant.

Analysis of the individual PPT sites indicated that the effect of fatigue on PPT varied by sex and by testing site. For the thoracic site, PPT was significantly higher in both groups postfatigue (main effect of fatigue, $F = 9.891$; $p = 0.004$). Thoracic PPT was also higher in males than in females prefatigue and postfatigue (main effect of sex, $F = 7.709$; $p = 0.009$). At the lumbar site, there was a significant fatigue by sex interaction ($F = 8.031$; $p = 0.008$). Bonferroni-corrected post hoc comparisons indicated that males had higher PPT than females postfatigue ($p = 0.024$) and that there was a significant increase in PPT postfatigue in males ($p = 0.004$) but not in females. At the hamstring site, PPT was higher postfatigue in both groups (main effect of fatigue $F = 11.660$; $p = 0.001$). There was also a trend toward a significant fatigue by sex interaction ($F = 4.111$; $p = 0.051$) but post hoc comparisons by sex were nonsignificant. At the calf site, PPT increased significantly postfatigue in both males and females (main effect of fatigue $F = 20.866$; $p = 0.001$). There was a trend toward males having higher PPT at the calf (main effect of sex $F = 3.964$; $p = 0.055$).

At the wrist, there was no effect of fatigue on PPT (main effect of fatigue $F = 0.191$; $p = 0.665$). Males had a higher PPT at the wrist than females (main effect of sex $F = 8.346$; $p = 0.007$). At the digit site, there was no main effect of fatigue (main effect of fatigue $F = 0.359$; $p = 0.554$) or sex ($F = 2.567$; $p = 0.120$). There was a significant fatigue by sex interaction ($F = 4.581$; $p = 0.041$) but none of the post hoc comparisons were significant.

3.2. Relationships between Baseline PPT, Change in PPT, and Psychological Characteristics. Data from the PCS and the KSS were log-transformed to meet assumptions of normality. Relationships between baselines PPT, change in PPT, and psychological characteristics across the entire group and for each sex individually are shown in Table 2 and significant findings are reported below.

For baseline PPT, greater central sensitization was significantly associated with lower average PPT at baseline ($r = -0.352$; $p = 0.041$; Figure 3(a)). In males only, a greater history of insomnia was associated with lower PPT at baseline ($r = -0.593$; $p = 0.042$).

For change in PPT following the Sorensen test, greater increase in average PPT postfatigue was significantly associated with higher average PPT at baseline ($r = 0.576$; $p = 0.001$;

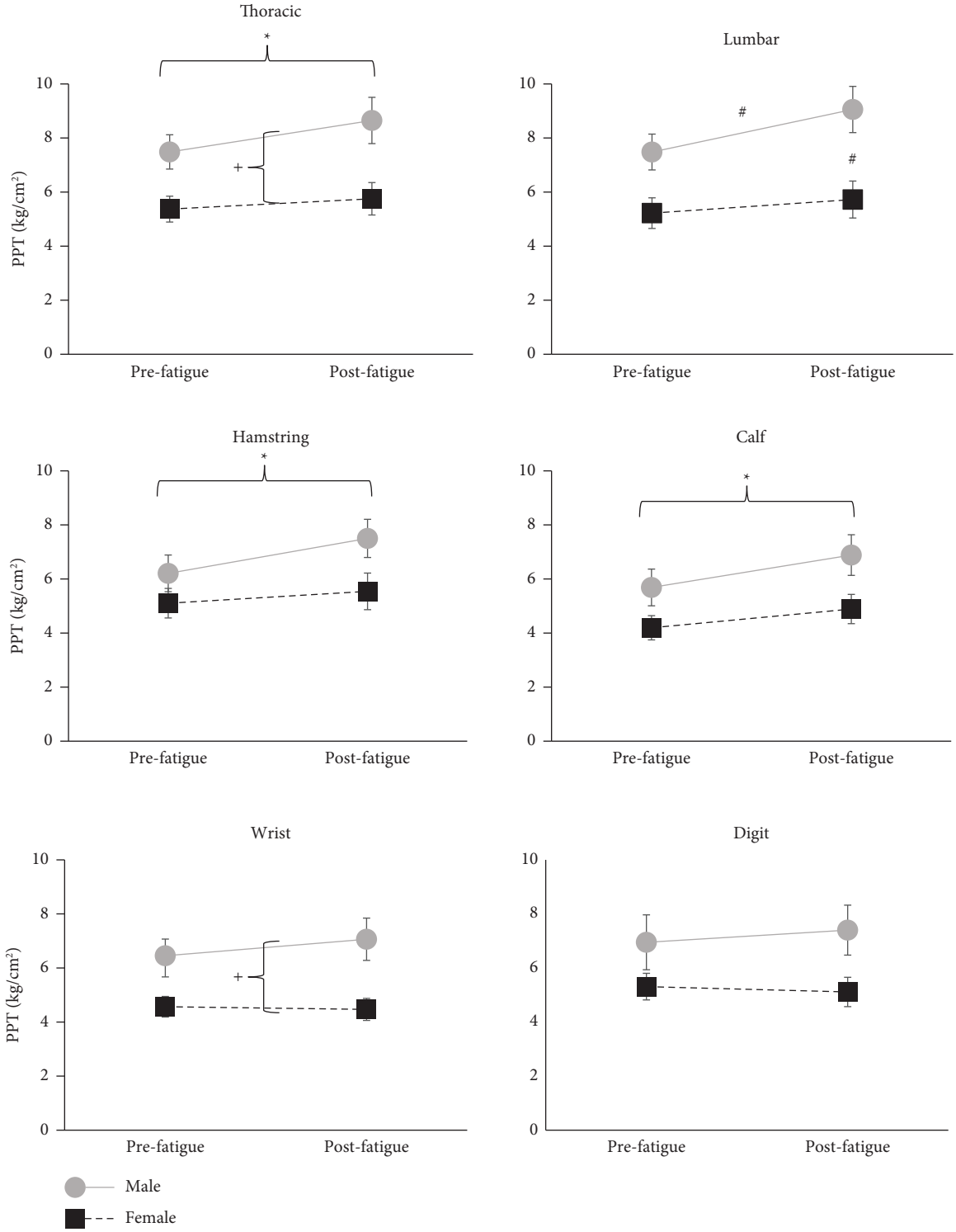


Figure 2: Pressure-pain threshold (PPT) prefatigue and postfatigue in male and female participants. *indicates significant main effect of fatigue. +indicates significant main effect of group. #indicates significant pairwise post hoc comparison for interaction between fatigue and group.

Figure 3(b)). With the sexes considered separately, this relationship was only significant in females ($r = 0.630$; $p = 0.002$). Greater pain catastrophizing was significantly associated with a smaller change in PPT in response to fatigue in females ($r = -0.461$; $p = 0.031$).

4. Discussion

Our study demonstrates that isometric contractions held to failure result in an increase in pressure-pain threshold in healthy individuals at local muscle sites but not at sites that

Table 2: Linear relationships between psychosocial factors, average baseline pressure pain threshold, and average change in pressure-pain threshold postfatigue.

		Average baseline	Average change
Anxiety, HADS-A	Entire sample	−0.201	−0.096
	Female	0.111	−0.042
	Male	−0.300	0.154
Depression, HADS-D	Entire sample	−0.175	−0.107
	Female	−0.069	−0.088
	Male	−0.277	0.062
Central sensitization, CSI	Entire sample	−0.352*	−0.274
	Female	−0.329	−0.254
	Male	−0.136	−0.063
Pain catastrophizing, PCS	Entire sample	−0.321	−0.266
	Female	−0.285	−0.461*
	Male	−0.391	−0.059
Sleepiness, KSS	Entire sample	−0.235	0.001
	Female	−0.350	−0.266
	Male	−0.236	0.379
Insomnia, ISI	Entire sample	−0.179	−0.228
	Female	0.101	−0.106
	Male	−0.593*	−0.303
Average baseline	Entire sample	n/a	0.576*
	Female	n/a	0.629*
	Male	n/a	0.382

*Statistically significant correlation.

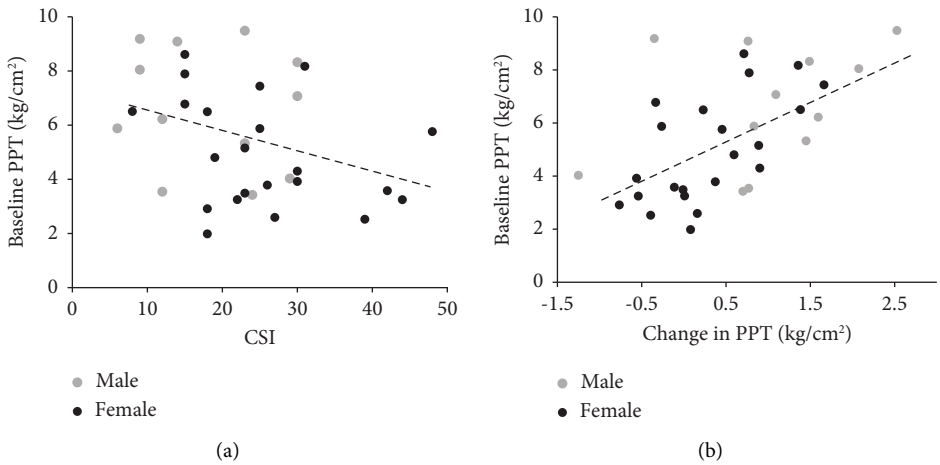


Figure 3: (a) Significant linear relationship between baseline pressure-pain threshold (averaged across sites, PPT) and score on the Central Sensitization Inventory (CSI); $r = -0.352$; $p = 0.041$. (b) Significant linear relationship between baseline pressure-pain threshold (average across sites, PPT) and change in PPT postfatigue; $r = 0.576$; $p = 0.001$.

are remote to the fatiguing exercise. Contrary to our hypothesis, the increase in PPT in response to fatiguing exercise was more pronounced in men than in women. Importantly, individuals with higher PPT at baseline had the greatest increase in PPT in response to fatigue. Even in our healthy participants, elevated CSI scores were associated with lower baseline PPT. The influence of psychosocial factors on baseline PPT and fatigue-induced changes in PPT were sex-dependent.

Our findings confirm the hypoalgesic effect of isometric exercise. Earlier studies have indicated that reduced pain sensitivity in response to exercise is most pronounced following prolonged, low-intensity, isometric contractions. This suggests that recruitment of high-threshold motor units may be an important factor in the hypoalgesic response [14]. Mechanistic studies investigating the causes of EIH have predominantly focused on adaptations in response to chronic, whole-body aerobic exercise in animal models [13]. This work has highlighted the influence of endogenous opioid, serotonergic, and endocannabinoid systems. These mechanisms produce generalized pain inhibition. Other work probing localized and generalized responses to isometric exercise in humans has suggested that generalized EIH may occur as a result of increased blood pressure or altered attention, but some research study has also demonstrated that effects are largest in the contracting muscle,

suggestive of a local or segmental effect [9]. In the present study, significant increases in PPT following the fatiguing exercise occurred at the sites overlying the spinal and hip extensor muscles. These muscles are known to fatigue during the Sorensen test [49, 50]. The local modulation of PPT in the fatigued muscles may be due to afferent inhibition in response to stimulation of sensory fibers during the fatiguing contraction [9]. In this study, the PPT at the calf site also increased following the Sorensen test. The contribution of the calf musculature to maintenance of the Sorensen test position has not previously been reported. However, it is likely that the gastrocnemius is active during the test to develop a knee flexor moment that keeps the heels stabilized against the test equipment. In our study, we did not observe generalized EIH, as there were no changes in PPT at the wrist and digit sites that were remote to the exercise. Previous work reported increased PPT at the thenar eminence following the Sorensen test [3]. We speculate that the amount of muscular tissue overlying remote sites may influence the extent of measured EIH due to differences in tissue thickness, tissue stiffness, and density of mechanoreceptors. Additionally, our findings are consistent with recent work suggesting that generalized EIH is less likely to occur following fatiguing isometric exercise of the back musculature in comparison with fatiguing exercise of the limb musculature [51]. The reasons for this are unclear but may be related to varying exercise intensity when exercising axial or limb muscles or differing muscle fiber types [51].

In contrast with earlier work using the Sorensen test paradigm [3], we found that the increase in PPT in response to fatiguing exercise occurred more consistently in male participants. Other studies using PPT have variously reported that EIH following isometric contraction is the same in men and women, that it is greater in women, or that it is greater in men [52–54]. The conflicting findings from these studies may in part be due to varying fatigue protocols [53]. In the present study, participants held the Sorensen position for as long as possible, until failure, rather than for a standardized length of time. This ensured that participants of all capabilities reached the limit of their muscle endurance. Although the duration of the hold time varied widely across individuals (20 seconds to 250 seconds), the average hold time (126 seconds) was greater than the standardized time used in the previous study (120 seconds) [3]. Our study supports earlier work suggesting that sex differences in EIH emerge primarily in response to more demanding exercise [53]. The smaller amount of EIH evident in female participants in our study may also have been due to the female group tending to have higher levels of anxiety and higher scores on the CSI than male participants. Given the heterogeneity in the evidence for the influence of sex on EIH and the potential interaction with psychological and physiological factors, future studies would benefit from large cohorts of male and female participants matched for psychosocial characteristics and should investigate EIH in response to a range of exercise intensities and durations.

