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Research Article

Meta-Analysis of Randomized Controlled Trials: High-Intensity Electroacupuncture Outperforms Low-Intensity Electroacupuncture for Knee Osteoarthritis

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Abstract

Background: Electroacupuncture (EA) has been proven to be efficacious and safe in patients with knee osteoarthritis (KOA), yet the superior intensity current for pain control in KOA remains unspecified. The present meta-analysis aimed to assess the efficiency of high-intensity and low-intensity EA in pain relief and functional improvement in KOA. Methods: A thorough and comprehensive literature search for randomized controlled trials (RCTs), all looking at the intensity of EA for KOA, was carried out in PubMed, EMBASE, Cochrane Library, clinicaltrials.gov, China National Knowledge Infrastructure (CNKI), China Science Journal Citation Report (VIP) and Wanfang database. All databases were searched from the available date of inception until the latest issue (Apr 2022). The study quality was evaluated via the Jadad five-point scale. Ultimately, a meta-analysis of all eligible RCTs was conducted utilizing Review Manager 5.3. Results: Three studies with 472 individuals were included in the Meta-analysis. The pain intensity reductions are significantly different between the high-intensity EA group and low-intensity EA group (MD=-0.22, 95%CI=-0.26 to -0.18, P< 0.00001). There is no significant difference between the two groups in the

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WOMAC index (MD=-3.62, 95%CI=-12.22 to 4.98, P= 0.41). High-intensity EA group significantly improve the emotional scale (ES) in comparison to the low-intensity EA group (MD=-0.72, 95%CI=-0.76 to -0.67, P< 0.00001). Conclusion: The findings of this work indicated that high-intensity EA provides superior pain relief and emotional scale in KOA patients. Moreover, both high-intensity and low-intensity EA exert a significant functional improvement effect in KOA.

Keywords

High Intensity, Electroacupuncture, Knee Osteoarthritis, Meta-Analysis

1. Introduction

Knee osteoarthritis (KOA) is a common degenerative joint disease among elderly adults and is characterized by progressive erosion of the articular cartilage. The prevalence of symptomatic KOA is about 8.1% in China, which varies according to sociodemographic, economic, and geographic factors [1]. KOA is the leading cause of chronic knee pain and dysfunction worldwide, and the quality of life is also impaired in the advanced stage. Nonpharmacological treatment, including health education, weight control, joint activity, acupuncture, and biomechanical therapies, plays a crucial role in the early-to-middle stages of KOA [2].

Electroacupuncture (EA), an essential form of acupuncture, has been widely used to treat KOA for a long time. EA has been proven to be efficacious and safe for relieving pain and improving physical functions in patients with KOA [3, 4]. Previous studies indicated some influence factors, such as current intensity, frequency of EA, and acupoints selection, which are the significant factors affecting the curative effect [5-7]. There is no consensus or guidelines for the optimal intensity of EA, and direct evidence of evidence-based medicine is also lacking. The purpose of this meta-analysis was to compare the effectiveness of high-intensity and low-intensity EA for pain relief and functional improvement in KOA.

2. Materials and Methods

2.1. Search Strategy

A thorough and comprehensive literature search for RCTs, looking at the intensity of EA for KOA, was carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The following bibliographic databases were searched: PubMed, EMBASE, Cochrane Library, Clinicaltrials.gov, China National Knowledge Infrastructure (CNKI), China Science Journal Citation Report (VIP), and Wanfang database. The search strategy was: (osteoarthritis OR osteoarthrosis OR degenerative arthritis) AND (electroacupuncture OR electrical acupuncture) AND (randomized controlled trial OR randomized OR clinical trial). All words were searched as free text and, where applicable, also as keywords. We conducted searches across all databases from their respective inception dates up to April 2022. No restrictions in language or publication year were applied. We also searched for relevant studies by reviewing the reference lists of retrieved studies and previous systematic reviews.

