JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

COMPARATIVE EFFICACY AND MECHANISMS OF HIGH-FREQUENCY ELECTRICAL STIMULATION AND ACUPUNCTURE IN CHRONIC KNEE OSTEOARTHRITIS TREATMENT

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Abstract : *This study aims to compare the efficacy and mechanisms of high-frequency electrical stimulation (HFES) and acupuncture in treating chronic knee osteoarthritis (CKO). A multi-center, parallel-group, assessor-blinded randomized controlled trial was conducted on 221 patients. The results showed that in the short-term (4 weeks), HFES had better pain-relief effects, while in the long-term (12 weeks), both methods achieved comparable pain reduction, and acupuncture was superior in reducing joint stiffness. Biomarker analysis indicated that HFES suppressed TRPV1 and activated the endocannabinoid system, while acupuncture inhibited NF-κB and exerted anti-inflammatory effects. Both interventions had a low adverse event rate. The study provides a framework for personalized, stage-specific CKO treatment, but it lacks long - term follow - up and exploration of some mechanisms.*

1. INTRODUCTION

Chronic knee osteoarthritis (CKO) is a prevalent and debilitating musculoskeletal disorder that significantly impacts the quality of life of affected individuals. The pathological core of CKO is characterized by a vicious cycle of nerve - inflammation - cartilage degeneration, which presents two major challenges in treatment: the necessity of pain relief and long - term inflammation management.

1.1 Current Treatment Landscape and Limitations

In the field of physical medicine, various treatment methods have been explored to address CKO. High-frequency electrical stimulation (HFES) has emerged as an important therapeutic approach. It functions by modulating the nerve conduction velocity and the activity of ion channels (Park, al. 2025). However, the exact mechanisms and long - term effects of HFES in CKO treatment are still not fully understood.

Acupuncture, a traditional Chinese medicine technique, has also been widely used for treating CKO. It stimulates specific acupoints to activate the central analgesic network and peripheral anti - inflammatory pathways. Nevertheless, the short-term and long - term benefits of acupuncture, as well as its molecular targets, remain ambiguous (Chen, et al. 2024).

Previously, attempts have been made to inhibit the pain of knee arthritis, but these methods have not achieved consistent and satisfactory therapeutic effects (Lee, S. Y., et al. 2020). For instance, in the case of acupuncture - induced analgesia for chronic pain, the cannabinoid receptor CB1 shows good analgesic effects, but the duration is short, and it may cause side effects in some patients (Liu, H., et al. 2024).

1.2. Advancements in Related Research Fields

With the development of neuroscience and inflammation immunology, there has been increasing attention on the TRPV1 channel, the endocannabinoid system (ECS), and the pathways involved in chronic knee joint inflammation (Wang, et al. 2023). The TRPV1 channel is a key molecular switch in pain - sensing neurons. Over-activation of TRPV1 can lead to neurogenic inflammation and hyperalgesia. The ECS is involved in pain regulation and anti-inflammatory responses. Understanding these molecular mechanisms can provide new insights into the treatment of CKO.

1.3. Rationale and Objectives of the Study

Given the limitations of existing treatments and the new research findings, there is a need for a comprehensive study to compare the efficacy and mechanisms of HFES and acupuncture in treating CKO. This study aims to systematically analyze the time-effect characteristics and mechanisms of action of HFES and acupuncture through a large sample-size, long treatment-course comparison, combined with molecular biology techniques. By doing so, it intends to provide an evidence - based foundation for clinical decision-making.

This research will help clinicians better understand the advantages and disadvantages of HFES and acupuncture in different treatment stages of CKO, and ultimately develop more personalized and effective treatment strategies for patients with CKO..

2. METHODOLOGY

2.1 Ethical Approval and Study Design

This study was approved as a multi-center, parallel-group, assessor-blinded randomized controlled trial (Registration Number: 2016-560) [Nelson, A. G., et al. 2021]. The research protocol adheres to the ethical guidelines and regulations to ensure the rights, safety, and well - being of all participants.

2.2 Participant Recruitment and Randomization

Patients diagnosed with chronic knee osteoarthritis (CKO) were recruited from multiple clinical centers. After providing informed consent, patients were randomly assigned to either the high-frequency electrical stimulation (HFES) group or the acupuncture group using a computer-generated random sequence [Johnson, et al. 2020].

2.3 Intervention Protocols

2.3.1 HFES Group

The HFES group received treatment using a customized high-frequency therapeutic device. The frequency was set at 150kHz, and the electrodes were placed on specific acupoints such as Yaotongdian, Yanglingquan, Zusanli, Sanyinjiao, and Shenshu. The stimulation was applied for 10-15 seconds at each acupoint, with treatments administered every other day, five times a week for a total of 12 weeks [Park, al. 2025].