Consistent with earlier work [55], baseline PPT was higher in males than females in this study. Factors that may account for the sex difference in pain sensitivity include the influence of sex hormones on nociception and differences in the function of the descending opioid system [55]. Sex differences in baseline PPT may also be due in part to differences in muscle size. Binderup et al. [56], proposed that as women have smaller muscle bulk on average, the size of the algometer probe head is relatively larger, leading to a lower PPT due to spatial summation. The results of our study lend support to this hypothesis, as we found PPT differences by sex at every site except for the 3rd digit, the only site where there is little muscle tissue.

Importantly, we found that the extent of EIH was linearly related to baseline PPT. Participants who demonstrated lower pain sensitivity at baseline had greater EIH. Vaegter et al. [57] have previously reported that increased pain sensitivity, and higher intensity of clinical pain at baseline, reduces exercise-induced hypoalgesia in individuals with back pain. Our findings demonstrate that the influence of baseline pain sensitivity on EIH extends to healthy individuals without pain. This indicates that a uniform hypoalgesic response to isometric exercise should not be assumed, even in healthy adults. We also demonstrate in this study that even in a population of healthy adults, higher scores on the Central Sensitization Index are associated with lower PPT at baseline. This is despite the fact that average scores on the CSI in our study were well below the threshold of 40 that has been suggested as the cutoff score for clinically relevant central sensitization in patient populations [58–60] and were also lower than scores previously reported in nonpatient cohorts [59]. The frequency of our participants reporting diagnoses associated with central sensitization (22%) was also far lower than that reported in patient populations [59]. Existing evidence for the relationship between scores on the CSI and quantitative measures of pain sensitivity in patient populations is mixed [26], but our study suggests an association between biopsychosocial characteristics identified by the CSI and pain sensitivity in healthy adults.

Other factors influencing baseline PPT or change in PPT postfatigue were sex-dependent. Females with higher pain catastrophizing scores demonstrated less hypoalgesia in response to the fatiguing exercise. Our findings build upon work by Naugle et al. [52], who reported that levels of pain catastrophizing were predictive of exercise-induced changes in the temporal summation of heat pain. The relationship between pain catastrophizing and reduced EIH may be a result of reduced descending opioid pain inhibition. It is not clear why the influence of pain catastrophizing on hypoalgesia was only evident in women, as, unlike in previous studies [52], there was no difference in pain catastrophizing scores between men and women in our cohort. Our study did not find significant relationships between sleep quality and baseline PPT or a change in PPT following fatiguing exercise in the combined group analysis. However, in males, we demonstrate that greater insomnia was associated with reduced PPT at baseline. The difference between our findings and previous work may be due to the fact that the KSS and ISI scales quantify state-sleepiness and the perceived level of current insomnia [41, 42], rather than long-term sleeping impairment. Additionally, levels of sleep

disturbance reported in this study were below the threshold for clinically significant impairment [42] and were far lower than in studies involving experimental sleep deprivation.

There were some limitations to our study. The sample had an unequal distribution of male and female participants. Of note, changes in PPT in response to exercise were more pronounced in the smaller male cohort, indicating that our findings were not influenced by a lack of statistical power in the male group. Additionally, as in all studies investigating fatigue, it is difficult to prove objectively that muscle fatigue has occurred. We did not quantify the loss of force production following the Sorensen test, but loss of force production at the end of the test was indicated by the individuals' inability to continue maintaining the test position. In a previous study, using the same Sorensen paradigm in a cohort of young healthy adults, we confirmed with electromyography that fatigue occurs in the lumbar extensor muscles during the test [49]. We have also demonstrated that this fatigue persists for five to ten minutes after completion of the test, which was more than enough time to complete our PPT testing at all sites [49]. Finally, in this study, the mechanical stimuli were applied manually using a pressure dynamometer. It is possible therefore that the rate of pressure application varied slightly across testing repetitions. However, we minimized this potential confound by having the same trained tester apply the PPT stimuli to all participants.

4.1. Clinical Implications. The Biering–Sorensen test is a simple way to induce spinal and hip extensor fatigue and to assess EIH in healthy individuals and in clinical pain populations. Our findings of a significant relationship between PPT and scores on the CSI suggest that PPT testing may be a useful quantitative adjunct to self-report central sensitization questionnaires in the clinical setting. Isometric strengthening exercise is often recommended as an intervention for individuals with low back pain, and training that includes isometric extensor exercises such as "planks" or "bird dogs" is a common component of rehabilitation. However, since our study shows that the extent of EIH depends upon pain sensitivity at baseline, individuals with LBP with high baseline pain sensitivity may not respond in the same way to isometric exercise as back-healthy controls. Future studies should clarify if fatiguing isometric exercise reduces pain sensitivity in all patients with low back pain.

5. Conclusion

Isometric spinal and hip exercise held to failure produces a local hypoalgesic response. This occurs in both males and females, but to a greater extent in males. In healthy participants, there is greater EIH in those with lower pain sensitivity at baseline. In individuals without a clinical pain condition, a higher self-reported rating on the CSI is associated with a lower baseline PPT.

Data Availability

Data are available upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Scatterplots are provided showing the relationship between pressure-pain threshold and the Hospital Anxiety and Depression Scale, Insomnia Severity Index, Pain Catastrophizing Scale, and Karolinska Sleepiness Scale. STROBE Statement-checklist of items that should be included in reports of observational studies. (*Supplementary Materials*)

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Research Article

Rapid Improvement in Neck Disability, Mobility, and Sleep Quality with Chronic Neck Pain Treated by Fu's Subcutaneous Needling: A Randomized Control Study

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Background. Chronic neck pain is a common musculoskeletal disorder caused by overuse of neck and upper back muscles or poor posture, and it is commonly combined with a limited range of motion in the neck and shoulders. Most cases will recover within a few days; however, the symptoms often recur easily. Fu's subcutaneous needling (FSN) is a new therapeutic approach used to treat patients with chronic neck pain. However, there is no solid evidence to support the effectiveness of FSN on chronic neck pain and disability. *Methods*. Participants ($n = 60$) with chronic neck pain for more than 2 months with pain intensity scored by visual analog scale (VAS) more than five were enrolled in this trial. Participants were equally randomized into the FSN or transcutaneous electrical nerve stimulation (TENS) group who received interventions once a day on day 1, day 2, and day 4. They were assessed by outcome measurements during pre- and post-treatment and followed up for 15 days. *Results*. The VAS was immediately reduced in the FSN and TENS groups and sustained for 15 days of follow-up (all $P < 0.001$). The immediate effects were also observed as the pressure pain threshold increased in the FSN group on day 2 ($P = 0.006$) and day 4 ($P = 0.023$) after treatment, and tissue hardness decreased by FSN on day 1 and day 2 after treatment (both $P < 0.001$). FSN and TENS treatment improved neck disability and mobility; moreover, FSN promoted participants to receive better sleep quality, as determined by PSQI assessment ($P = 0.030$). TENS had no benefit on sleep quality. *Conclusion*. FSN was able to relieve pain and relax muscle tightness. Notably, FSN significantly improved neck disability and mobility and enhanced sleep quality. These findings demonstrated that FSN could be an effective alternative treatment option for patients with chronic neck pain. Clinical Trial Registration: ClinicalTrials.gov Identifier: NCT03605576, registered on July 30, 2018.

1. Introduction

The number of people with neck pain increases daily, and it has become a serious social problem in modern life. Acute neck pain is caused by overuse of the neck and upper back muscles or poor posture or injury, and it is usually combined with a limited range of motion [1]. Symptoms are often resolved without any treatment in a few days. However, most people experience recurrence of symptoms; pain that persists for more than 2 months without improvement is categorized as chronic neck pain that leads not only to upper back pain but also to functional decline that affects daily life, work, and sleep quality [1]. In 2017, more than 280 million cases of neck pain were reported, and the trend of age-standardized point prevalence did not decrease from 1990 [2]. Furthermore, about 10% of the population live with neck disability due to chronic neck pain [1–3]. The prevalence is greater in females than in males [4]. The highest prevalence, annual incidences, and years lived with disability from neck pain have been reported in developed regions (such as east Asia, western Europe, North Africa, and the Middle East) and high-income areas (e.g., North America) [2]. These epidemiological studies showed the urgent need to investigate new strategies for chronic neck pain treatment.

Treatments for chronic neck pain aim to relieve pain and recover functional disability. In general, rest, good posture, and intake of non-steroidal anti-inflammatory drugs are good options for managing neck pain [5]. However, some patients experience recurrent symptoms that persist without improvement. To alleviate these symptoms, some clinical practices are routinely used for chronic neck pain treatment. Transcutaneous electrical nerve stimulation (TENS) is a non-invasive therapy that is widely used in clinics. TENS treatment over the acupuncture points plus infrared irradiation can effectively reduce neck pain [6]. Furthermore, needle therapy is an effective alternative treatment for chronic neck pain. For example, remote acupuncture on TE 5 (*Waiguan*) and LI 11 (*Quchi*) has been reported as an effective treatment to manage chronic neck pain caused by myofascial trigger points (MTrPs) on the upper trapezius muscle [7]. Deep dry needling on active MTrPs provides a beneficial effect on pain relief and neck disability on chronic neck pain [8]. Fu's subcutaneous needling (FSN) is an advanced acupuncture that is applied for the treatment of MTrP-induced musculoskeletal disorders [9]. FSN is manipulated by using a disposable needle penetrating the skin of the non-diseased area and targeting the subcutaneous layer rather than the dermis or muscle layer. The swaying and reperfusion approach are the effective features of FSN, distinct from traditional acupuncture or dry needling [9, 10]. These features support FSN as an acceptable and popular needle therapy. Recently, FSN was demonstrated as an effective therapy for lateral epicondylalgia treatment without adverse effects [11]. However, scientific-based evidence to support the effects of remote FSN on chronic neck pain is currently lacking.

In the present study, we evaluated the effectiveness of FSN on chronic neck pain by measuring visual analog scale (VAS), pressure pain threshold (PPT), tissue hardness (TH) meter, neck range of motion (NROM), neck disability index (NDI), and Pittsburgh sleep quality index (PSQI) as outcome measurements. Three treatment sessions were performed on day 1, day 2, and day 4, with assessments before each treatment session and immediately after treatment, as well as on day 8 and day 15 for follow-up.

2. Materials and Methods

2.1. Participants. Subjects who participated in this study were enrolled from the Departments of Physical Medicine and Rehabilitation and Acupuncture in the China Medical University Hospital according to an open-label, randomized controlled trial. This study was approved by the Institutional Review Board of the China Medical University Hospital (CMUH107-REC2-031) and registered with ClinicalTrials.gov (Identifier: NCT03605576). All patients had completed their informed consent to participate in this study, and the research was conducted in accordance with the principles of the Declaration of Helsinki.

The inclusion criteria were based on (1) adults older than 20 years old; (2) having chronic neck pain for more than 2 months, as defined by the International Association of the Study of Pain, updated in 2011 [12], and VAS greater than 5 points; (3) patients with myofascial pain on the upper back; and (4) pain that was not effective for previous medication or physical therapy. Participants were excluded based on the criteria of (1) contraindications for FSN or TENS treatment, such as serious medical problems, recent trauma, or pregnancy; (2) history of drug abuse (including excess alcohol) that affected pain assessments; (3) received neck, upper back, or upper and lower limb surgery; (4) people with central or peripheral nerve disease; (5) cognitive dysfunction could not be matched with the experimenter; and (6) people with cardiac pacemakers and epilepsy, because electrode patches could not be placed on the skin.

Participants were randomly divided into FSN as the experimental group or TENS as the control group by a raffle system and allocated to the FSN or TENS group (Figure 1). A total of 61 participants were enrolled, but one participant was excluded because of VAS smaller than 5. The participants (60 patients) were divided and allocated into two arms: an experimental group who underwent FSN treatment (30 patients) and a placebo group who underwent TENS treatment (30 patients) via raffle (Figure 1). Every participant received the intervention of FSN or TENS. Three treatment sessions in this experiment were performed on day 1, day 2, and day 4, with assessments before each treatment session and immediately after treatment, as well as the following day 8 and day 15 for follow-up (Figure 2). All the treatments were conducted by the same acupuncturist who worked in the medical center in Taiwan for more than 5 years.