2.2. Study Eligibility Criteria

The inclusion criteria were as follows: (1) Study design: RCT; (2) Study population: patients with KOA; (3) Intervention: high-intensity EA vs. low-intensity EA. The high-intensity EA group was defined as intensity of currently more than 2mA, which was strong enough to reach the patients' tolerance threshold value. The intensity of the low-intensity EA group was between 0 and 0.5mA; (4) Outcome measurement: provides an assessment of pain intensity, recorded using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or visual analog scale (VAS); (5) Study has full text that could be obtained. Studies were excluded if they did not meet these criteria.

Exclusion criteria: (1) Review, Meta-analysis or commentaries; (2) Animal studies; (3) Meeting abstract and data were not available; (4) Not randomized controlled trial; (5) Intensity of current was not reported in the article.

The search results from the seven databases were imported into EndNote X7 software for data management. Articles were independently screened by two reviewers based on the inclusion and exclusion criteria. In cases of disagreement, a third reviewer was consulted, and included articles were rechecked.

2.3. Informed Consent

This research does not involve human participants or patient data, so we do not need to provide a statement of informed consent. Informed consent is typically only required when the research involves human participants and the data.

2.4. Data Extraction

Two reviewers extracted data from the included studies manually. A standard data extraction form was developed for

data collection. The following information was systematically extracted as characteristics of each randomized trial: study design, demographic characteristics, study duration, quality criteria, intervention details, outcome measures, and risk of bias. If multiple papers originated from the same study, only the complete study or the most recent one was included. Any discrepancies in data extraction and quality assessment between the two reviewers were resolved through discussion with a third reviewer.

2.5. Quality Assessment

Methodological quality was assessed using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) [8]. Bias was assessed as a judgment (high, low, or unclear) for elements from five domains: (1) randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. The RoB 2 was used to evaluate the reliability of the evidence.

2.6. Statistical Analysis

All data analyses were conducted by Review Manager Software Version 5.3 (Cochrane Collaboration, Oxford, UK). The continuous data for Meta-analysis were expressed as mean difference (MD) with a 95% confidence interval (CI), while dichotomous data were presented as risk ratio (RR) with 95%CI. The heterogeneity across studies was estimated using the Chi-square and Higgins tests. If heterogeneity was at $P>0.10$ or $\leq 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used. The overall effect was tested using a Z-score with significance at $P<0.05$.

3. Results

3.1. Study Selection

The literature selection process and results were shown in Figure 1. According to the PRISMA flow diagram screening sequence, the search strategy retrieved 388 related articles. After reviewing titles and abstracts based on the inclusion criteria, 41 articles were retained for full-text review. Ultimately, three studies with 472 individuals were included in the Meta-analysis [7, 9, 10]. The total sample size was based on the intent-to-treat (ITT) population.

3.2. Study Characteristics and Quality Assessment

Essential characteristics of the included studies are presented in Table 1. The included RCTs were published between 2015 and 2019, all published in English. Moreover, all three RCTs were conducted in China. Details of the baseline patient characteristics are described in Table 2.

A graphic summarizing the risk of bias was produced from discussions among the authors, as shown in Figure 2. All RCTs reported the specific method of the random sequence generation and described the dropout or withdrawal. One study [9] had a low risk of bias while two studies [7, 10] had some concerns about bias risk due to deviations from intended interventions.

3.3. Pain Intensity Reduction

All three RCTs evaluating the pain intensity utilize VAS score reduction as the primary or secondary outcome. VAS scores were assessed using a numerical rating scale of 0-10, in which a decreasing score represents the reduction in pain intensity. The pain intensity reductions are significantly different between the high-intensity EA group and the low-intensity EA group (MD=-0.22, 95%CI=-0.26 to -0.18, P< 0.00001; Figure 3), suggesting that high-intensity EA is favorable for pain intensity reduction. These studies show a moderate degree of heterogeneity (P =0.10, I^2=56%).

3.4. Functional Improvement

Two RCTs provide specific, relevant data for comprehensive analysis of WOMAC. The WOMAC index consists of three domains; the final score ranges from 0 to 96, and a low score indicates function improvement and less pain. There is no significant difference between the two groups in the WOMAC index (MD=-3.62, 95%CI=-12.22 to 4.98, P= 0.41; Figure 4). These studies show a moderate degree of heterogeneity (P =0.06, I^2=71%).

