

Acupuncture Modalities Differentially Modulate Pain and Joint Damage in a Rat Model of Knee Osteoarthritis

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Background: Osteoarthritis (OA) is a leading cause of chronic pain and disability worldwide. Acupuncture-based therapies, including Electroacupuncture (EA), bee venom acupuncture (BVA), and laser acupuncture (LA), have shown individual efficacy in OA treatment, yet direct comparisons under standardized conditions remain lacking.

Objective: This study compared the therapeutic effects of EA, BVA, and LA in a monosodium iodoacetate (MIA)- induced OA in a rat model using consistent treatment protocols and evaluation metrics.

Methods: Forty-eight male Sprague-Dawley rats were randomly assigned to six groups: control, OA, manual acupuncture (MA), EA, BVA, and LA. All treatments were administered at acupoint GB34 three times per week for four weeks, beginning one week after MIA induction. Pain behavior was assessed weekly via paw withdrawal threshold testing. Post-treatment analyses included micro-computed tomography (micro-CT) imaging and histological evaluation.

Results: EA and LA significantly alleviated pain behaviors beginning at Weeks 2–3 and demonstrated superior joint preservation and cartilage integrity by Week 4 ($p < 0.001$ vs OA). BVA produced early analgesic effects and moderate structural protection, MA showed partial therapeutic benefits. EA and LA yielded the most consistent and comprehensive improvements among the treatments.

Conclusion: LA and EA at GB34 could potentially improve pain hypersensitivity, bone structure, and cartilage degradation. Our study provides a direct comparison of LA, EA, MA, and BVA under standardized conditions and may inform patients and healthcare practitioners considering acupuncture therapy options for OA management.

Keywords: comparative acupuncture therapies, electroacupuncture, knee osteoarthritis, laser acupuncture, rat model

Introduction

Osteoarthritis (OA) is a primary cause of disability and chronic pain, impacting approximately 500 million people worldwide, with forecasts of almost one billion by 2050.^{1,2} OA considerably lowers the quality of life due to its characteristic progressive joint deterioration, pain, and loss of mobility. Though they provide short-term comfort, non-steroidal anti-inflammatory medicines (NSAIDs) and corticosteroids present significant gastrointestinal, cardiovascular, and renal hazards when used long-term.^{3,4} While effective for some, surgical interventions are invasive, costly, and not universally accessible.

These restrictions have fueled a rise in interest in integrative and alternative treatments. The monosodium iodoacetate (MIA) model has been a valuable instrument for reproducing important OA characteristics in preclinical research. Therefore, it is a promising avenue for assessing new, non-pharmacologic treatments.^{5,6} The GB34 acupoint, located near the fibular head, is often used for joint-related indications in both experimental and clinical settings. Evidence suggests that stimulation at GB34 can modulate inflammatory processes and promote cartilage preservation.^{7–9}

Acupuncture has gained recognition for its affordability,¹⁰ safety,^{11,12} and effectiveness in managing musculoskeletal pain. The American College of Rheumatology conditionally recommends it for knee OA,¹³ with reviews supporting its pain-

relieving and functional benefits.^{14–17} Acupuncture treatments such as Electroacupuncture (EA), bee venom acupuncture (BVA), and laser acupuncture (LA) differ in mechanism while sharing common targets. Although previous studies have noted the therapeutic benefits of LA, EA, and BVA in OA.^{18–23} This study is the first to directly compare these treatments under the same conditions. This direct comparison fills a critical gap in the literature, providing valuable insights for clinical decision-making in integrative pain management. The potential impact of these findings on the future of pain management is significant.

Methods

Ethics Statement

This study was approved by the Dongshin University Animal Committee (DSU-2024-07-04). All animal care and experiments were conducted under the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and Dongshin University Institutional Animal Care and Use Committee policies.

Animals and Osteoarthritis Induction

Forty-eight male Sprague-Dawley rats (8 weeks old, 240–280 g; SAMTAKO Korea) were housed under controlled conditions ($22 \pm 2^\circ\text{C}$, reversed 12-hour light/dark cycle) with ad libitum access to food and water.