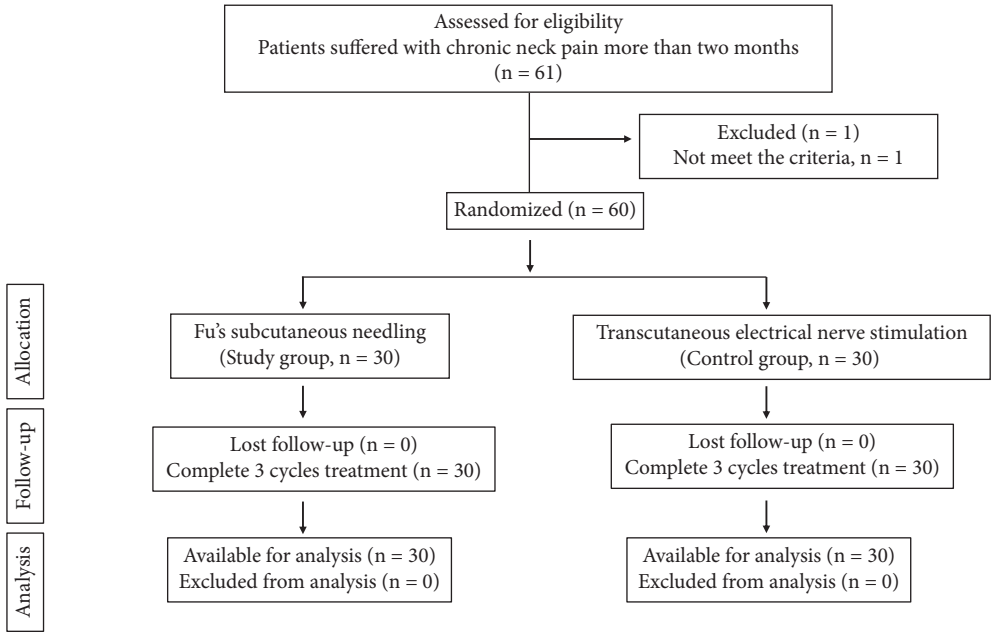

Figure 1: Consort flow diagram.

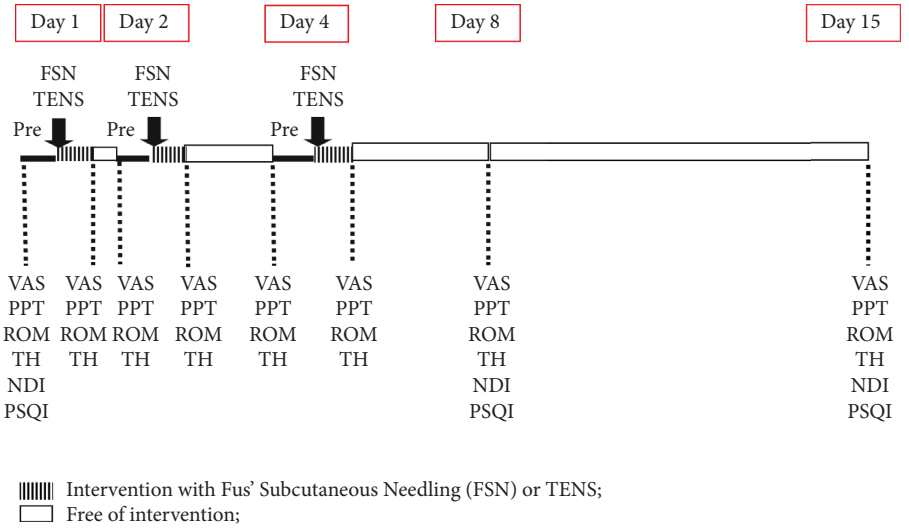

Figure 2: Study design. All participants were treated with FSN or TENS as described in Materials and Methods. Pre: before intervention; FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; VAS: visual analog scales; PPT: pressure pain threshold; ROM: active neck range of motion; TH: tissue hardness; NDI: neck disability index; PSQI: Pittsburgh sleep quality index.

2.2. Intervention Procedures. Participants in the experimental group were treated by using a disposable Fu's subcutaneous needle (Nanjing FSN Medical Co., Ltd., Jiangsu, China) on the radial aspect of the forearm extensors muscle. The needle was inserted into the subcutaneous layer with the whole needle body by holding the inserting device (Figure 3(a)). The insertion point was on the midpoint of the extensor muscle of the affected forearm (the center between the midpoint of cubital crease to elbow tip to the center of transverse crease of the wrist, Figure 3(b)). To ensure that the needle was inserted into the subcutaneous layer rather than the dermis or muscle layers, participants were asked for no pain sensations or soreness during the whole process of insertion. The core needle receded, and the protuberance of the soft tube seat was fixed in the slot of the core seat so that the needle tip was no longer exposed outside, followed by starting a swaying movement (Figures 3(c)–3(e)). The tip of the needle should be maintained at the same horizontal level during swaying by using the thumb and the middle finger to hold the core base, and the index finger and the ring finger were separated on the left and right side of the middle finger to sway in a seesaw-like sector one after the other (Figure 3(f)). Time and frequency of swaying was 50 times within 30 s. After swaying, the participants were asked to shrug their shoulders and raise their head for 10 s and then rest for the same intermission (Figure 4(a)). In this step, the

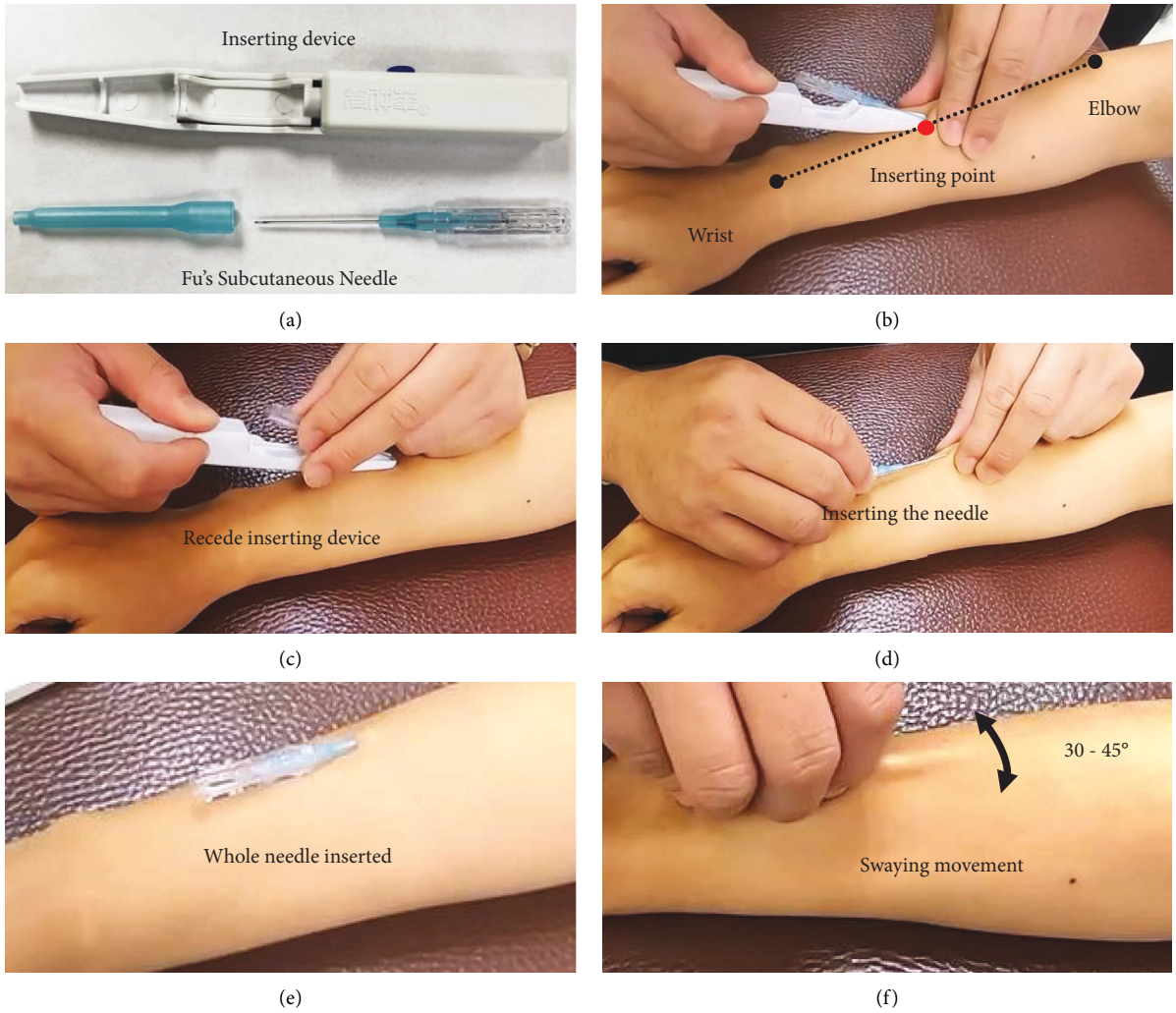

Figure 3: Procedure of Fu's subcutaneous needling. FSN was performed with a disposable Fu's subcutaneous needle (bottom) and inserting device (top) (a). The inserting point was on the midpoint between wrist and the elbow of the affected forearm (b). Holding the Fu's subcutaneous needle and receding inserting device (c). Inserting the needle into subcutaneous layer (d) until the whole needle is inserted (e). Swaying the needle in a 30-to-45-degree movement (f).

physician could help participants perform the exercise of contraction of the upper trapezius muscle with resistance (Figure 4(b)). The cycle was repeated up to three times for 2 min. After finishing the two actions called the "reperfusion approach," with FSN embedded subcutaneously, we removed the needle afterward.

Participants in the TENS group were treated with transcutaneous electrical nerve stimulator (Well-Life Healthcare Limited, Taiwan), with the electrodes attached to acupoints TE 5 (*Waiguan*) and LI 11 (*Quchi*), according to the guidance of WHO. The treatment parameters were set to pulse width of 200 μs, frequency of 200 Hz, and continuous wave for 20 min.

2.3. Outcome Measurements

2.3.1. Visual Analog Scales. VAS is a subjective tool that is commonly used to evaluate pain intensity [13, 14]. Participants were subjected to evaluations of the score of pain severity from no pain (score 0) to intolerable pain (score 10) in a 10-cm-long scale. The results were recorded in every pre-treatment (pre-Tx) and post-treatment (post-Tx) on day 1, day 2, and day 4 and followed up to day 8 and day 15 (Figure 2).

2.3.2. PPT for MTrPs of Upper Trapezius Muscles. We used a semi-objective tool by Pressure Algometry (OE-220, ITO CO., Ltd., Tokyo, Japan) as Fischer's methods to evaluate PPT [15, 16]. First, the physician found the MTrP of upper trapezius muscles and marked the point. The metal probe of pressure algometry was attached vertically to the MTrP, and the press was increased by 1 kg/s. When the participant felt uncomfortable or in pain gradually, this point indicated the threshold of latent MTrP. A point of intolerable pain indicated the threshold of active MTrP. The test was replicated three times at 60 s intervals of the same level of pain by participants. The results of the threshold of active MTrP were recorded, and the mean of the PPT of MTrPs of upper trapezius muscles was calculated.

(a) (b)

Figure 4: Reperfusion approach of Fu's subcutaneous needling. The participant was asked to grab the chair and shrug her shoulder on the same affected arm (a) and extend the neck with resistance by the acupuncturist's push (b) for the contraction of the upper trapezius muscle. The horizontal dashed line indicated the right shoulder shrugging.

2.3.3. Tissue Hardness of Upper Trapezius Muscles. Soft tissue stiffness was measured by using a tissue hardness meter (OE-220, ITO Co., Ltd., Tokyo, Japan) and applied in clinical studies recently [17–19]. The physician placed the metal probe of the tissue hardness meter vertically onto the MTrP of the upper trapezius muscle and pressurized by 1 mm/s. The test was finished when reaching a 10 mm measurement distance. The average of three readings was used for tissue hardness analysis. Every test had a 1 min intermission.

2.3.4. Neck Range of Motion. Cervical Range of Motion (CROM) instrument (Performance Attainment Associates, 958 Lydia Drive, Roseville, MN 55113) was used to assess NROM [20–22]. A gravity inclinometer was used to measure the NROM when participants performed the actions of flexion, extension, left rotation, right rotation, left-side bending, and right-side bending. The three inclinometers on the top, at the front, and at the lateral of the device indicated the 3D angle of neck motion (Figures 5(a)–5(f)).

2.3.5. Neck Disability Index. Neck disability index (NDI) was modified from the Oswestry Low Back Pain Index [23], and it is the most popular self-rated neck disability instrument due to neck pain [24]. Each of the 10 items was scored from 0 to 5 to achieve a sum of 50 scores. Participants finished the questionnaire before day 1 experiment and on day 8 and day 15 follow-up. The scoring sum below 5 indicated no activity limitation. The sum of 5–14 indicated a mild disability. The sum of 15–24 indicated an intermediate disability. The sum of 25–34 indicated a severe disability. The sum over 34 indicated complete activity limitation.

2.3.6. Pittsburgh Sleep Quality Index. PSQI is the most effective tool to evaluate sleep quality in adults [25, 26]. The questions comprised subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, step disturbance, use of sleeping medication, and daytime dysfunction during the past month. In each item, a score of 0 indicated no difficulty, whereas a score of 3 indicated severe difficulty. The global score of total items yielded a range from 0 to 21. A global score of 5 or more was considered poor sleep quality.

2.4. Statistical Analysis. Statistically significant differences ($P < 0.05$) among the results were calculated by using Statistical Package for Social Science (SPSS 18.0) for Windows. All data were expressed as mean ± standard deviation (SD). Baseline characteristics analysis of age, sex, VAS, PTT, TH, NROM, NDI, and PSQI was conducted via Student's *t*-test. For inferential statistics, the within-group analysis of all

Figure 5: Neck range of motion assessment. Participants were asked to wear the Cervical Range of Motion (CROM) instrument. Zeroing the gravity inclinometer at the front (a), at the lateral (b), and on the top (c) of the device before assessment. The red arrow of three inclinometers indicated the angle of zero. The angle change was measured when participants did the action of neck movement, that is, right-side bending (d), flexion (e), and right rotation (f).

variables was conducted by paired sample t-test, whereas the between-group analysis of the variables was conducted by independent two-sample t-test.