3.5. Emotional Scale (ES)

ES was available in two studies. Meta-analysis reveals that the high-intensity EA group significantly improves the ES compared to the low-intensity EA group (MD=-0.72, 95%CI=-0.76 to -0.67, P< 0.00001; Figure 5). No significant heterogeneity was observed between studies (P = 0.42, I^2= 0%).

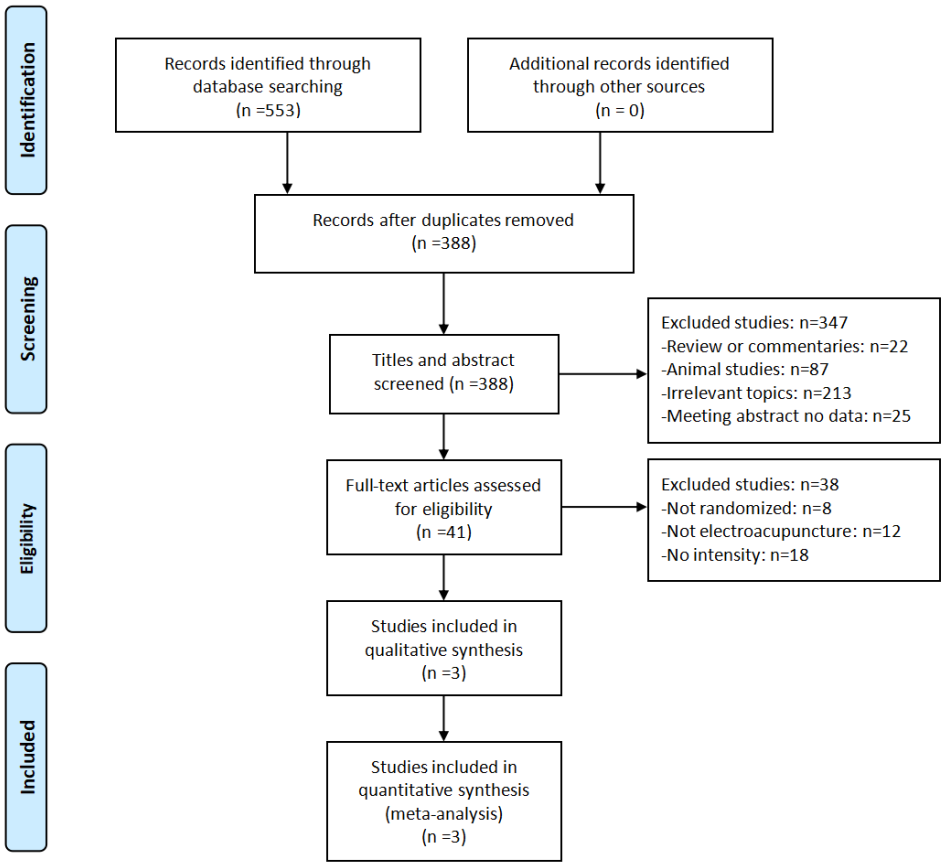

Figure 1. *The PRISMA flow diagram of study selection.*

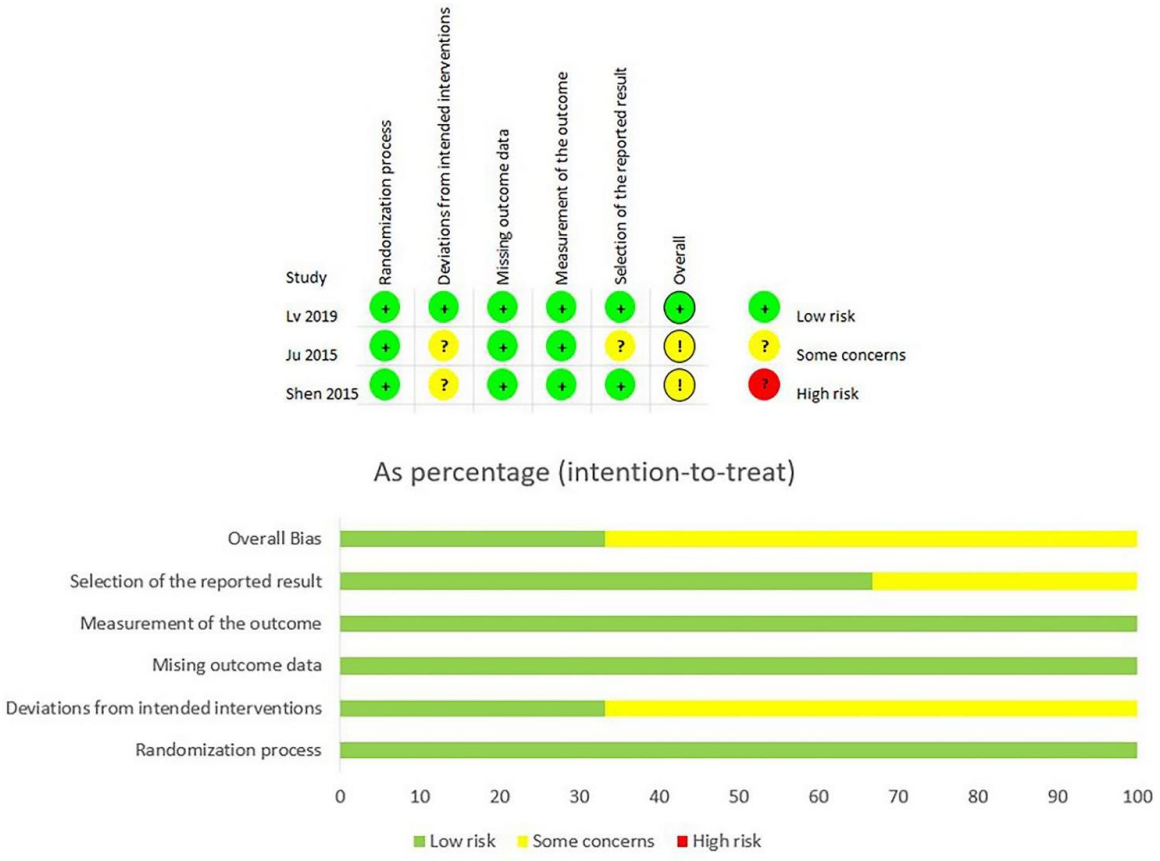

Figure 2. *Risk of bias assessment.*

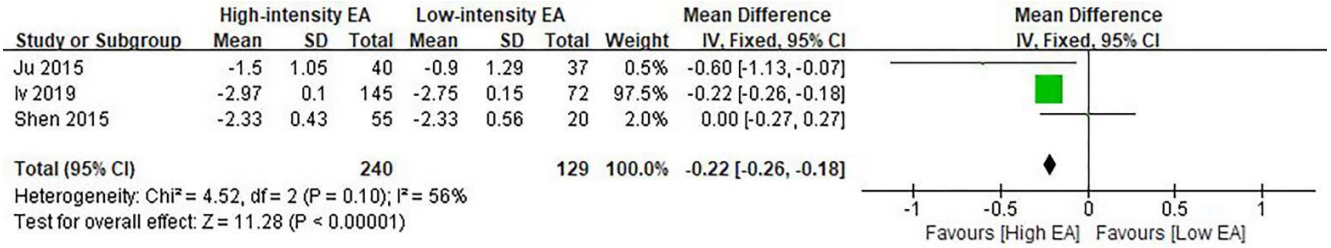

Figure 3. *The pain intensity reduction.*

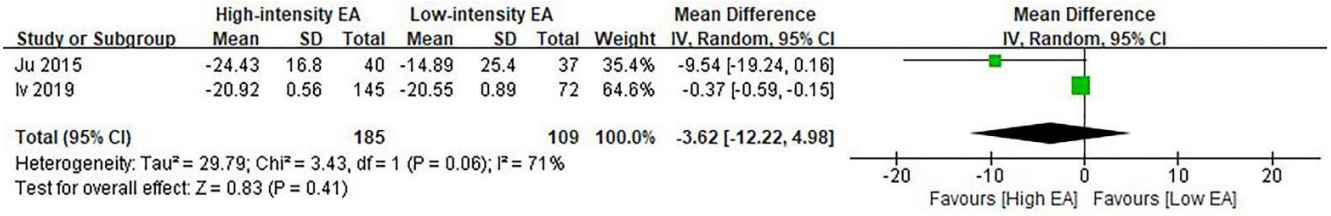

Figure 4. *The WOMAC scores reduction.*

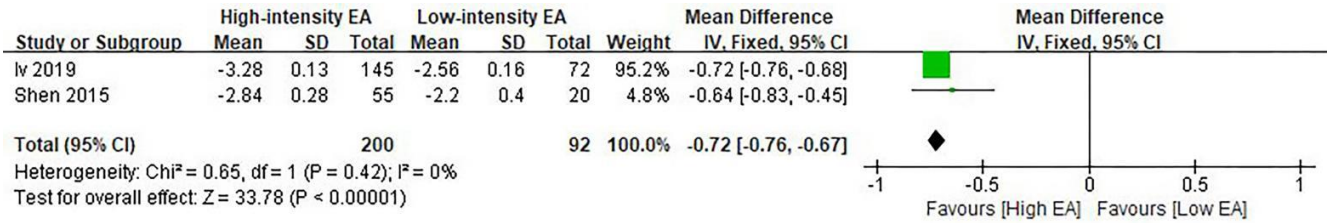

Figure 5. *The ES scores reduction.*

Table 1. *Characteristics of included studies.*

Study	**Lv 2019**	**Ju 2015**	**Shen 2015**
Design	RCT	RCT	RCT
Country	China	China	China
Patient (n)	301	80	91
Acupoints	EX-LE 5, ST 35, ST 34, SP10	GB34, ST34, EX-LE4, EX-LE5, ST36, and SP9	EX-LE 5, ST 35, ST 34, SP10