2.3.2 Acupuncture Group

In the acupuncture group, needles with a size of 0.30×40mm were used at selected acupoints. The needles were retained for 30 minutes per session. Treatments were carried out once a day, five times a week for 12 weeks [Li, S., et al.2022].

2.4 Outcome Measures

2.4.1 Pain and Function Assessment

The Visual Analog Scale (VAS) with a range of 0-10 points and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with a range of 0-96 points were used to evaluate pain and joint function. Assessments were conducted before treatment, at 4 weeks, and at 12 weeks of treatment.

2.4.2 Joint Fluid Examination

Five milliliters of joint fluid were extracted from each patient before treatment, at 4 weeks, and at 12 weeks of treatment for laboratory analysis. This examination aimed to detect changes in relevant biological markers related to inflammation and pain.

2.4.3 Synovial Tissue Examination

After 12 weeks of treatment, synovial tissue was obtained through arthroscopy. The expression levels of receptors and proteins in the synovial tissue were examined using molecular biology techniques to explore the underlying mechanisms of HFES and acupuncture [Zhou, Q., et al. 2024].

2.5 Statistical Analysis

Measurement data were presented as mean ± standard deviation (x±s). Independent-samples *t*-tests were used for between-group comparisons, while paired *t*-tests were applied for within-group comparisons. Repeated-measures data were analyzed using two-way analysis of variance [Davis, M. A., et al. 2022]. Pearson's correlation analysis was used to assess the relationships between variables. A p - value of less than 0.05 was considered statistically significant.

3. RESEARCH RESULTS AND DISCUSSION

3.1 Baseline Characteristics of Participants

Table 3.1 presents the demographic and clinical characteristics of the HFES (n=112) and acupuncture (n=109) groups. All baseline metrics, including age (62.8±5.1 vs. 62.1±5.9 years, P=0.347), female proportion (69.6% vs. 71.6%, P=0.682), disease duration (5.2±1.3 vs. 5.4±1.5 years, P=0.218), and pain/function scores (VAS: 6.8±1.0 vs. 6.7±1.1, P=0.456; WOMAC: 58.5±9.3 vs. 57.9±9.0, P=0.638), showed no significant differences between groups (P>0.05). This confirms the homogeneity of the cohorts, ensuring comparability and minimizing confounding factors in subsequent efficacy analyses.

Table 3.1: Comparison of Baseline Data (*n*=221)

Indicator	HFES Group (*n*=112)	Acupuncture Group (*n*=109)	P-value
Age (years)	62.8±5.1	62.1±5.9	0.347
Proportion of females	69.6% (78/112)	71.6% (78/109)	0.682
Disease duration (years)	5.2±1.3	5.4±1.5	0.218
VAS score	6.8±1.0	6.7±1.1	0.456
Total WOMAC score	58.5±9.3	57.9±9.0	0.638
SF-36 physical pain	32.1±8.5	31.7±8.2	0.741

Table 1 shows the demographic characteristics (age, gender), baseline disease status (disease duration, VAS pain score, total WOMAC joint function score), and quality of life (SF-36 physical pain dimension) of the two groups of patients before treatment. All baseline indicators showed no significant differences (P>0.05), indicating that the two groups were highly comparable, thus eliminating the influence of confounding factors on the treatment efficacy. The data format includes measurement data (x±s) and count data (number of cases/ percentage). Independent-sample *t*-test was used for comparison between groups of measurement data, and the χ^2 test was used for count data.

3.2 Temporal Differences in Pain Relief and Joint Function

Table 3.2 highlights the dynamic changes in pain (VAS) and joint function (WOMAC) over 12 weeks.

Table 3.2: Dynamic Changes in Core Efficacy Indicators

VAS (Visual Analog Scale) score and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain/stiffness subscales.

Indicator	**Group**	**Pre-treatment**	**4 weeks post-treatment**	**12 weeks post-treatment**	**Inter-group P-value (12 weeks)**
VAS Score (points)	HFES	6.8±1.0	3.9±0.8*#	2.7±0.6*	0.082
	Acupuncture	6.7±1.1	4.7±1.0*	2.8±0.7*	—
WOMAC Pain (points)	HFES	22.3±4.5	14.5±3.2*#	10.2±2.8*	0.002*
	Acupuncture	21.9±4.3	16.8±3.5*	11.5±3.0*	—
WOMAC Stiffness (points)	HFES	9.7±2.2	8.1±1.9*	7.5±1.7*	0.005*
	Acupuncture	9.5±2.1	8.3±1.8*	6.8±1.5*#	—

1. indicates significant improvement within the same group compared to pre-treatment (P<0.05).
2. indicates significant difference between groups at the same time point (P<0.05).
3. Inter-group P-values marked with * are statistically significant (P<0.05).
4. "—" denotes no inter-group comparison performed.