3. Results

3.1. Baseline Characteristics of Two Groups of Participants in the Study. The baseline characteristics and outcome measurements of the two groups are shown in Table 1. The mean of age was 52.73 ± 9.81 years for the FSN group and 52.16 ± 16.10 years for the TENS group, without significant differences ($P = 0.870$). The number of female participants was higher than the number of male participants in both groups (male: female, 10 : 20 for FSN; 8 : 22 for TENS). The affected side of the neck in the left and right sides were 17 and 13 participants for FSN and 14 and 16 participants for TENS, respectively. The VAS value was not significantly different in the FSN group compared with that in the TENS group (5.95 ± 1.36 for FSN and 6.71 ± 1.80 for TENS, $P = 0.069$). TH was similar in the two groups (56.75 ± 8.03 for FSN; 56.80 ± 9.49 for TENS, $P = 0.985$). No significant difference was observed in PPT (37.40 ± 5.11 for FSN; 39.31 ± 6.63 for TENS, $P = 0.216$) and NROM, including flexion, extension, left rotation, right rotation, left-side bending, and right-side bending in the two groups. Outcome assessments by questionnaire of NDI and PSQI showed no significant difference. No significant difference was found in all baseline values between the two groups. These results provide a well-randomized prospective study for further investigation.

3.2. FSN Treatment Reduces Chronic Neck Pain and Tissue Hardness Immediately. To understand the immediate effect of FSN on chronic neck pain, we evaluated the VAS, PPT, and TH before and after treatment. The data are shown in

Table 1: Baseline characteristics of participants in two groups.

Characteristic	FSN	TENS	P value
Number	30	30	
Age (year)	52.73 ± 9.81	52.16 ± 16.10	0.870
Gender, male/female, number (%)	10/20 (33%/67%)	8/22 (27%/73%)	
ASON, left/right, number (%)	17/13 (57%/43%)	14/16 (47%/53%)	
VAS (0–10)	5.95 ± 1.36	6.71 ± 1.80	0.069
PPT (N)	37.40 ± 5.11	39.31 ± 6.63	0.216
TH (%)	56.75 ± 8.03	56.80 ± 9.49	0.985
NROM index (degrees)			
Flexion	49.80 ± 12.47	47.60 ± 11.97	0.489
Extension	49.43 ± 14.46	53.13 ± 12.71	0.297
Left rotation	54.13 ± 11.39	54.83 ± 12.84	0.824
Right rotation	57.56 ± 12.21	56.96 ± 9.75	0.834
Left side bending	41.03 ± 10.75	40.90 ± 11.16	0.963
Right side bending	37.50 ± 8.61	35.30 ± 10.12	0.368
NDI (0–50)	8.43 ± 4.09	10.16 ± 5.84	0.189
PSQI (0–21)	10.67 ± 3.05	10.80 ± 3.81	0.882

Data were expressed as mean ± SD; P value was tested with an independent two-sample t-test. ASON: the affected side of neck; FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; VAS: visual analog scale; PPT: pain pressure threshold; TH: tissue hardness of muscle; NROM: neck range of motion; NDI: neck disability index; PSQI: Pittsburgh sleep quality index.

Table 2: Immediate effects of FSN and TENS groups on VAS, PPT, and TH.

	FSN			TENS			Difference		
	Pre-tx	Post-tx	P^a	Pre-tx	Post-tx	P^a	FSN	TENS	P^b
Day 1									
VAS (1–10)	5.95 ± 1.36	3.18 ± 2.43	<0.001	6.71 ± 1.80	5.38 ± 2.21	<0.001	−2.76 ± 1.68	−1.33 ± 1.02	<0.001
PPT (N)	37.40 ± 5.11	35.50 ± 8.19	0.117	39.31 ± 6.63	34.65 ± 8.11	<0.001	−1.89 ± 6.42	−4.66 ± 4.60	0.060
TH (%)	56.75 ± 8.03	50.80 ± 6.38	<0.001	56.80 ± 9.49	54.06 ± 6.71	0.079	−5.95 ± 7.72	−2.73 ± 8.22	0.124
Day 2									
VAS (1–10)	4.30 ± 2.05	2.50 ± 2.31	<0.001	5.61 ± 2.00	4.43 ± 2.19	<0.001	−1.80 ± 1.37	−1.18 ± 0.79	0.038
PPT (N)	32.21 ± 9.19	34.27 ± 11.13	0.006	31.77 ± 9.70	31.56 ± 10.19	0.738	2.06 ± 3.80	−0.20 ± 3.29	0.017
TH (%)	55.75 ± 7.12	50.78 ± 6.86	<0.001	56.14 ± 6.03	55.26 ± 7.49	0.596	−4.97 ± 6.00	−0.87 ± 8.95	0.042
Day 4									
AS (1–10)	3.58 ± 2.42	1.93 ± 2.24	<0.001	5.20 ± 1.58	3.90 ± 1.44	<0.001	−1.65 ± 1.15	−1.30 ± 0.74	0.169
PPT (N)	34.08 ± 11.95	36.03 ± 12.16	0.023	30.54 ± 9.55	31.25 ± 9.38	0.107	1.95 ± 4.46	0.70 ± 2.31	0.178
TH (%)	53.74 ± 7.95	53.12 ± 6.95	0.705	57.29 ± 4.81	55.86 ± 8.13	0.326	−0.62 ± 8.89	−1.43 ± 7.86	0.709

Data were expressed as mean ± SD.P^a value was tested with a paired sample t-test.P^b value was tested with an independent two-sample t-test. FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; VAS: visual analog scale; PPT: pain pressure threshold; TH: tissue hardness of muscle.

Table 2 and Figure 6. VAS (pre-Tx: 5.95 ± 1.36 vs. post-Tx: 3.18 ± 2.43, $P < 0.001$) and TH (pre-Tx: 56.75 ± 8.03 vs. post-Tx: 50.80 ± 6.38, $P < 0.001$) significantly improved in the FSN group on day 1, except PPT (pre-Tx: 37.40 ± 5.11 vs. post-Tx: 35.50 ± 8.19, $P = 0.117$). For the TENS group, VAS (pre-Tx: 6.71 ± 1.80 vs. post-Tx: 5.38 ± 2.21, $P < 0.001$) and PTT (pre-Tx: 39.31 ± 6.63 vs. post-Tx: 34.65 ± 8.11, $P < 0.001$) also significantly improved, except TH (pre-Tx: 56.80 ± 9.49 vs. post-Tx:54.06 ± 6.71). In the difference comparison (Table 2), FSN was more effective in pain relief (−2.76 ± 1.68 for FSN, −1.33 ± 1.02 for TENS, $P < 0.001$), not in PPT (−1.89 ± 6.42 for FSN, −4.66 ± 4.60 for TENS, $P = 0.060$) and TH (−5.95 ± 7.72 for FSN, −2.73 ± 8.22 for TENS, $P = 0.124$) compared with TENS. On day 2, VAS (pre-Tx: 4.30 ± 2.05, post-Tx: 2.50 ± 2.31, $P < 0.001$), PPT (pre-Tx: 32.21 ± 9.19, post-Tx: 34.27 ± 11.13, $P = 0.006$), and TH (pre-Tx: 55.75 ± 7.12, post-Tx: 50.78 ± 6.86, $P = 0.001$) significantly improved in the FSN group. However, TENS only significantly improved VAS (pre-Tx: 5.61 ± 2.00, post-Tx: 4.43 ± 2.19, $P < 0.001$), not PPT ($P = 0.738$) and TH ($P = 0.596$), on day 2. The comparison of differences revealed that FSN was more effective on VAS (FSN: −1.80 ± 1.37, TENS: −1.18 ± 0.79, $P = 0.038$) and PPT (FSN: 2.06 ± 3.80, TENS: −0.20 ± 3.29, $P = 0.017$) and TH (FSN: −4.97 ± 6.00, TENS: −0.87 ± 8.95, $P = 0.042$) than TENS after the second course of treatment.

After an intermission of 1 day, the day 4 evaluation results showed that FSN still had a significant effect on VAS (pre-Tx: 3.58 ± 2.42, post-Tx: 1.93 ± 2.24, $P < 0.001$) and PPT (pre-Tx: 34.08 ± 11.95, post-Tx: 36.03 ± 12.16, $P = 0.023$) but not on TH ($P = 0.705$). Only a significant effect on VAS (pre-Tx: 5.20 ± 1.58, post-Tx: 3.90 ± 1.44, $P < 0.001$) was

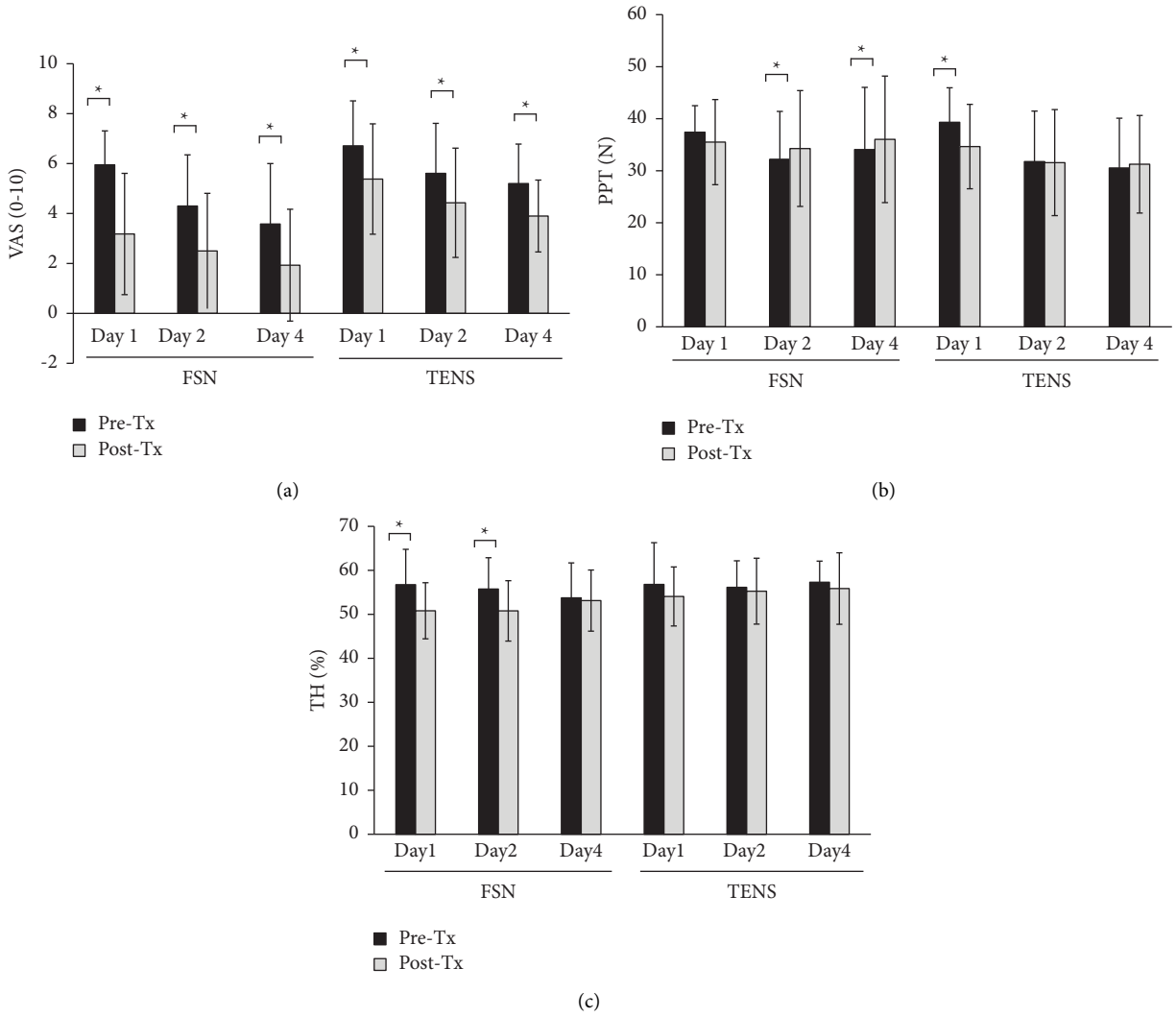

Figure 6: Comparison the immediate effects of the two groups. The pretreatment and posttreatment value of VAS (a), PPT (b), and TH (c) was measured in three treatment sessions in both groups. Asterisks (*) showed the $P < 0.05$. VAS: visual analog scale, PPT: pressure pain threshold, and TH: tissue hardness.

Table 3: Short-term and long-term effects of FSN and TENS groups on VAS, PPT, and TH.