Current intensity	H group: > 2mA L group: < 0.5mA	H group: 5-6mA L group: < 2mA	H group: 2-5mA L group: < 0.5mA
Treatment period (weeks)	2	4	2
Main outcome measures	VAS, WOMAC, CPM function, NPRS, ES, PPI, adverse events	VAS, WOMAC, TNFα, IL-1β, IL-6, apelin levels	DNIC, VAS, NPRS, ES

*RCT: randomized controlled trial; H group: high-intensity EA group; L group: low-intensity EA group; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; CPM: Conditioned pain modulation; NPRS: numeric pain rating scale; ES: emotional scale; PPI: present pain intensity; DNIC: Diffuse injury inhibitory controls

Table 2. Baseline patient characteristics.

Study	Group	N	Gender (Female,%)	Age, (years)	BMI
Lv 2019	High intensity EA	145	73.1	64.6	22.67
	Low intensity EA	72	79.2	63.7	22.46
	Sham EA	75	80.0	61.9	22.93
Ju 2015	High intensity EA	40	65.0	62.0	27.4
	Low intensity EA	37	73.0	61.0	26.7
Shen 2015	High intensity EA	55	80.0	66.1	/
	Low intensity EA	20	80.0	69.3	/
	Sham EA	12	50.0	68.9	/

4. Discussion

Drawing on the existing literature, to our knowledge, this Meta-analysis is the first to assess high-intensity and low-intensity EA with KOA patients. Three RCTs with 472 patients were included, and the overall methodological quality of the included studies was moderate. The results of this meta-analysis suggested that high-intensity EA provides superior pain relief and emotional scale in KOA patients. Moreover, both high-intensity and low-intensity EA exert a significant functional improvement effect in KOA.

EA is widely used in the clinical treatment of KOA, which has the advantages of definite curative effects, few side effects, and low cost [11-14]. However, the application of EA on KOA pain lacks a standardized parameter and optimized program. In recent years, most trials of EA in KOA patients were performed using the maximum tolerable intensity of current [5, 15, 16], strong but comfortable intensity [13, 17], or description of needles began to vibrate slightly [6, 12]. One study adopted the fixed current intensity of 0.2 mA [3]. In addition, some articles do not mention the intensity of EA [18, 19].