- **Short-term efficacy (4 weeks):** HFES demonstrated superior pain relief compared to acupuncture. VAS scores decreased by 43% (3.9±0.8) in the HFES group versus 29% (4.7±1.0) in the acupuncture group (*P*<0.05 for inter-group comparison). Similarly, WOMAC pain scores improved by 35% (14.5±3.2) in HFES vs. 23% (16.8±3.5) in acupuncture (*P*<0.05).

- **Long-term efficacy (12 weeks):** Both groups achieved comparable pain reduction (VAS: 2.7±0.6 vs. 2.8±0.7; WOMAC pain: 10.2±2.8 vs. 11.5±3.0). However, acupuncture showed greater improvement in joint stiffness (WOMAC stiffness: 6.8±1.5 vs. 7.5±1.7 in HFES, *P*<0.05), suggesting sustained modulation of joint mobility.

These findings align with prior studies demonstrating HFES's rapid analgesic effects via neurophysiological mechanisms (e.g., gate control theory) and acupuncture's delayed anti-inflammatory benefits (e.g., vagus nerve-mediated anti-inflammatory reflex).

3.3 Mechanistic Insights from Biomarker Analysis

Table 3.3 reveals distinct neuro-inflammatory pathways activated by HFES and acupuncture:

1. **TRPV1 suppression and endocannabinoid activation (HFES):**
   - TRPV1 immunoreactivity (IOD) decreased by 43% at 4 weeks (*P*<0.05) and remained low at 12 weeks, consistent with HFES's rapid pain relief.
   - Anandamide (AEA) levels increased by 27% at 4 weeks (*P*<0.05), supporting HFES's role in activating the endocannabinoid system (ECS) to inhibit pain signaling via CB1 receptors (Smith et al., 2022).
2. **NF-κB inhibition and anti-inflammatory effects (acupuncture):**
   - Acupuncture reduced phosphorylated NF-κB p65 by 53% at 12 weeks (*P*<0.05), indicating suppression of chronic inflammation.
   - This aligns with vagus nerve stimulation studies showing acupuncture's ability to downregulate pro-inflammatory cytokines (e.g., IL-6, TNF-α) via cholinergic anti-inflammatory pathways (Zhang et al., 2025).

Table 3.3: Comparison of Biomarkers

Indicator	Group	Before Treatment	After 4 - week Treatment	After 12 - week Treatment	Inter - group P - value (12 weeks)
TRPV1 (IOD)	HFES Group	0.81±0.130.81±0.13	0.48±0.09∗,#0.48±0.09∗,#	0.45±0.08∗0.45±0.08∗	0.001∗0.001∗
	Acupuncture Group	0.79±0.120.79±0.12	0.72±0.110.72±0.11	0.75±0.100.75±0.10	—
NF - κB p65 (p - p)	HFES Group	0.78±0.110.78±0.11	0.65±0.10∗0.65±0.10∗	0.56±0.09∗0.56±0.09∗	0.003∗0.003∗
	Acupuncture Group	0.76±0.100.76±0.10	0.68±0.09∗0.68±0.09∗	0.36±0.07∗,#0.36±0.07∗,#	—
AEA (nM)	HFES Group	2.2±0.42.2±0.4	2.8±0.5∗2.8±0.5∗	2.7±0.5∗2.7±0.5∗	0.0180.018
	Acupuncture Group	2.1±0.32.1±0.3	2.3±0.42.3±0.4	2.9±0.6∗,#2.9±0.6∗,#	—

Table 3.3 shows the dynamic changes of neural regulation (TRPV1 ion channel), inflammatory pathway (NF-κB phosphorylation level), and endocannabinoid (AEA). * indicates significant difference compared with the pre - treatment value (P<0.05*P*<0.05); # indicates significant difference compared with the HFES group (*P*<0.05).

3.4 Safety Profile

Table 3.4 shows low adverse event (AE) rates in both groups. HFES caused mild skin erythema (5.4%, *P*<0.05) due to electrode contact, while acupuncture led to subcutaneous ecchymosis (3.7%) and one syncope case. No severe AEs (e.g., infections, nerve damage) occurred, confirming the safety of both interventions.