Male rats were used to reduce differences in pain and inflammatory responses caused by sex hormones. This decision was based on previous research showing that pain from OA varies significantly with a rat's age and sex.²⁴

OA was induced via intra-articular injection of monosodium iodoacetate (MIA; Sigma-Aldrich, St. Louis, MO). MIA was dissolved in 30 μL of sterile saline at 1 mg. Under brief isoflurane anesthesia, the injection was administered into the medial side of the patellar ligament of both knees using a 19-gauge, 0.5-inch needle, ensuring the needle did not penetrate the cruciate ligaments. The control group received an equivalent volume of sterile saline. Post-injection, the limbs were gently massaged before returning the rats to their housing.

Experimental Groups

Rats were randomly assigned to six groups ($n = 8$ per group): Control (Con): No OA induction or treatment. OA: MIA-induced OA without treatment. Manual Acupuncture (MA): MIA-induced OA treated with manual acupuncture at GB34. Invasive Laser Acupuncture 830nm (830nm): MIA-induced OA treated with 830nm invasive laser acupuncture at GB34. Electroacupuncture (EA): MIA-induced OA treated with Electroacupuncture at GB34. Bee Venom Acupuncture (BVA): MIA-induced OA treated with bee venom acupuncture at GB34.

Acupuncture Treatments

All acupuncture treatments commenced one-week post-MIA injection and were administered three times per week for four weeks.

Manual Acupuncture (MA): Sterile acupuncture needles (0.25 mm diameter, 13 mm length) were inserted bilaterally at GB34 to a depth of approximately 5 mm. Needles were manually stimulated with gentle twirling for 30 seconds every minute during a 3-minute session.

Invasive Laser Acupuncture 830nm: Using the Ellise device (Wontech Co. Ltd., Daejeon, Republic of Korea), an optic fiber-coupled laser diode was inserted into sterile acupuncture needles. The laser was set at 50Hz, 20mW, and applied for 3 minutes per session at GB34 on both legs to a depth of 5 mm.

Electroacupuncture (EA): Sterile stainless-steel acupuncture needles (0.25 mm diameter, 13 mm length) were inserted bilaterally at GB34 to a depth of approximately 5 mm. Electrical stimulation was applied using a constant current EA device, delivering alternating frequencies of 2/10 Hz at an intensity of 1 mA for 3 minutes per session.

Bee Venom Acupuncture (BVA): A 0.1 mL injection of bee venom solution (1.0 mg/mL) was administered subcutaneously at GB34 using a 30-gauge insulin syringe to a depth of approximately 5 mm.

Behavioral Assessment

Joint pain severity was assessed using the paw withdrawal threshold (PWT) test with manual von Frey filaments. Rats were acclimatized for 10 minutes in individual boxes. A filament with a bending force of 0.6 g was applied perpendicularly to the plantar surface of each hind paw until it bent slightly, and the response was recorded. If no response was observed, a filament with the next higher force was used; if a response occurred, the next lower force was applied. This up-down method continued until a pattern of responses allowed for calculating the 50% withdrawal threshold. Each paw was tested three times, with a 3-minute interval between tests. The mean values were used for statistical analysis. PWT assessments were conducted before MIA induction and weekly thereafter for four weeks.

Behavioral and structural outcomes were assessed up to 4 weeks post-MIA and treatment, a time window known to capture pain progression, early cartilage, and bone alterations in MIA-induced OA models.^{25,26}

Micro-Computed Tomography (Micro-CT) Imaging

After the treatment period, the rats were euthanized using a carbon dioxide (CO₂) gas chamber via a gradual-fill method, following the AVMA Guidelines for the Euthanasia of Animals (2020 Edition). This approach ensured a humane endpoint, minimizing pain and distress. The right knee joints were harvested, fixed in 4% paraformaldehyde, and subjected to micro-CT scanning using the Quantum GX2 imaging system. Data were analyzed using AccuCT™ software (PerkinElmer).

Histological Analysis

Following micro-CT scanning, knee joint tissues were decalcified in 0.5M ethylenediaminetetraacetic acid (EDTA, pH 8.0) for twentyone days, with the solution changed every two to three days. After decalcification, tissues were dehydrated through a graded ethanol series, cleared in xylene, and embedded in paraffin wax. Paraffin blocks were sectioned sagittally at nine μm thickness using a microtome. Safranin O/fast green staining was used to assess cartilage integrity. The severity of osteoarthritis was evaluated using the Osteoarthritis Research Society International (OARSI) scoring system and the Mankin score.