Many trials investigated the efficiency and safety of EA in KOA, yet the superior intensity current for pain control in KOA remains unspecified. Lv et al. undertook an RCT to compare the effect of high-intensity EA with low-intensity EA or sham EA on chronic pain in patients with KOA. They concluded that high-intensity EA is the most effective in alleviating pain intensity in KOA. Moreover, at least 2 weeks duration is necessary for EA to exert a clinical effect on KOA [9]. Another study by Ju et al. revealed that both high-intensity and low-intensity EA treatment effectively reduces pain symptoms and improves function in KOA patients [7]. In a mouse model of KOA, the optimized parameters of EA inhibiting chronic pain were low frequency and high-intensity (2 Hz + 1 mA) [20].

So far, the mechanism of EA for KOA has yet to be fully illuminated. EA may potentiate the endogenous cannabinoid system and the expression of CB1 receptors on GABAergic neurons in the midbrain to enhance the 5-HT-related descending inhibitory control and diffuse noxious inhibitory controls (DNIC) function during KOA [20]. Some animal experiments have confirmed that EA could relieve neuropathic pain via the upregulation of glutamate transporters in the spinal cord of rats [21, 22]. Ju's study showed that plasma levels of IL-6 and apelin were significantly inhibited by high-intensity EA, which may contribute to the effects of high-intensity EA in treating KOA [7]. Moreover, high-intensity EA may strengthen the conditioned pain modulation (CPM) function, thus preventing the development of chronic pain in KOA.

The intensity of EA is one of the critical factors that can influence treatment efficacy, in addition to the dose and frequency of EA, placebo effects, and expectations. A systematic review demonstrated that the effect of acupuncture might be dose-dependent, with a higher dosage related to better treatment outcomes in terms of relief of pain and dysfunction in patients with KOA [23]. Tu et al. assessed the efficacy of intensive acupuncture 3 times weekly for 8 weeks in KOA patients. They demonstrated that intensive EA results in less pain and better function at week 8, and these effects persist through week 26 [6].

The results of these analyses may be scientifically and clinically important. For the first time, we have demonstrated that high-intensity EA is superior to low-intensity EA in pain relief for KOA patients. What we have done will add evidence of evidence-based medicine to consensus or guidelines for the treatment of KOA in the future. Nevertheless, there are some limitations in this study. One limitation of the study is the relative paucity of high-quality RCTs referring to the current intensity of EA. More RCTs are needed to verify our results in the future. Another potential limitation is that adverse events of high-intensity and low-intensity EA were not reported in detail in these RCTs, so it is still necessary to further validate the safety of high-intensity and low-intensity EA. Finally, a

publication bias was not performed due to the inadequate number of eligible studies.

5. Conclusions

The findings of this work indicated that high-intensity EA provides superior pain relief and emotional scale in KOA patients. Moreover, both high-intensity and low-intensity EA exert a significant functional improvement effect in KOA.

Abbreviations

EA: Electroacupuncture
KOA: Knee Osteoarthritis
RCTs: Randomized Controlled Trials
CNKI: China National Knowledge Infrastructure
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses
CNKI: China National Knowledge Infrastructure
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
VAS: Visual Analog Scale
RoB2: Risk-of-Bias Tool for Randomized trials
MD: Mean Difference
CI: Confidence Interval
RR: Risk Ratio
ITT: Intent-to-Treat
ES: Emotional Scale
DNIC: Diffuse Noxious Inhibitory Controls
CPM: Conditioned Pain Modulation

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Author Contributions

Chen Zihang: searched and extracted the publications, drafted the manuscript
Liang Xingsen: drafted the manuscript
Wang Huajun: searched and extracted the publications.
Zheng Xiaofei: designed the study, drafted the manuscript
All the authors: designed the study, analyzed, reviewed, and approved the contents of the manuscript.

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Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflicts of interest.

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