	Pre-tx	Day 8	P^a	Difference	P^c	Day 15	P^b	Difference	P^c
VAS (0–10)									
FSN	5.95 ± 1.36	2.81 ± 1.94	<0.001	−3.16 ± 1.78	0.204	2.06 ± 1.70	<0.001	−3.95 ± 1.61	0.093
TENS	6.71 ± 1.80	4.21 ± 1.57	<0.001	−2.50 ± 2.01		3.63 ± 1.52	<0.001	−3.08 ± 1.95	
PPT (N)									
FSN	37.40 ± 5.11	35.43 ± 10.86	0.589	−1.27 ± 11.67	0.017	36.09 ± 12.14	0.158	−0.48 ± 12.98	0.020
TENS	39.31 ± 6.63	31.28 ± 8.88	<0.001	−8.02 ± 8.51		31.28 ± 9.68	<0.001	−8.02 ± 9.17	
TH (%)									
FSN	56.75 ± 8.03	55.77 ± 5.73	0.310	−1.47 ± 9.42	0.957	53.83 ± 6.56	0.567	−3.27 ± 10.53	0.500
TENS	56.80 ± 9.49	55.95 ± 9.49	0.594	−0.85 ± 8.64		55.62 ± 5.64	0.462	−1.18 ± 8.66	

Data were expressed as mean ± SD; P value was tested with an independent two-sample t-test. [a]Compares the value in pre-Tx and on day 8 of FSN or TENS group. [b]Compares the value on day 8 and on day 15 of FSN or TENS group. [c]compares the value of difference between FSN and TENS group. FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; VAS: visual analog scale; PPT: pain pressure threshold; TH: Tissue hardness of muscle.

observed in the TENS group. However, the difference between FSN and TENS in VAS, PPT, and TH was not significant.

3.3. Short-Term and Long-Term Effects of FSN on Pain Relief. In VAS test, both FSN and TENS demonstrated a decrease in pain scale on day 8 and day 15 ($P < 0.001$ in all tests; Table 3

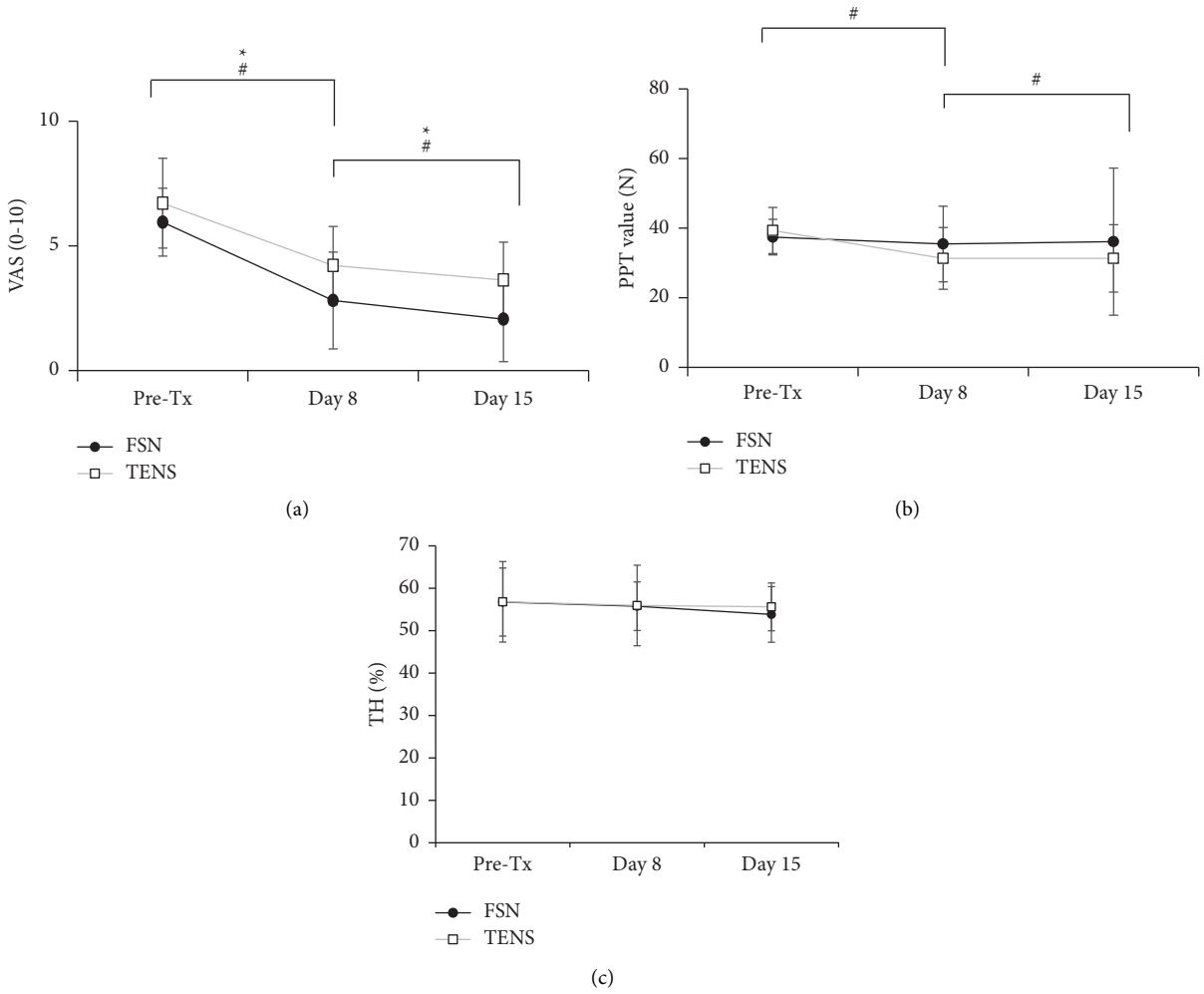

Figure 7: Comparison the short-term and long-term effects of the two groups. The value of VAS (a), PPT (b), and TH (c) was measured on day 1 before treatment and followed up to day 8 and day 15 in both groups. Asterisks (*) and hashtag (#) showed the $P < 0.05$ in FSN or TENS group, respectively. VAS: visual analog scale, PPT: pressure pain threshold, TH: tissue hardness, PFG: pain free grip, FSN: Fu's subcutaneous needling, and TENS: transcutaneous electrical nerve stimulation.

Table 4: Short-term and long-term effects of FSN and TENS groups on NDI.

	Pre-tx on day 1	Day 8	P^a	Day 15	P^b
FSN	8.43 ± 4.09	6.83 ± 4.39	0.010	4.96 ± 4.23	<0.001
TENS	10.16 ± 5.84	8.33 ± 5.73	0.036	7.36 ± 5.70	0.001

Data were expressed as mean ± SD; P value was tested with a paired sample t-test. [a]Compares the value in pre-Tx and on day 8 of FSN or TENS group. [b]Compares the value on day 8 and on day 15 of FSN or TENS group. FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; NDI: neck disability index.

and Figure 7). Only TENS decreased PPT on day 8 and day 15 ($P < 0.001$), whereas FSN had no significant effect on PTT. In addition, no significant decrease in TH was found in both groups on day 8 and day 15. Interestingly, TENS had a more significant decrease of PPT compared with FSN on day 8 and day 15 (day 8: −1.27 ± 11.67 for FSN, −8.02 ± 8.51 for TENS, $P = 0.017$; day 15: −0.48 ± 12.98 for FSN, −8.02 ± 9.17 for TENS, $P = 0.020$; Table 3).

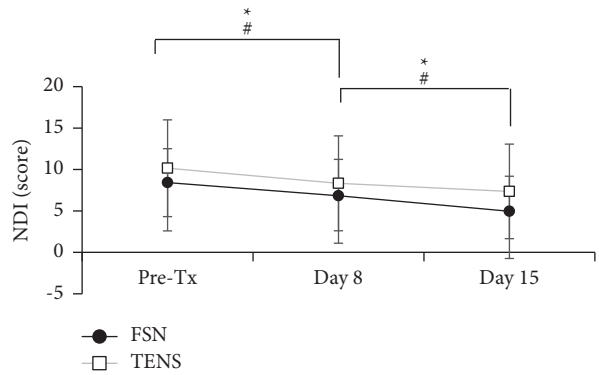

Figure 8: Comparison of the short-term and long-term effects on NDI. The score of NDI was measured on day 1 pre-treatment and followed up to day 8 and day 15 in both groups. Asterisks (*) and hashtag (#) showed the $P < 0.05$ in FSN or TENS group, respectively. FSN: Fu's subcutaneous needling, TENS: transcutaneous electrical nerve stimulation; NDI: neck disability index.

Table 5: Immediate effects of FSN and TENS groups on NROM.

	FSN			TENS		
	Pre-tx	Post-tx	*P*	Pre-tx	Post-tx	*P*
Day 1						
Flexion	49.80 ± 12.47	55.50 ± 11.15	<0.001*	47.60 ± 11.97	51.16 ± 11.05	0.001*
Extension	49.43 ± 14.46	54.76 ± 12.24	<0.001*	53.13 ± 12.71	56.33 ± 14.03	0.043*
Left rotation	54.13 ± 11.39	60.10 ± 9.72	<0.001*	54.83 ± 12.84	57.56 ± 10.40	0.052
Right rotation	57.56 ± 12.21	63.30 ± 10.48	<0.001*	56.96 ± 9.75	60.26 ± 9.81	0.002*
Left side bending	41.03 ± 10.75	44.13 ± 9.79	0.034*	40.90 ± 11.16	44.33 ± 10.90	0.044*
Right side bending	37.50 ± 8.61	42.53 ± 6.86	<0.001*	35.30 ± 10.12	39.66 ± 8.78	0.001*
Day 2						
Flexion	54.23 ± 10.83	57.80 ± 11.04	0.001*	52.33 ± 11.67	54.46 ± 11.61	0.030*
Extension	52.46 ± 12.55	57.20 ± 11.80	0.001*	52.83 ± 12.16	56.56 ± 11.70	<0.001*
Left rotation	58.26 ± 9.08	60.76 ± 9.55	0.034*	59.50 ± 11.38	61.40 ± 11.06	0.040*
Right rotation	60.10 ± 11.05	62.73 ± 9.64	0.040*	59.00 ± 9.25	63.06 ± 8.43	0.002*
Left side bending	43.26 ± 9.77	47.53 ± 8.57	0.010*	41.80 ± 10.99	45.06 ± 9.06	0.005*
Right side bending	40.13 ± 7.17	44.30 ± 7.44	<0.001*	38.00 ± 9.72	41.70 ± 9.02	<0.001*
Day 4						
Flexion	57.16 ± 11.52	58.70 ± 11.22	0.115	53.20 ± 12.31	55.36 ± 11.11	0.048*
Extension	55.06 ± 10.57	58.70 ± 9.70	<0.001*	56.16 ± 11.34	59.16 ± 11.06	0.002*
Left rotation	57.63 ± 10.41	59.76 ± 8.69	0.077	59.63 ± 9.89	62.30 ± 8.17	0.003*
Right rotation	61.33 ± 11.25	65.63 ± 9.29	0.016*	62.30 ± 8.81	63.30 ± 9.06	0.187
Left side bending	44.03 ± 9.17	48.16 ± 8.95	<0.001*	45.03 ± 10.37	47.30 ± 9.27	0.077
Right side bending	44.16 ± 9.50	47.10 ± 8.46	0.011*	40.80 ± 8.41	43.76 ± 8.63	0.001*

Data were expressed as mean ± SD; *P* value was tested with a paired sample *t*-test. FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; NROM: neck range of motion. Asterisks (*) showed the $P < 0.05$ in FSN or TENS group, respectively.

3.4. FSN Improved Neck Disability, Mobility, and Sleep Quality. Chronic neck pain commonly induces limitations of neck range of motion, followed by poor sleep quality. To estimate the effect of FSN on neck mobility, we analyzed the subjective questionnaire of NDI and objective NROM. The data in Table 4 and Figure 8 showed that the score of NDI improved by FSN from 8.43 ± 4.09 on day 1 pre-Tx to 6.83 ± 4.39 on day 8 ($P = 0.010$), and the effectiveness was sustained to day 15 (4.96 ± 4.23, $P < 0.001$). The effectiveness of TENS on NDI was from 10.16 ± 5.84 on day 1 pre-Tx to 8.33 ± 5.73 on day 8, $P = 0.036$; and to 7.36 ± 5.70 on day 15, $P = 0.001$. The two groups showed significant effects on short-term and long-term NDI assessment.

To understand further the effect of FSN on neck mobility, NROM was measured during pre- and post-treatment. Both FSN and TENS had benefits on neck motion upon treatment at days 1 and 2, except left rotation in the TENS group (Table 5). After an intermission of 1 day, FSN had benefits on the action of extension, right rotation, right rotation and left/right-side bending on day 4 treatment, whereas TENS had benefits on the actions of flexion, extension, left rotation, and right-side bending (Table 5). On day 8 and day 15 follow-up, both FSN and TENS had benefits on all active neck motion, except TENS for neck extension (Table 6).

Improvement in sleep quality is an important outcome to assess the effectiveness of therapy. The results of the self-reported PSQI questionnaire indicated that FSN was beneficial for participants to achieve better sleep quality on day 15 follow-up compared with TENS (in the FSN group, from 10.67 ± 3.05 on day 1 pre-Tx to 10.43 ± 2.69 on day 8, $P = 0.504$, and to 9.93 ± 2.74 on day 15, $P = 0.030$; in the TENS group, from 10.80 ± 3.81 in pre-Tx day 1 to 10.26 ± 3.67 on day 8, $P = 0.290$, and to 10.26 ± 3.18 on day 15, $P = 0.252$; Table 7).

