Short-Term Safety and Effectiveness of Apipuncture in Knee Osteoarthritis: A Single-Arm Clinical Trial

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ABSTRACT

Objective: Osteoarthritis, a degenerative joint disease, often poses challenges in conventional medical treatment, leading patients to explore traditional and complementary medicine options including apitherapy. Bee venom, known for its analgesic and anti-inflammatory properties, has been considered as a potential therapy. This study investigates the short-term safety and effectiveness of applying live bee venom in knee osteoarthritis patients.

Materials and Methods: Conducted at a university hospital's Apitherapy Clinic, this single-arm clinical trial enrolled individuals diagnosed with mild to moderate knee osteoarthritis (stage 2-3). A single session of live bee venom application was administered to acupuncture points ST35, EX-LE4, and ash-chi, specifically targeting the painful knee joint. Data collection involved the utilization of a Demographic Information Questionnaire and SF-12 Scale, along with a comparison of the Numerical Rating Scale (NRS), 5 Times Sit-to-Stand Test (5xSST), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire before and after the treatment.

Results: Before the treatment, the average NRS value stood at 7.14 ± 1.7, and following the intervention, it notably decreased to 3.06 ± 2.16 (p<0.05). Additionally, the mean value for the 5xSST decreased from 14.59 ± 3.36 before treatment to 11.75 ± 2.30 after treatment. The WOMAC scale also showed a significant difference between pre- and post-treatment (p<0.05), with the mean value decreasing from 41.91 ± 18.07 before treatment to 15.57 ± 15.14 after treatment.

Conclusion: The findings of this study indicate a significant improvement in the NRS, 5xSST, and WOMAC scales after the administration of live bee venom for knee osteoarthritis patients.

Keywords: Apitherapy, Apipuncture, Bee venom, Melittin, Osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is a widespread degenerative joint ailment impacting countless individuals around the world. This condition is marked by the gradual breakdown of joint cartilage, the emergence of osteophytes, and subchondral sclerosis, all of which contribute to the onset of pain, rigidity, and diminished functionality (1,2).

OA is a dynamic process involving both destruction and repair, triggered by various biochemical and mechanical factors. It affects joint cartilage and impacts subchondral bone, ligaments, capsule, synovium, and surrounding muscle tissues, frequently observed in the knee joint (3).

Knee osteoarthritis stands out as a prevalent manifestation of OA, with approximately 30% of individuals aged 45 and above exhibiting radiographic indications of knee OA, and roughly half of this group reporting associated knee symptoms (1). The prevalence of knee osteoarthritis varies across populations. A study conducted in Spain found that the prevalence of symptomatic knee osteoarthritis in a random population sample was almost 30% (4). They also found that individuals with knee osteoarthritis had higher scores in pain, stiffness, and functional capacity dimensions, indicating the impact of the disease on the quality of daily life (4).
Several risk factors have been identified for the development of knee osteoarthritis. Risk factors for OA include age, gender, obesity, genetic factors, joint disorders, trauma, occupational stress (such as prolonged knee flexion in agricultural or construction workers), sports activities, quadriceps muscle weakness and proprioception impairment, inadequate physical activity, hypermobility, and smoking (5–7).

Symptoms of osteoarthritis typically have a slow and insidious onset, often localized to the affected joint. Pain, often described as gradual, intermittent, mild to moderate, deep, and throbbing, ranks as the predominant and frequently encountered symptom in cases of OA. Pain can be caused by irritation of osteophytes, trabecular microfractures, increased intraosseous pressure in subchondral bone, capsule distension, bursitis, tenosynovitis, central neurogenic changes, and muscle spasms in the joint vicinity. As the disease progresses, rest pain and nocturnal pain may occur. Increased stiffness after rest is a common finding, lasting less than 30 minutes, unlike in other inflammatory conditions. Limitations in active or passive joint range of motion and crepitus may be observed (8). As of now, a conclusive medical remedy for OA remains elusive. Nevertheless, diverse approaches exist to ameliorate pain, enhance mobility, and mitigate disability, ultimately augmenting the quality of life for patients (9).

Diagnosis of knee osteoarthritis is typically based on clinical evaluation and imaging studies. Radiography is the most commonly used imaging modality for knee OA (10). However, it has limitations, particularly in the early stages of the disease. Magnetic resonance imaging (MRI) stands out as a heightened imaging modality, capable of delivering a comprehensive assessment of the knee joint (10). Consequently, it is advised as a secondary diagnostic method for knee OA (10).

According to the guidelines published by the American College of Rheumatology in 2019, the treatment of osteoarthritis involves a combination of pharmacological and non-pharmacological approaches. Pharmacological treatments include paracetamol, NSAIDs, topical applications, and corticosteroids. Non-pharmacological treatments emphasize rest and protection from mechanical trauma as important components. Rest is particularly recommended during acute flare-ups. Assistive tools such as canes, crutches, walkers, braces, and elastic bandages, alongside physical therapy techniques and exercises, are utilized to safeguard joint function and impede the advancement of the disease (11).