Statistical Analysis

Data were analyzed using R software (version 4.3.2) and presented as mean ± standard deviation (SD). Data was assessed for normality using the Shapiro–Wilk test, and a parametric method was applied. Comparisons between groups were made using one-way analysis of variance (ANOVA) followed by Tukey’s post hoc test for multiple comparisons. A p-value < 0.05 was considered statistically significant.

Results

Acupuncture Therapies Progressively Alleviate Pain Behaviors in MIA-Induced OA Rats

Paw withdrawal thresholds (PWT) were monitored over time to assess acupuncture’s impact on mechanical allodynia. Before MIA-injection, all groups exhibited similar baseline PWTs (15.2±0.9g), confirming no pre-existing differences. One-week post-MIA induction, all groups showed a rapid and sustained reduction in PWT, confirming pain hypersensitivity (Figure 1A) while the control group remained stable. Acupuncture-treated rats showed progressive recovery. By Week 2, EA and LA groups showed modest improvements ($p < 0.05$; $p < 0.01$ vs OA) while MA and BVA groups did not show any significant improvement. From Week 3 onward, LA and EA exhibited further gains ($p < 0.01$), with all three modalities demonstrating significant pain reversal by the final week (LA: $p < 0.001$; EA: $p < 0.01$; MA: $p < 0.05$). Weekly comparisons revealed that LA maintained a significant reduction from week two onwards, EA was improved on week two and four and MA started showing improvement from week four (Figure 1B).

Micro-CT Imaging Demonstrates Joint Preservation and Inhibition of Pathological Ossicle Formation

Micro-CT imaging revealed that untreated OA knees displayed classic signs of joint degeneration: subchondral erosion, trabecular irregularity, and surface damage (Figure 2). In contrast, the EA, LA, and BVA groups maintained better joint morphology, smoother bone contours, and preserved trabeculae.