4. Discussion

To our knowledge, this study was the first to uncover and demonstrate the effectiveness of FSN in chronic neck pain treatment. We examined the improvement in VAS, PPT, TH, NROM, and outcome measurement of NDI and PSQI after treatment in patients with chronic neck pain. The results of this clinical trial showed that FSN had significant benefits on VAS, NDI, and sleep quality at 15 days follow-up compared with TENS treatment.

TENS is a widely used modality in clinical practice for chronic neck pain with advantages of non-invasive, safe, and immediate effects on pain relief [27]. It is based on electrodes attached to the pain area or acupoints for current transmission. This action stimulates non-nociceptive neuron fibers to block pain transmission in accordance with gate control theory [28]. However, its effectiveness is controversial [29, 30]. A meta-analysis of clinical studies showed insufficient evidence regarding treatment with TENS in patients with chronic neck pain [30]. Nevertheless, we observed immediate pain reduction after TENS treatment on day 1, day 2, and day 4 (Table 2), and TENS-reduced pain effect was sustained to day 8 and day 15 follow-up (Table 3).

Purpose-based acupoints are used for the treatment of various symptoms in ancient acupuncture theories. Needling on different acupoints produces distinct effects. For

Table 6: Short-term and long-term effects of FSN and TENS groups on NROM.

	Pre-tx	Day 8	P^a	Day 15	P^b
Flexion					
FSN	49.80 ± 12.47	56.30 ± 10.50	0.004*	58.50 ± 10.10	<0.001*
TENS	47.60 ± 11.97	54.96 ± 9.96	<0.001*	57.26 ± 10.94	<0.001*
Extension					
FSN	49.43 ± 14.46	56.30 ± 10.50	<0.001*	57.20 ± 11.01	<0.001*
ENS	53.13 ± 12.71	56.00 ± 9.72	0.066	56.16 ± 11.42	0.058
Left rotation					
FSN	54.13 ± 11.39	59.30 ± 9.62	0.002*	61.83 ± 9.12	<0.001*
TENS	54.83 ± 12.84	61.50 ± 7.96	0.001*	62.53 ± 7.40	0.002*
Right rotation					
FSN	57.56 ± 12.21	62.60 ± 10.26	0.024*	64.70 ± 8.23	0.001*
TENS	56.96 ± 9.75	63.86 ± 9.77	<0.001*	63.56 ± 9.79	<0.001*
Left side bending					
FSN	41.03 ± 10.75	44.76 ± 7.48	0.013*	47.06 ± 8.37	0.002*
TENS	40.90 ± 11.16	47.33 ± 9.21	<0.001*	47.30 ± 11.48	0.001*
Right side bending					
FSN	37.50 ± 8.61	43.80 ± 7.09	<0.001*	45.66 ± 8.38	<0.001*
TENS	35.30 ± 10.12	42.33 ± 8.35	<0.001*	43.83 ± 8.53	<0.001*

Data were expressed as mean ± SD; P value was tested with a paired sample t-test. [a]Compares the value in pre-Tx and on day 8 of FSN or TENS group. [b]Compares the value on day 8 and on day 15 of FSN or TENS group. Asterisks (*) showed the $P < 0.05$ in FSN or TENS group, respectively. FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; NROM: neck range of motion.

Table 7: Effectiveness of FSN and TENS groups on sleep quality via self-reported PSQI questionnaire.

	Pre-tx on day 1	Day 8	P^a	Day 15	P^b
FSN	10.67 ± 3.05	10.43 ± 2.69	0.504	9.93 ± 2.74	0.030*
TENS	10.80 ± 3.81	10.26 ± 3.67	0.290	10.26 ± 3.18	0.252

Data were expressed as mean ± SD; P value was tested with a paired sample t-test.[a] Compares the value in pre-Tx and on day 8 of FSN or TENS group. [b]Compares the value on day 8 and on day 15 of FSN or TENS group. Asterisks (*) showed the $P < 0.05$. FSN: Fu's subcutaneous needling; TENS: transcutaneous electrical nerve stimulation; PSQI: Pittsburgh sleep quality index.

example, acupuncture at SI 3 (*Houxi*) and TE 3 (*Zhongzhu*) is effective for acute neck pain caused by stiff neck or cervical spondylosis [31, 32]. In chronic neck pain treatments, TE 5 (*Waiguan*) and LI 11 (*Quchi*) are commonly used in acupuncture and TENS [7]. However, the needling points of FSN are on the midpoint of the extensor muscle of forearm, not on the acupoints or MTrPs, different from conventional acupuncture in our study. A treatment strategy focusing on the upper trapezius muscle may be the key to eliminating the condition. For example, muscle energy technique and ischemic compression technique on upper trapezius active MTrPs have a short-term effect on pain relief in patients with nonspecific neck pain [33, 34]. In this study, we observed the remote effect of FSN; needling the distal location from the MTrP area led to pain relief and a sustained effect on neck motion and sleep quality (Tables 2, 3, and 5–7). The mechanism may be that needling the myofascial layer triggered the signal transduction of connective tissue to relax the tightened muscles, that is, upper trapezius muscle for chronic neck pain. By combining the swaying and reperfusion approach, FSN effectively relieved neck pain and promoted the remission of the limitation of NROM. Swaying movement of the FSN in the subcutaneous layer released the muscular tension of affected muscles, resulting in pain relief and decreased tissue hardness immediately. The reperfusion approach rapidly restored blood flow, and re-congestion in damaged muscle resulted in accelerated tissue repair. The resistance action of contraction of the upper trapezius muscle helped with the recovery of the disorder.

Tissue hardness or stiffness is the ability of muscle to resist deformation when doing activities. Increase in tissue hardness implies that someone requires more power and energy to respond to the activity of the agonist and antagonistic muscle. The difference between the affected side and the normal side of neck and shoulders can break the coordination. Our data supported the improvement effect of FSN on TH in the first 2 days of treatment. With improvement in neck pain and tissue hardness, FSN could improve neck disability (Table 5). Most people have a problem of poor posture due to looking downward to work or using their cellphone or personal computer for a long period. Immense stress makes people have an involuntary shrug that can cause neck pain. Exercises can improve one's posture to correct positions that prevent neck pain or intervertebral disc herniation [35]. Self-training of the neck muscle is recommended for patients with chronic neck pain and effectively reduces neck pain [36]. If patients are treated with FSN and combine exercise practice, they may stop the disease process of neck pain and the symptoms. The efficacy of combination treatments needs more investigation.

Needle therapy, including dry needling, for chronic neck pain is usually used with more than one filament needle to needle into the MTrPs directly or nearby areas; however, the effectiveness of dry needling on chronic neck pain is equivocal, recently reported by a long-term follow-up trial [37] and a meta-analysis study [38]. Furthermore, given that most people are high responders to needle pain [39], remote therapy and needle-less methods are the better options for

health care. Remote injection with anesthetics has been demonstrated to be an effective treatment for chronic neck pain [40]. The analgesic effects of intramuscular lidocaine injection act on voltage-gated sodium channels to block nerve conduction and sensation in the peripheral nervous system [41]. In our study, we observed that remote FSN on chronic neck pain benefitted pain relief. FSN is suitable for patients who fear needle pain by using the disposable needle insertion away from MTrPs, and this method involves minimal pain.

The FSN needle is inserted into the subcutaneous layer, which contains adipose tissue, connective tissues, and numerous vascular and neural networks. Half a century ago, Boguslaw Lipinski reported that the potential mechanism of acupuncture relies on the piezoelectric effect from connective tissues [42]. Furthermore, the neural pathway is the mechanism involved in acupuncture [43], which is applied to nervous system diseases [44]. The effect of acupuncture was blocked by local anesthetic injection in a rat model [45], indicating that peripheral sensory nerves are involved in the action of acupuncture. The mechanical connective tissue reaction instead of neural mechanism in FSN treatment was first investigated in a rabbit model in 2012 [46]. Monitoring the endplate noise from rabbit myofascial trigger spots (MTrSs) with FSN intervention demonstrated that FSN to MTrSs of distal ipsilateral gastrocnemius muscle can initially increase the irritability of MTrS in proximal biceps femoris muscle, followed by a suppression effect after cessation of needling, but these observations were not found in the contralateral side [46]. This hypothesis was also supported in the study of Langevin and her colleagues [47], who hypothesized that mechanical coupling between the needle and connective tissue with winding of tissue around the needle during needle rotation transmits a mechanical signal to connective tissue cells that may explain local and remote, as well as long-term, effects of acupuncture. Unlike Hsieh and her colleagues' animal study of dry needling [48], the mechanism for the effectiveness of dry needling and acupuncture to MTrP-induced disorders was related to an intact neural network. The effectiveness of remote FSN may go through the piezoelectricity and mechanical connective tissue reaction instead of neural mechanism.

4.1. Limitations. This study had some limitations. First, patients with chronic neck pain usually have an accompanying disability such as limited neck motion and poor sleep quality. The disorder is not restricted to elders only; up to 67% of the young population (aged 18–29 years) have had a 12-month prevalence of chronic neck pain [49]. Young people often recover more quickly than elders. In our study, only four young people were recruited in the TENS group with a smaller VAS score of 5 and 6. This may not influence the effect of FSN or TENS on chronic neck pain in this study. Second, patients with the TENS intervention in this study comprised the control group; however, it was not a real placebo group compared with the FSN group. A sham FSN design is needed to be an ideal placebo group when compared with the FSN group to evaluate the treatment's effectiveness. Sham FSN may be designed by intervention with a swaying or reperfusion approach alone, or without both procedures. As expected, the sham FSN may not provide any improvement on chronic neck pain symptoms, but neck pain decreased while the FSN needle was penetrated into the skin. However, choosing an ineffectual treatment was impossible for subjects in this study. We were obliged to take TENS as the control group to compare the effectiveness of FSN on chronic neck pain. The small sample size was another limitation of this study, which resulted in a small statistical power. Small sample sizes make some results inconclusive. For example, a significant improvement was observed for neck disability in the FSN and TENS groups and sleep quality in the FSN group only (Table 4, Figure 8, and Table 7). However, we could not prove the beneficial effects of FSN compared with TENS treatment via difference analysis on day 8 and day 15 follow-up, even if the difference was greater in the FSN group than in the TENS group (all $P > 0.05$), Supplementary Table 1 and Supplementary Table 2. Future research is required to establish a large population involving other institutes to amplify the statistical power and reach conclusive results.

5. Conclusions

This study is the first to investigate FSN treatment of chronic neck pain with scientific evidence by using several objective evaluation tools in a clinical setting. FSN could not only relieve neck pain but also it improved the PPT and TH. Notably, FSN significantly improved neck disability and enhanced sleep quality.

Data Availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of China Medical University Hospital (CMUH107-REC2-031) and was registered at ClinicalTrials.gov (Identifier: NCT03605576)

Consent

Informed consent was obtained from all participants involved in the study and was retained and archived by corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Conceptualization was performed by Ching-Hsuan Huang, Mao-Feng Sun, Zhonghua Fu, Jian Sun, and Li-Wei Chou. Data curation was performed by Ching-Hsuan Huang.

Funding acquisition was performed by Li-Wei Chou. Investigation was performed by Ching-Hsuan Huang. Methodology was performed by Ching-Hsuan Huang, Zhonghua Fu, Jian Sun, and Li-Wei Chou. Analysis was performed by Ching-Hsuan Huang and Lung-Hung Tsai. Supervision was performed by Mao-Feng Sun. Original draft was prepared by Ching-Hsuan Huang and Lung-Hung Tsai. Review and editing were done by Ching-Hsuan Huang, Lung-Hung Tsai, and Li-Wei Chou. All authors have read and agreed to the published version of the manuscript. Ching-Hsuan Huang and Lung-Hung Tsai contributed equally to this work.

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Supplementary Materials

Supplementary Table 1. Difference comparison of NDI in two groups. *Supplementary Table 2.* Difference comparison of PSQI in two groups. (*Supplementary Materials*)

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Research Article

Correlation Analysis between Tamoxifen and Lumbar Intervertebral Disc Degeneration: A Retrospective Case-Control Study

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Objectives. To investigate the correlation between tamoxifen (TAM) and lumbar intervertebral disc (IVD) degeneration (IVDD). *Methods*. The patients who visited the department of spine surgery from January 2015 to December 2020 were retrospectively reviewed. Those with a history of breast cancer surgery were identified and their data were collected. These data included patients' age, body mass index (BMI), menstrual history, postoperative history, drug treatment plan, and imaging data. The participants were divided into the TAM group and the non-TAM group. Lumbar IVDD was assessed by lumbar lordosis (LL), vertebral CT density, lumbar disc height index (DHI), Modic changes, and modified Pfirrmann grading score. SPSS 20 was used for statistical analysis. *Results*. A total of 75 patients were included in this study, 46 patients in the TAM group and 29 patients in the non-TAM group. No significant differences were present in age, BMI, postoperative history, LL, and vertebral CT density between the two groups. The DHI of L1/2 and L2/3 in the TAM group was lower compared to the non-TAM group ($P = 0.038$ and $P = 0.034$, respectively), while comparisons regarding the DHI of L3/4, L4/5, and L5/S1, and the average DHI between TAM and non-TAM groups were not significant. The modified Pfirrmann grading scores of the L1/2 and L2/3 IVDs in the TAM group were higher than those in the non-TAM group ($P = 0.004$ and $P = 0.025$, respectively). Comparisons of L3/4, L4/5, and L5/S1 between the two groups were not significant. The comparisons regarding the occurrence of Modic changes did not show a significant difference between the TAM and non-TAM groups. *Conclusions*. This study indicates that there might be some positive correlation between TAM use and lumbar IVDD. In particular, the degeneration of L1/2 and L2/3 has shown a correlation with TAM use.