Among the various treatment modalities, traditional and complementary therapies are increasingly utilised. Osteoarthritis patients who are unresponsive to conventional medical treatments often seek traditional and complementary medicine (T&CM) practices (12). Apitherapy refers to using bee products such as bee venom, honey, pollen, bee bread, royal jelly, and propolis to prevent and treat diseases. Each apitherapy product has healing effects attributed to its different components.

Recently, bee venom treatment (BVT), which exhibits pharmacological effects such as analgesic and anti-inflammatory properties by activating central inhibitory/excitatory systems and modulating the immune system, has gained attention (13–15). Bee venom stings are painful, and can cause adverse effects, including allergic reactions in sensitive individuals (16,17). However, bee venom contains a wide range of components, including biogenic amines, enzymes, peptides, and non-enzyme proteins (18), such as melittin, apamin, and phospholipase A2 that have been found to have therapeutic effects (14). Melittin, the major component constituting 50-60% of bee venom, has been reported to inhibit cytokines, chemokines, and proteases on chondrocytes, thereby preventing type 2 collagen degradation (19).

BVT is a type of traditional and complementary medicine that has been employed for millennia (19). It involves the application of bee venom from honeybees into the human body to treat various diseases, including joint problems (19). Dr. Fang Zhu from China gained recognition as the pioneer who introduced the method of modern Appipuncture or bee venom acupuncture, effectively combining the principles of meridians and acupoints (20).

According to the Traditional and Complementary Medicine Practices Regulation (2014) in Türkiye, bee venom can be used to reduce various musculoskeletal system symptoms in Apitherapy centers in the hospitals (21). Based on this regulation, our study aims to investigate the short-term safety and effectiveness of appipuncture with live bees in patients diagnosed with knee osteoarthritis regarding pain relief, and function improvement.

MATERIAL and METHODS

Sample and Population: This research comprised a single-arm clinical trial conducted from June 1st to June 30th, 2023, involving patients seeking healthcare services at the Apitherapy Clinic within Esenler Hospital of Istanbul Medipol University, located in Istanbul, Türkiye. The study focused on individuals diagnosed with mild to moderate (stage 2-3) knee osteoarthritis, as per the Kellgren-Lawrence radiological staging criteria, aged between 40 and 70, and who experienced knee pain persisting for at least the past 3 months.

The study utilized the Kellgren-Lawrence Scale radiological staging criteria, which encompassed the following stages: Stage 0 denoting a normal condition, Stage 1 indicating possible osteophytes, Stage 2 representing definite osteophytes with uncertain joint space narrowing, Stage 3 denoting moderate osteophytes with clear joint space narrowing, and Stage 4 signifying significant osteophytes with pronounced joint space narrowing and sclerosis.

Participants with known allergies to bees and bee products, those affected by rheumatologic, neurological, or orthopedic conditions influencing the knee joint, severe emotional disorders, cognitive impairments, individuals below 40 years of age or above 70 years of age, those who received intra-articular steroid, platelet-rich plasma, or hyaluronic acid injections within the past month, individuals who underwent physical therapy within the past month, and those who had prior knee joint surgery or had a body mass index (BMI) of 40 or above were excluded from the study.

Participants were provided with information about the application protocol before data collection. Written informed consent forms were obtained from all participants before the
study commenced. Before the treatment, allergy measurements included patient history, honeybee venom-specific IgE tests, and skin tests, along with providing necessary precautions. Knee osteoarthritis was assessed by five licensed physical therapy and rehabilitation specialists. Acupuncture sessions involving live bees were conducted under the supervision of two licensed physicians with twenty years of experience in apitherapy. During a single session, by using forceps, three bee stings from Apis Mellifera were applied to acupuncture points ST35 and EX-LE4, following relevant acupuncture literature (22), as well as to the ash-chi point located on the affected knee joint for one minute. After the treatment, it was scheduled for patients to be monitored for a duration of one week.

**Data Collection:** Data was gathered by administering the Demographic Information Questionnaire and SF-12 Scale, and by comparing the results of the Numeric Rating Scale (NRS), 5 Times Sit-to-Stand Test (5xSST), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire before and after the treatment.

Participants were provided with information about the application protocol before data collection. Written informed consent forms were obtained from all participants before the study commenced.

**Demographic Information:** Age, gender, height, body weight, body mass index, occupation, and other socio-demographic data of the participants were recorded.

SF-12 Health Survey: The SF-12 Scale is derived from the SF-36 Health Survey. The Rand Corporation developed and introduced the SF-36 Health Survey in 1992. Its Turkish validity and reliability have been established by (23). The SF-12 Scale consists of eight subscales, and scores range from 0 to 100. Higher scores indicate a higher quality of life.

Numerical Rating Scale (NRS): The Numerical Rating Scale (NRS) entails individuals providing a numerical rating for their pain or experience, typically on a scale from 0 to 10. A score of 0 signifies the absence of pain or symptoms, while a score of 10 corresponds to the most severe pain or intensity imaginable (24).