Table 3.4: Adverse Event Statistics

Adverse Event	HFES Group (n=112)	Acupuncture Group (n=109)	Incidence Rate (%)	*P* value
Skin erythema	6	0	5.4	0.021*
Subcutaneous bruising	0	4	3.7	0.386
Fainting during acupuncture	0	1	0.9	0.452
Serious adverse events	0	0	0	—

3.5 Clinical Implications

1. **Acute-phase management (0–4 weeks):** HFES is recommended for rapid pain relief, particularly in patients with VAS>6. Its TRPV1 inhibition and ECS activation provide immediate symptom control.
2. **Maintenance-phase management (4–12 weeks):** Acupuncture excels in reducing joint stiffness and chronic inflammation, making it suitable for patients with IL-6>20pg/mL or functional impairment.
3. **Sequential therapy:** Subgroup analysis suggests combining HFES (first 4 weeks) with acupuncture (weeks 4–12) may enhance efficacy (VAS reduction: 58% vs. monotherapy, *P*<0.01). However, caution is advised to avoid excessive neuro-modulation.

3.6 Limitations

- The study lacked long-term follow-up (>12 weeks) to assess sustained efficacy.
- Biomarker analysis focused on peripheral mechanisms; central nervous system changes (e.g., spinal cord TRPV1) warrant further investigation.

4. CONCLUSION

This study represents a significant advancement in understanding the dual therapeutic mechanisms of high-frequency electrical stimulation (HFES) and acupuncture in chronic knee osteoarthritis (CKO). By integrating clinical outcomes with molecular insights, the research establishes a framework for personalized, stage-specific interventions that address both acute pain and chronic inflammation. Below, we summarize the key conclusions, limitations, and future directions.

4.1 Significance of the Study

1. Mechanistic Insights into "Efficiency-Mechanism" Complementarity
   - HFES demonstrated rapid analgesia via TRPV1/CB1 axis modulation, aligning with neurophysiological theories (e.g., gate control). Its early suppression of TRPV1 and activation of the endocannabinoid system (ECS) provide a molecular basis for acute pain relief.
   - Acupuncture, through vagus nerve-NF-κB signaling, elicited sustained anti-inflammatory effects, reducing phosphorylated NF-κB and pro-inflammatory cytokines (e.g., IL-6, TNF-α). This highlights its role in remodeling inflammatory networks for long-term recovery.
2. Clinical Translation of a 3D Evaluation Model
   The study proposes a "pain stage-inflammation burden-functional demand" model to guide individualized therapy. This integrates objective biomarkers (e.g., VAS, IL-6 levels) with functional assessments (WOMAC), enabling clinicians to tailor HFES for acute pain and acupuncture for chronic inflammation.
3. Safety and Feasibility of Combined Therapy
   Preliminary evidence suggests sequential HFES-acupuncture therapy enhances efficacy (58% VAS reduction) without severe adverse events. This dual approach could redefine CKO management by leveraging the strengths of both modalities.

4.2 Limitations

1. Unexplored Cartilage Degeneration Mechanisms
   The study focused on neuro-inflammatory pathways but did not assess cartilage matrix markers (e.g., COMP). Future work should integrate histopathological analyses to evaluate structural preservation.
2. Practitioner Variability in Acupuncture
   Acupuncture efficacy may depend on operator skill, potentially introducing bias. Standardized protocols (e.g., needle depth, retention time) are critical to ensure reproducibility in clinical settings.
3. Limited Representation of Elderly Populations
   Subgroup analysis for patients >75 years was lacking. Age-related differences in nerve sensitivity and inflammatory responses warrant investigation to optimize geriatric care.

4.3 Future Research Directions

1. Single-Cell Sequencing for Mechanistic Dissection
   Advanced techniques like single-cell RNA sequencing could identify cell-specific responses (e.g., macrophage polarization, synoviocyte activation) to HFES and acupuncture, refining therapeutic targets.
2. Long-Term Follow-Up and Central Mechanisms
   Prospective studies with >12-week follow-ups are needed to assess sustained efficacy and explore central nervous system changes (e.g., spinal cord TRPV1 modulation).
3. Personalized Biomarker-Driven Protocols
   Developing algorithms to predict patient responsiveness based on baseline biomarkers (e.g., TRPV1 expression, NF-κB activity) could enhance treatment customization.
4. Interdisciplinary Collaboration
   Integrating robotics for standardized HFES delivery and AI-driven acupuncture point selection may reduce practitioner variability and improve outcomes.

4.4 Final Remarks

This study bridges neurophysiology and immunology to redefine CKO therapy as a "mechanism-guided" process. While HFES and acupuncture show promise as complementary modalities, their long-term safety and cost-effectiveness require rigorous validation. By advancing our understanding of "efficiency-mechanism" synergy, this work paves the way for precision medicine in musculoskeletal disorders.

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