1. Introduction

Lower back pain is one of the most common and important public health problems that afflict adults, bringing significant life troubles and social and economic burdens [1, 2]. Intervertebral disc (IVD) degeneration (IVDD) is an important cause of lower back pain, but the mechanism of IVDD is still unclear. The cause of IVDD may be related to a decrease in the number of nucleus pulposus cells (NPCs) and disruption of the extracellular matrix (ECM) balance caused by age, inflammation, trauma, genetics, and other factors [3, 4]. An earlier preliminary clinical study showed that ovariectomy (OVX) resulted in a significant decrease in the estrogen level of patients; moreover, the Pfirrmann grading of the lumbar IVDs in OVX patients was higher than that in normal patients [5]. A large number of experiments have evidenced that estrogen can enhance the tolerance of NPCs to inflammation and oxidative stress, reduce cell apoptosis, and improve cell survival rate [3, 4, 6–8]. Therefore, the level of estrogen can influence the progression of IVDD.

Endocrine therapy is an important treatment for certain tumors, such as breast and ovarian cancer, which can effectively reduce tumor metastasis and improve patient survival. Tamoxifen (TAM), a selective estrogen receptor

modulator, is commonly used in premenopausal estrogen receptor (ER)-positive breast cancer patients. However, a large number of studies have found that the use of TAM negatively affects the bones, uterus, and other organs [9, 10]. Previous investigations have revealed the expression of estrogen receptors in IVD tissues; so far, however, no studies have reported the effect of estrogen receptor modulators (e.g., TAM) on IVDD [4].

Thus, this study retrospectively analyzed and compared IVDD between breast cancer patients who took TAM and those without TAM, in order to investigate the correlation between TAM and IVDD.

2. Materials and Methods

2.1. Patients. The postoperative breast cancer patients who visited the department of spine surgery from January 2015 to December 2020 were retrospectively reviewed and divided into two groups based on the use of TAM: the TAM group and the non-TAM group (breast cancer patients treated without TAM after surgery). Patients in the TAM group received TAM at a dose of 10 mg/bid for at least six months.

2.2. Inclusion Criteria

(1) Postoperative breast cancer patients without menopause took TAM or those who did not take TAM

(2) Patients who have complete clinical data

2.3. Exclusion Criteria

(1) Patients who failed to receive regular postoperative chemotherapy

(2) Patients suffering from endocrine system and immune system diseases that may affect hormone levels

(3) Patients with spinal trauma, spinal fracture, and history of spinal surgery

2.4. Data Collection and Calculations. The postoperative data of female breast cancer patients in the department of spinal surgery were retrospectively analyzed. The following patient data were analyzed: age, body mass index (BMI), menstrual history, postoperative history of breast cancer, and drug treatment plan. Imaging data included lumbar MRI, CT, and X-ray. Lumbar lordosis (LL) was measured by a lumbar X-ray or CT of the angle between the tangent line of the upper endplate of the L1 vertebral body and the S1 vertebral body in the lateral lumbar spine (Figure 1(a)). The lumbar disc height index (DHI) was calculated using the following formula (Figure 1(b)) [11, 12]:

$$\left(\frac{\text{intervertebral anterior edge height + posterior edge height}}{\text{intervertebral upper body width + lower body width}}\right) \times 100\%. \quad (1)$$

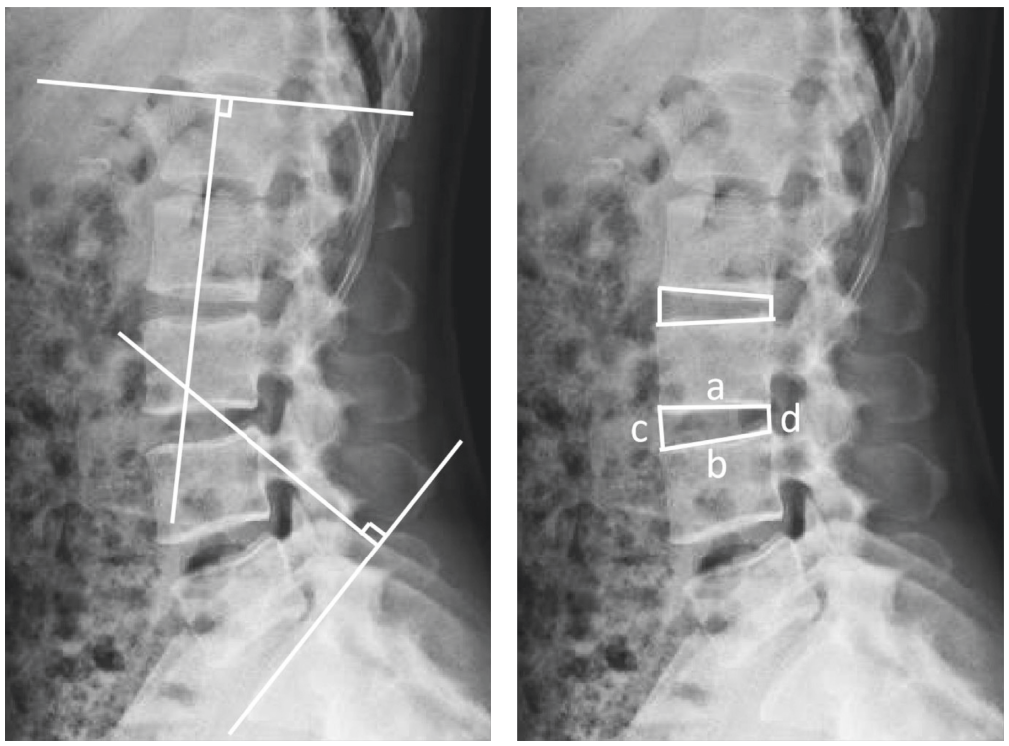
MRI T2-weighted sagittal images were utilized to assess the degree of IVDD at the L1/L2–L5/S1 levels using the modified Pfirrmann grading system, as per Figure 2 and Table 1 [13, 14]. MRI T1- and T2-weighted sagittal images were used to evaluate whether Modic changes appeared in the upper and lower endplates of the vertebral body and the bone marrow, as shown in Figure 3 [15]. The average vertebral CT density of the five vertebral bodies was measured by CT. All data were collected and evaluated by two independent spinal surgeons, and significant differences were resolved by a consensus. This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University, in accordance with the provisions of the Declaration of Helsinki. Informed consent was obtained from each patient before the study, and all data remained anonymous.

2.5. Statistical Analysis. Statistical analysis was performed using SPSS 20 (SPSS Inc., Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation (SD). The comparisons of age, postoperative history, LL, vertebral CT density, and lumbar DHI were performed by the independent sample *t*-test, whereas the comparison of the modified Pfirrmann grading score and occurrence of Modic changes were conducted by a non-parametric test. $P < 0.05$ was considered statistically significant.

3. Results

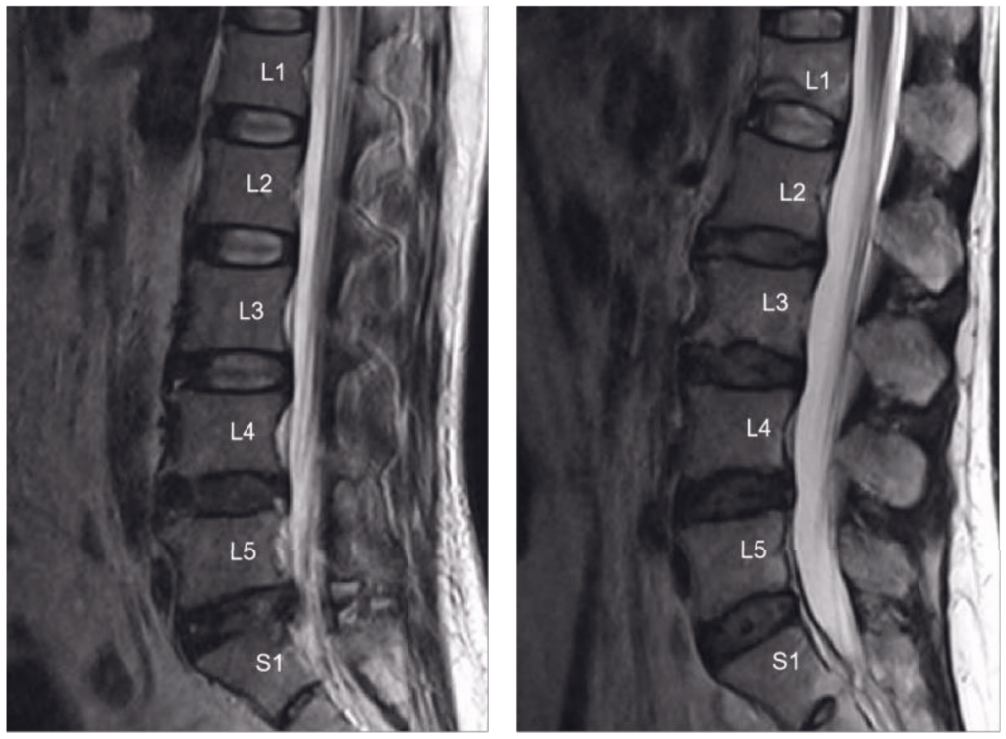
A total of 75 patients were enrolled in this study, including 46 patients in the TAM group and 29 patients in the non-TAM group. No significant differences were present in age, BMI, and postoperative history between the two groups. The LL of the TAM group (31.15 ± 9.26) was higher than that of the non-TAM group (30.54 ± 6.96), but there was no significant difference. In addition, there was no significant difference in vertebral CT density between the TAM group (185.21 ± 53.66) and the non-TAM group (184.23 ± 50.03), as shown in Table 2.

DHI of L1/2, L2/3, L3/4, L4/5, and L5/S1 is 24.96 ± 4.04, 27.28 ± 5.16, 30.05 ± 5.70, 32.06 ± 5.21, and 28.63 ± 6.18 in the TAM group and 26.86 ± 3.41, 29.68 ± 3.72, 31.23 ± 3.81, 31.35 ± 5.11, and 28.49 ± 7.46, respectively, in the non-TAM group (Table 3). The L1/2 and L2/3 DHI in the TAM group were lower than those in the non-TAM group ($P = 0.038$ and $P = 0.034$, respectively), whereas comparisons regarding the DHI of L3/4, L4/5, and L5/S1 between TAM and non-TAM groups were not significant. The average DHI of the TAM group (29.69 ± 3.08) was higher than that of the non-TAM group (28.52 ± 3.47), but there was no statistical difference, as shown in Table 3.



(a) (b)

Figure 1: Lumbar lordosis (LL) and lumbar disc height index (DHI) measurements. (a) LL: the angle between the tangent line of the upper endplate of the L1 vertebral body and S1 vertebral body in the lateral lumbar spine. (b) DHI: (intervertebral leading-edge height + posterior edge height)/(intervertebral upper body width + lower body width) * 100%, where a is the intervertebral upper body width, b is the intervertebral lower body width, c is the intervertebral anterior edge height, and d is the intervertebral posterior edge height.

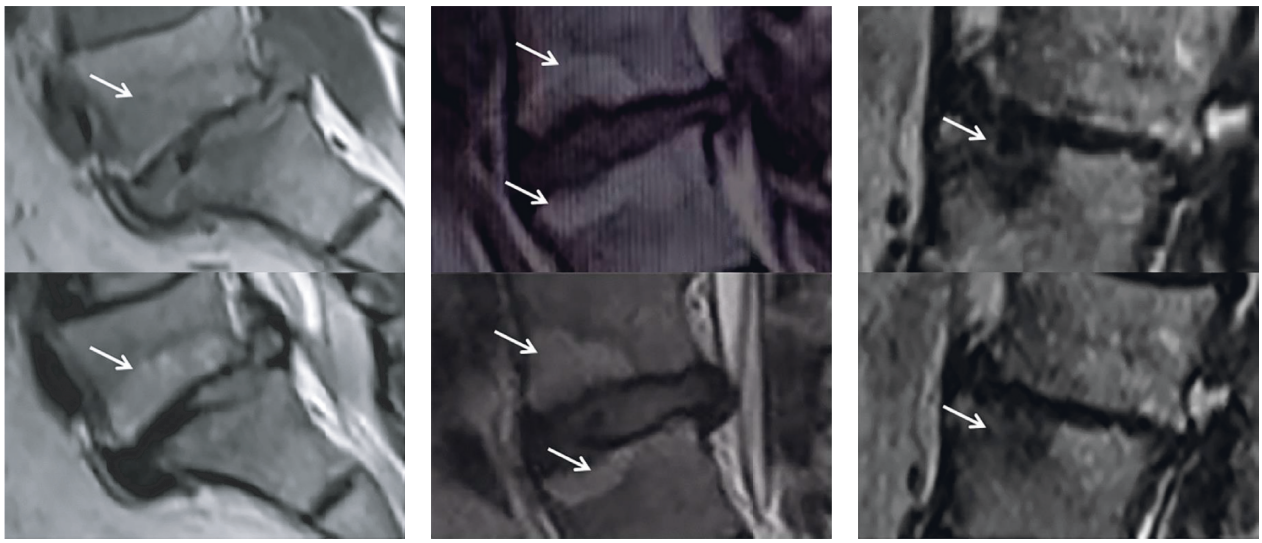


(a) (b)

Figure 2: MRI T2-weighted sagittal images were used to assess the degree of IVDD at the L1/L2–L5/S1 levels by the modified Pfirrmann grading system. (a) The modified Pfirrmann grading scores from L1/2 to L5/S1 were 2, 2, 3, 4, and 4 for a patient in the non-TAM group, respectively. (b) The modified Pfirrmann grading scores from L1/2 to L5/S1 were 2, 4, 4, 4, and 4 for a patient in the TAM group, respectively.