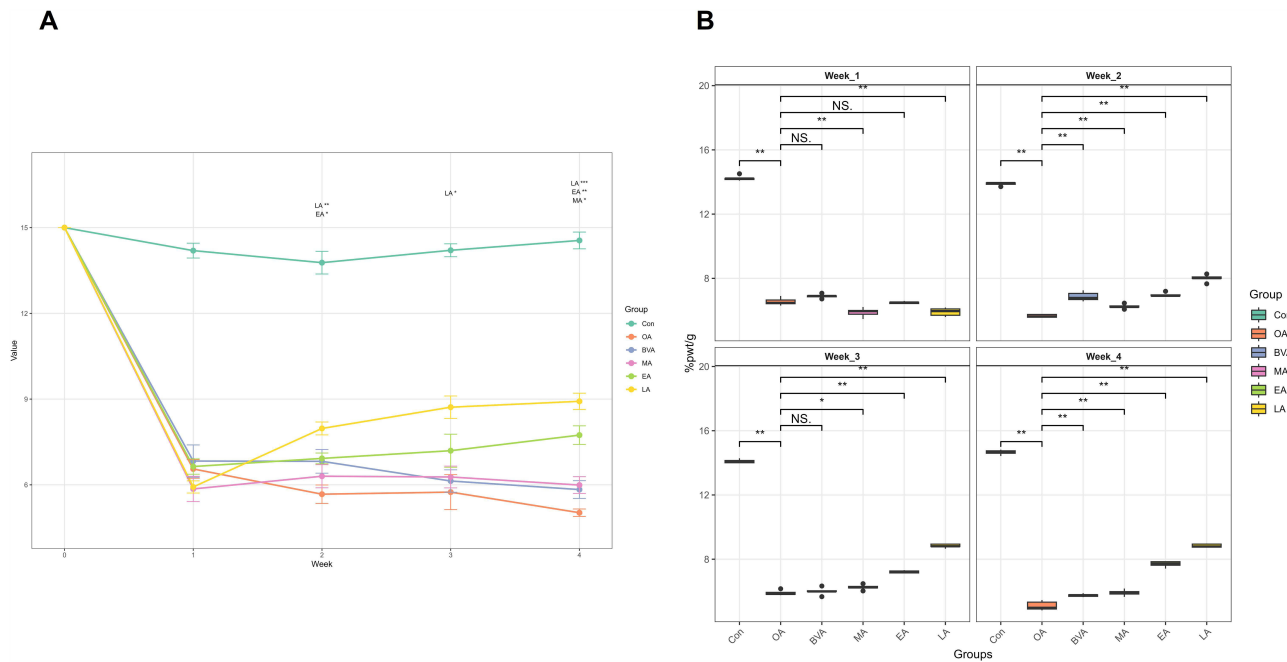


Figure 1 Changes in paw withdrawal threshold over 4 weeks across different treatment groups in MIA-induced OA rats. **(A)** Changes in paw withdrawal threshold over time. **(B)** PWT values for groups from Week_1 to Week_4; n=8 per group. Data are presented as the mean \pm standard deviation; $p < 0.05$, $p < 0.05$, $p < 0.01$, $p < 0.001$ compared with the OA group.

Abbreviations: Con, control; OA, osteoarthritis; BVA, bee venom acupuncture; MA, manual acupuncture; EA, electro-acupuncture; LA, laser acupuncture.

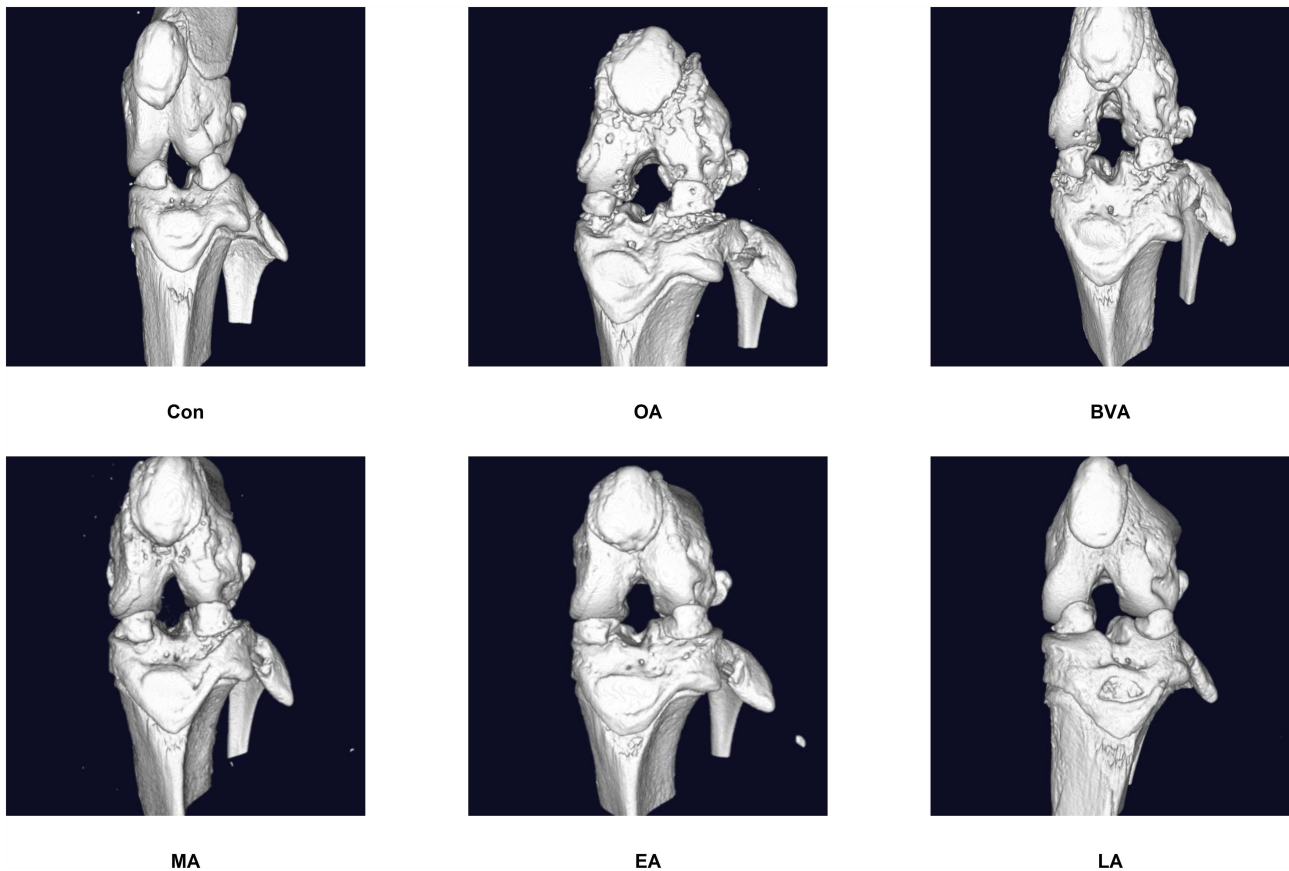


Figure 2 Representative micro-CT 3D images. The control knee maintains trabecular subchondral plate integrity with a smooth contour; the OA knee exhibits clear bone erosion following MIA induction. n=8.

Abbreviations: Con, control; OA, osteoarthritis; BVA, bee venom acupuncture; MA, manual acupuncture; EA, electro-acupuncture; LA, laser acupuncture.

Meniscal ossicles, indicative of OA progression, were significantly enlarged in OA rats (Figure 3). LA significantly reduced ossicle volume and area ($p < 0.006$ and $p < 0.006$ vs OA). EA, BVA and MA groups exhibited moderate effects.

Laser and Electroacupuncture Preserve Cartilage Integrity

Safranin-O/Fast Green staining revealed severe cartilage erosion, proteoglycan loss, and chondrocyte disarray in OA rats (Figure 4). EA and LA groups retained matrix staining and structural integrity, similar to the control group. BVA and MA showed partial preservation.

Quantitative scoring confirmed these findings (Figure 4). OA rats had significantly elevated cartilage damage scores (ANOVA, $p < 2.2e-16$). EA and LA had the lowest scores ($p < 0.0001$ vs OA), while BVA and MA showed intermediate reductions ($p < 0.001$, $p < 0.01$, respectively).

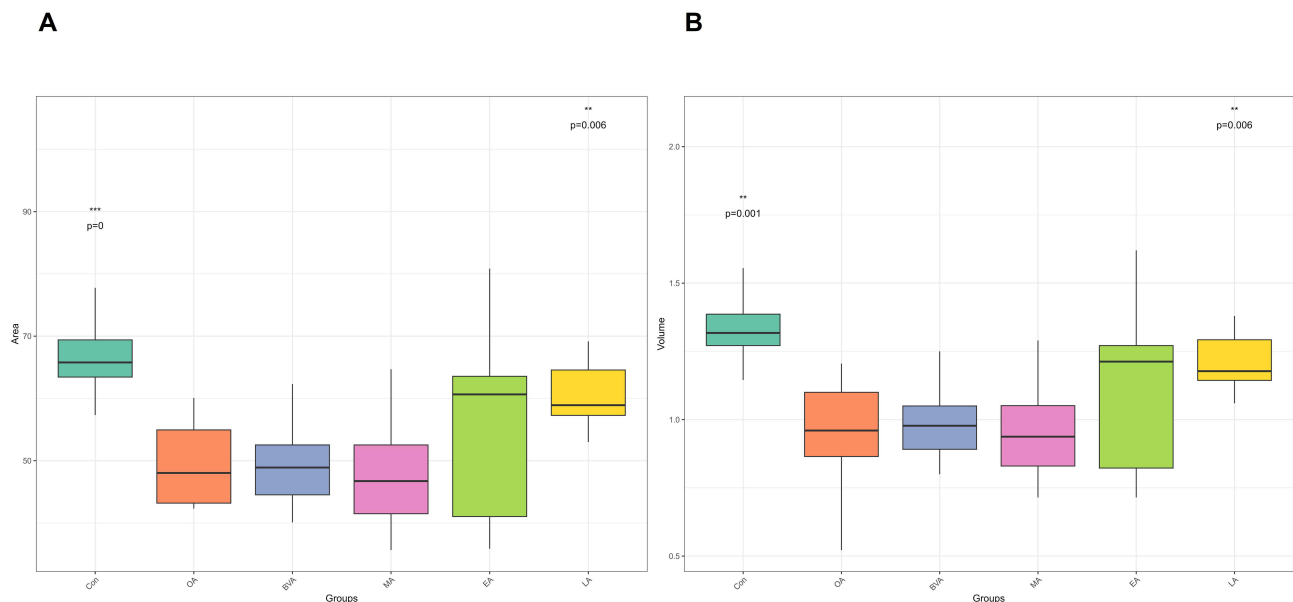


Figure 3 Micro-CT analysis of the hind knee joint in MIA-induced OA rats; (A) Area, (B) Volume of the meniscal ossicles. The area and volume of meniscal ossicles, abnormal bone formations within the knee meniscus, across different groups compared to the OA group. Error bars represent standard deviation. *p*-values indicate significant differences compared to the OA group. $n=8$. Data are presented as the mean \pm standard deviation; $p < 0.05$, $p < 0.01$, $p < 0.001$.