Table 1: Modified Pfirrmann grading system.

	Strength of nucleus pulposus and inner annulus fibrosus	Signal difference between the inner and outer sides of the posterior annulus fibrosus	Intervertebral disc height
Grade 1	Homogeneous high signal, equivalent to cerebrospinal fluid (CSF)	Obvious	Normal
Grade 2	High signal, lower than CSF, higher than presacral fat	Obvious	Normal
Grade 3	High signal, lower than presacral fat	Obvious	Normal
Grade 4	Moderate signal, higher than the outer annulus fibrosus	Not obvious	Normal
Grade 5	Low signal, equivalent to low outer annulus fibrosus	Not obvious	Normal
Grade 6	Low signal	Not obvious	Reduced less than 30%
Grade 7	Low signal	Not obvious	Reduced 30%–60%
Grade 8	Low signal	Not obvious	Reduced more than 60%



(a) (b) (c)

Figure 3: Modic classification for vertebral endplate changes (the patients pictured were not included in the study). (a) Type I: decreased signal on T1- and increased signal on T2-weighted images. (b) Type II: increased signals on both T1- and T2-weighted images. (c) Type III: decreased signals on both T1- and T2-weighted images.

Table 2: Comparisons of patient age, BMI, postoperative history, lumbar lordosis, and average vertebral CT density.

	Age (years)	BMI (kg/m^2)	Postoperative history (years)	Lumbar lordosis (°)	Average vertebral CT density
TAM group ($n = 46$)	47.43 ± 6.37	24.85 ± 4.83	5.29 ± 3.65	31.15 ± 9.26	185.21 ± 53.66
Non-TAM group ($n = 29$)	46.72 ± 7.14	24.27 ± 5.49	5.31 ± 2.74	30.54 ± 6.96	184.23 ± 50.03
P value	0.655	0.635	0.983	0.761	0.937

Table 3: Comparisons of the lumbar disc height index for each lumbar disc and the average value.

	Disc height index (%)					
	L1/2	L2/3	L3/4	L4/5	L5/S1	Average
TAM group ($n = 46$)	24.96 ± 4.04	27.28 ± 5.16	30.05 ± 5.70	32.06 ± 5.21	28.63 ± 6.18	29.69 ± 3.08
Non-TAM group ($n = 29$)	26.86 ± 3.41	29.68 ± 3.72	31.23 ± 3.81	31.35 ± 5.11	28.49 ± 7.46	28.52 ± 3.47
P value	0.038*	0.034*	0.522	0.561	0.930	0.141

* indicates a significant difference ($P < 0.05$).

All the patients' IVDs from L1/2 to L5/S1 were evaluated through the modified Pfirrmann grading system. The modified Pfirrmann grading scores of the L1/2 and L2/3 IVDs in the TAM group were higher than those in the non-TAM group ($P = 0.004$ and $P = 0.025$, respectively), while the comparisons of L3/4, L4/5, and L5/

S1 between the two groups were not significant, as shown in Table 4.

All Modic changes were Modic type II changes. The comparisons regarding the occurrence of Modic changes did not show a significant difference between the TAM and non-TAM groups, as shown in Table 5.

Table 4: Comparisons of modified Pfirrmann grading of L1/2-L5/S1 IVD between the TAM group and the non-TAM group.

	TAM group ($n = 46$)/non-TAM group ($n = 29$)				
	L1/2	L2/3	L3/4	L4/5	L5/S1
Grade 1	0/0	0/0	0/0	0/0	0/0
Grade 2	24/25	17/17	6/8	2/3	4/4
Grade 3	12/2	16/10	19/12	10/9	13/3
Grade 4	8/1	8/1	14/9	23/12	11/13
Grade 5	0/1	3/0	5/0	9/3	10/6
Grade 6	1/0	1/1	2/0	1/2	8/3
Grade 7	1/0	1/0	0/0	1/0	0/0
Grade 8	0/0	0/0	0/0	0/0	0/0
P value	0.004*	0.025*	0.052	0.195	0.902

* indicates a significant difference ($P < 0.05$).

4. Discussion

IVDD is a primary cause of lower back pain. Although the etiology of IVDD is still unclear, recent studies have found that IVDD is accompanied by a decrease in the number of NPCs and disruption of the ECM balance. Furthermore, apoptosis, inflammation, and senescence of the NPCs can accelerate this process [1–4]. Anti-inflammatory and antioxidant factors have become a research hotspot in the field of IVDD. Many researchers have studied the correlation between estrogen and IVDD and found that estrogen can inhibit NPC apoptosis and delay the progression of IVDD through a variety of ways, for example, enhancing the anti-inflammatory and antioxidant capacity of NPCs, activating autophagy, promoting ECM synthesis, and inhibiting matrix metalloproteinases [3–7]. Our previous studies have shown that estrogen can inhibit apoptosis of NPCs by activating NF-κB and PI3K-Akt signaling pathways, which has been confirmed in animal experiments [6–8]. Wang et al. evidenced the expression of ER in IVD tissues [4]. The clinical study by Zhao et al. also established that OVX led to a significant decrease in the female estrogen level and promoted the progression of IVDD over a long period of time [5]. Therefore, the level of estrogen can influence the progression of IVDD.

Breast cancer is one of the most common tumors in women, and approximately 70% of them are ER-positive. Endocrine therapy in these patients can effectively reduce tumor metastasis and improve survival rates. TAM is the first choice for endocrine therapy in premenopausal ER-positive patients. As a selective estrogen receptor modulator, it can competitively bind to estrogen receptors, exerting antagonistic or estrogen-like effects [16, 17]. Studies have shown that TAM can affect other tissues or organs, such as the uterus and bones. The use of TAM can lead to endometrial thickening, polyps, and endometrial cancer. Jeon et al. found that TAM can delay postmenopausal bone mineral density (BMD) loss in women, which has been confirmed by animal experiments of ovariectomy, but the mechanism of TAM's action is still unclear [9, 10].

This study retrospectively analyzed and compared vertebral CT density, LL, lumbar DHI, and modified Pfirrmann grading of breast cancer patients who took TAM and those who did not take TAM, in order to investigate the correlation between TAM and lumbar IVDD. A total of 75 patients were enrolled, 46 patients in the TAM group and 29 patients in the non-TAM group.

Age, gender, and obesity are important factors that would influence IVDD. Many studies have confirmed that increasing age and abnormal obesity can promote the progression of IVDD [18, 19]. Ekşi M. Ş. et al. found that severe IVDD was more common in women than in men, and this difference was significant at all lumbar levels except L5/S1 [18]. This may be related to the differences in body structure and hormone levels caused by the gender. There are many ways of assessing the degree of obesity in patients, and the most commonly used is BMI [19, 20]. Fat content is also one of the indicators for evaluating obesity. Berikol G et al. found that subcutaneous fat tissue thickness at the L1/L2 level was better than BMI in predicting lower back pain and IVDD [20]. In this study, there were no significant differences in age and BMI between the two groups of patients. This reduced the interference of age and obesity on the results of this study. Moreover, the comparison of postoperative medical history between the two groups was not significant.

The normal lumbar physiological curvature is essential for the maintenance of the balance of the entire spine [1, 2]. Changes in LL can affect the internal balance of the spine and accelerate lumbar degeneration. Yang et al. found that reduced LL leads to decreased spinal elasticity and mobility, which may be a risk factor for IVDD [21]. In this study, spinal injury, spinal fracture, and other factors affecting the physiological curvature of the spine were excluded. The results showed no significant difference in LL between the two groups, although both groups had a lower than normal physiological curvature in adults, indicating that TAM did not significantly affect the physiological curvature of the spine.

Vertebral CT density values were used to assess the degree of osteoporosis in the patients [11]. Estrogen has a regulatory effect on multiple organs and systems, such as the reproductive organs and bones, especially in postmenopausal women, who suffer from severe osteoporosis due to reduced hormone levels [22]. However, previous studies on the relationship between vertebral BMD and IVDD have not yielded clear and consistent results. Most scholars, such as Salo et al., speculated that increased vertebral BMD promotes IVDD, caused by reduced nutrient supply to the IVD due to increased endplate calcification [23]. However, previous studies found no significant positive or negative correlation between vertebral BMD and IVDD [24–26]. This study established no significant difference in the vertebral CT density between the two groups, suggesting that TAM as an ER modulator does not significantly affect vertebral BMD

Table 5: Comparisons regarding the occurrence of Modic changes between the TAM group and the non-TAM group.

	L1/2	L2/3	L3/4	L4/5	L5/S1
TAM group ($n = 46$)	0	0	1	3	4
Non-TAM group ($n = 29$)	0	0	0	1	3
P value	—	—	0.427	0.567	0.812

in premenopausal women, but may affect the degree of IVDD through other pathways.

In the present investigation, the level of IVDD was assessed by the lumbar DHI and the modified Pfirrmann grading system [11, 12]. Akeda K et al. observed that the DHI of the elderly would decrease significantly over a decade, accompanied by an increase in the Pfirrmann grading score [27]. Wang et al. found that postmenopausal women had higher Pfirrmann grading scores than premenopausal women, suggesting more severe IVDD [4]. Zhao et al. also found that patients with OVX had a higher lumbar disc grading score than those without ovariectomies [5]. In this study, the comparison results of the two methods showed that TAM promoted the degeneration of the upper lumbar discs (L1/2, L2/3) with significant differences. However, no significant difference was detected in the grading of IVDD for the lower lumbar spine (L3/4, L4/5, and L5/S1). Additionally, no significant differences between the two groups were established in the average DHI. This finding suggests that TAM can promote IVDD, which is more remarkable in the upper lumbar spine [5]. The reason for the lack of an obvious difference in the lower lumbar spine may be that hormones are not the leading factors for IVDD in the lower lumbar spine. The location of the processes occurring during this stage is highly concentrated in the physiological bending part of the spine, a part with high mobility, which is thus susceptible to injury leading to IVDD [28, 29].

Modic et al. defined Modic changes as pathological signal changes in the upper and lower endplates of the vertebral body and the bone marrow. Modic changes were divided into 3 types by MRI signal changes [15]. Özcan-Ekşi EE et al. found that IVDs with Modic changes in the endplate were more prone to degeneration, especially Modic type I changes [30]. Modic changes are closely related to lower back pain and IVDD, but their specific mechanism is still unclear. We evaluated whether Modic changes occurred in the upper and lower endplates of each IVD by MRI and investigated the relationship between TAM use and Modic changes. In this study, Modic changes mainly occurred in the lower lumbar region, similar to the results of the modified Pfirrmann grading scores. There was no significant difference in the occurrence of Modic changes between the two groups, indicating that TAM had no significant effect on Modic changes.

Therefore, further studies on the effects of estrogen and drugs on IVDD, with the exclusion of other influencing factors, are still needed to elucidate all related mechanisms.

This study has some limitations. First, lower back pain is one of the main symptoms of lumbar IVDD. Considering that the spinal metastasis of breast cancer and osteoporosis may cause different degrees of pain, it is difficult to distinguish whether IVDD is the main cause of lower back pain, and thus, pain assessment was not performed in this study, such as visual analogue scale. Second, the sample size of this study is small, and many confounding factors might have affected the results. Therefore, prospective studies with larger sample sizes and longer follow-up periods are needed to comprehensively investigate the effect of TAM on IVDD in the future.

5. Conclusion

This study indicates that there might be some positive correlation between TAM use and lumbar IVDD. In particular, the degeneration of L1/2 and L2/3 has shown a correlation with TAM use.

Abbreviations

BMD: Bone mineral density
BMI: Body mass index
CT: Computed tomographic
CSF: Cerebrospinal fluid
ECM: Extracellular matrix
ER: Estrogen receptor
IVD: Intervertebral disc
IVDD: Intervertebral disc degeneration
MRI: Magnetic resonance imaging
NPCs: Nucleus pulposus cells
LL: Lumbar lordosis
DHI: Disc height index
OVX: Ovariectomy
TAM: Tamoxifen.

Data Availability

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

Ethical Approval

This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University, in accordance with the provisions of the declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest regarding this study.

Authors' Contributions

SY and WD conceived the study. XL and RZ performed data collection and statistical analysis. XL drafted the manuscript.

SR and SY revised the manuscript. All authors read and approved the final manuscript.

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