Abbreviations: Con, control; OA, osteoarthritis; BVA, bee venom acupuncture; MA, manual acupuncture; EA, electro-acupuncture; LA, laser acupuncture.

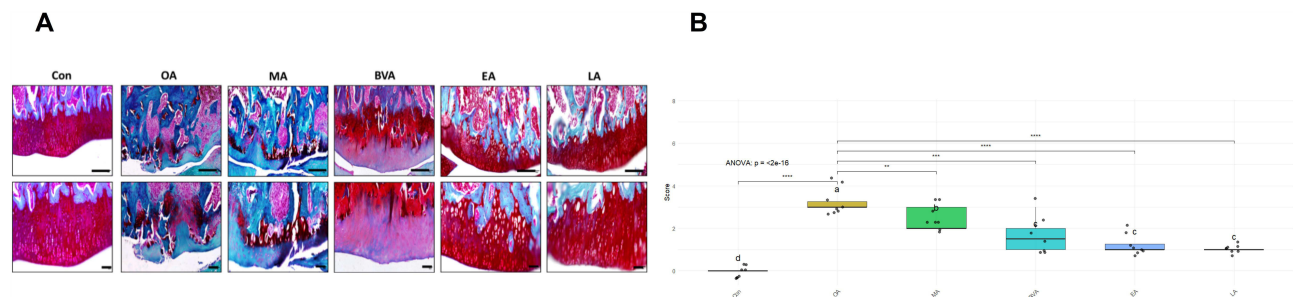


Figure 4 Histological images and quantification of cartilage degradation using Safranin-O/Fast Green staining. (A) Sagittal sections of rat knee joints from each group were stained with Safranin-O/Fast Green. Red staining indicates proteoglycan-rich cartilage, while loss of staining denotes matrix degradation. The OA group showed severe cartilage erosion and proteoglycan loss, whereas the EA and LA groups retained staining patterns similar to the control. Upper row: 10 \times magnification (scale bars = 100 μ m); Lower row: 20 \times magnification (scale bars = 50 μ m). (B) Quantitative assessment of cartilage damage using a modified OARSI scoring system. Boxplots represent median and interquartile range, with individual data points shown. EA and LA groups exhibited significantly lower cartilage scores compared to the OA group ($***p < 0.0001$, $**p < 0.001$, $*p < 0.01$; one-way ANOVA with Tukey's post hoc test). Groups with different letters differ significantly, while groups that share a letter do not differ significantly (a-d) ($p < 0.05$).

Abbreviations: Con, control; OA, osteoarthritis; BVA, bee venom acupuncture; MA, manual acupuncture; EA, electro-acupuncture; LA, laser acupuncture.

Discussion

Pain is often the earliest and most persistent symptom of OA, so this study focused on it. We set out to investigate whether EA, LA, and BVA could relieve pain and slow the progression of joint degeneration in MIA-induced OA rats. The results of our study not only confirm the potential of these acupuncture therapies and offer hope and optimism for the future of OA treatment.

Behaviorally, LA and EA improved pain thresholds by Week 2, and by Week 4, LA, EA, and MA significantly reversed mechanical hypersensitivity. Animals in the BVA group experienced some inflammation at the acupoint after treatment; this could account for the low PWT. These effects were verified by micro-CT findings, which showed preserved subchondral structure in EA and LA groups. Rarely assessed in preclinical acupuncture studies, ossicle formation was markedly inhibited by EA and LA, suggesting modulation of aberrant bone remodeling. Safranin-O staining further confirmed that EA and LA most effectively preserved cartilage integrity.

Previous studies have individually validated the efficacy of acupuncture treatments. For instance, Ma et al showed that early EA (at ST35/ST36) preserved cartilage and relieved pain, while delayed EA had reduced benefit.²⁷ Chen et al further revealed that EA acts via sympathetic β 2-adrenergic signaling to suppress IL-6, reduce synovial inflammation, and ameliorate pain behaviors.²² Our results align with these findings, as EA improved PWT threshold by week 2 and preserved cartilage, as confirmed by the histology scores.

LA has shown promise in modulating inflammation and promoting cartilage repair.^{21,28} Li et al demonstrated that 10.6 μ m infrared LA reduced MMP-13 expression, improved weight-bearing, and preserved cartilage in MIA-OA rats, resulting in LA's anti-inflammatory and chondroprotective potential.²⁹ In our study, invasive 830 nm LA produced similar benefits: pain thresholds improved significantly from Week 2, cartilage histology closely resembled that of the control group by Week 4 and reduced ossicle formation. These results suggest that LA, despite being a less invasive and more technologically modern modality, may offer outcomes comparable to EA in treating OA as the LA penetrates deeper into the skin.³⁰

BVA has demonstrated significant analgesic and anti-inflammatory effects through pharmacological mechanisms. Chen and Larivière (2010) reviewed bee venom's actions and noted its impact on opioid receptors and the suppression of proinflammatory cytokines such as TNF- α and IL-1 β .³¹ Our study supports this mechanistic framework as BVA-treated rats exhibited early pain relief (Week 2) and moderate histological protection. However, its structural preservation was less pronounced than that observed with EA and LA.

A subset of rats in the BVA group developed localized swelling and reduced mobility following the initial bee venom injections. Such responses are consistent with documented side effects of bee venom therapy, which include local inflammation, edema, and, in some cases, systemic reactions. For instance, a systematic review highlighted that bee venom therapy can lead to adverse events ranging from mild local reactions to severe systemic responses, depending on the dosage and administration method. Additionally, studies have reported that bee venom injections can cause localized swelling and pain in animal models. These adverse reactions were not observed in the other treatment groups.^{32,33}

Our findings align with a network meta-analysis by Corbett et al (2013), which found acupuncture among the most effective non-pharmacological treatments for knee OA.¹⁶ While their analysis was limited to clinical studies and did not distinguish between acupuncture types, our data add nuance by suggesting that different modalities may yield comparable overall benefits through distinct mechanisms.

Few studies have directly compared EA and LA. Kim et al (2019) evaluated EA and LA in a collagenase-induced arthritis model and reported superior outcomes with LA.²⁰ However, they did not incorporate BVA or assess multiple modalities simultaneously within the same framework. By integrating all three therapies, our study addresses this critical gap and provides clinicians and researchers with comparative evidence to inform integrative treatment strategies.

Understanding how each acupuncture treatment performs could guide therapy selection. Since EA, LA, and BVA function through distinct mechanisms, such as electrical stimulation, PBM, and biochemical immune modulation, understanding their relative effects in one system may inform future combined or personalized protocols. We prioritized functional and structural outcomes over molecular testing to ensure that our findings were closely related to the clinical characteristics of OA.

Conclusion

Acupuncture reduced both pain behaviors and cartilage degeneration in MIA-induced KOA, but the benefit was contingent upon the specific modality employed. LA had the most substantial and persistent therapeutic results, as indicated by changes in pain thresholds, cartilage, and bone structure. Its effectiveness outperformed that of EA and MA. In contrast, BVA had little efficacy and caused acute adverse reactions. This study suggests that the therapeutic efficacy of acupuncture for KOA is determined by the modality used, with laser-based approaches outperforming other methods. These findings emphasize the potential for adapting acupuncture modalities to disease pathophysiology and the importance of integrative, comparative research in advancing complementary OA therapies.

Abbreviations

BVA, bee venom acupuncture; CT, computed tomography; EA, electroacupuncture; EDTA, ethylenediaminetetraacetic acid; GB34, gall bladder 34 acupoint (yanglingquan); LA, laser acupuncture, MA, manual acupuncture; MIA, monosodium iodoacetate; OA, osteoarthritis; PWT, paw withdrawal threshold; PBM, photobiomodulation.

Data Sharing Statement

The data generated for the present study are available from the corresponding author, Gihyun Lee: glee@khu.ac.kr, and Jae-Hong Kim: nahonga@hanmail.net, upon reasonable request.

Ethical Statement

This study was approved by the animal care and use committee of Dongshin University (DSU-2024-07-04).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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