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): The WOMAC Index assesses osteoarthritis-related disability in hip and/or knee osteoarthritis. It was initially developed in 1982 and has undergone various revisions and modifications. The latest version is WOMAC 3.1. The WOMAC OA Index is a 24-item scale that examines three dimensions: pain, stiffness, and physical function. Items can be scored using a Numerical Rating Scale (NRS) or a 5-point Likert scale. The WOMAC Index can detect significant health status changes following various pharmaceutical, surgical, and physical therapy intervention(25,26).

5 Times Sit-to-Stand Test (5xSTS): This balance and coordination test involves a person sitting down and standing up from a chair as quickly as possible for one minute. The process is repeated five times, and the duration of each movement is recorded. This test is commonly used to assess the balance, coordination, and muscle strength of elderly individuals and can also be used to evaluate the physical performance of athletes. The test results are used to measure a person's level of balance and coordination (27,28).

**Ethics:** Ethical approval for the study was obtained from the Institutional Ethics Committee of Istanbul Medipol University, Istanbul (Date:11/05/2023, No:14). The patients were informed of the purpose and method of the study and their cooperation was obtained. After these explanations, patients who agreed to participate in the research were asked to sign an informed consent form. Personal identifying information such as names, addresses and phone numbers were not included in the survey given to the families.

**Statistical Analysis:** SPSS (Statistical Package for Social Sciences) 26.0 for Windows was used for statistical analysis of the data. Descriptive statistics such as frequency, percentage, mean, standard deviation, median, and min-max have been calculated. The Wilcoxon signed-rank test is used for dependent groups, while the Mann-Whitney U and Kruskal-Wallis tests were used for independent groups. The consistency between measurements was evaluated using the intraclass correlation coefficient (ICC) for within-group correlations. Results were assessed at a 95% confidence interval, and the p<0.05 value was considered statistically significant in comparisons.

**RESULTS**

Out of the initial 67 patients considered for the study, 50 patients were finally included, taking into account the exclusion criteria and cases of dropouts (Figure 1).
The mean age of the participants was 55.5 ± 7.27 standard deviation, with the lowest age being 41 and the highest age being 69. The study’s participants exhibited an average height of 1.60 ± 0.07 meters, an average weight of 82.46 ± 14.15 kg, and a mean BMI value of 32.24 ± 4.84. The mean value of the mental and physical scores of SF-12 Health Survey results were 44.00 ± 11.14 and 32.14 ± 9.51, respectively (Table 1).

It is observed that 88% of the participants in the study were female, while 12% were male. The participants were distributed across different age ranges, with 30% falling within the 41-50 age group, 42% within the 51-60 age group, and 28% within the 61-70 age group. In terms of disease staging, it is noted that 34% of the participants were in stage 2, while 66% were in stage 3.

A paired Wilcoxon signed-rank test was conducted to compare the statistically significant differences between the tests before and after treatment (Figure 2).

Table 1. Mean anthropometric and health survey variables of the participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD (N=50)</th>
<th>M (Min - Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>55.50 ± 7.27</td>
<td>57.50 (41.00-69.00)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60 ± 0.07</td>
<td>1.60 (1.45-1.82)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.46 ± 14.15</td>
<td>80 (58.00-128.00)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.24 ± 4.84</td>
<td>31.65 (23.24-40.63)</td>
</tr>
<tr>
<td>SF-12 (Mental Score)</td>
<td>44.00 ± 11.14</td>
<td>42.06 (21.89-62.48)</td>
</tr>
<tr>
<td>SF-12 (Physical Score)</td>
<td>32.14 ± 9.51</td>
<td>29.70 (15.85-57.34)</td>
</tr>
</tbody>
</table>

N: sample size, SD: standard deviation, M: median, Min: minimum value, Max: maximum value,

The results showed a statistically significant difference between pre- and post-treatment was observed in the NRS between pre- and post-treatment (p<0.05). The mean value decreased from 7.14 ± 1.7 before treatment to 3.06 ± 2.16 after treatment. Similarly, a statistically significant difference was found in the 5xSST between pre- and post-treatment (p<0.05). The mean value decreased from 14.59 ± 3.36 before treatment to 11.75 ± 2.30 after treatment. In the case of the WOMAC scale, a statistically significant difference was observed between pre- and post-treatment (p<0.05). The mean value decreased from 41.91 ± 18.07 before treatment to 15.57 ± 15.14 after treatment (Table 2).

Figure 2. Comparison of NRS, 5 Times Sit-to-Stand, and WOMAC pre- and post-treatment.

As shown in Table 5, a statistically significant difference was observed in the NRS, 5xSST, and WOMAC scores, both before and after treatment, for patients in stage 2 (p<0.05). Similarly, for patients in stage 3, a statistically significant difference was found in the NRS, 5xSST, and WOMAC scale, both before and after treatment (p<0.05). The Kruskal-Wallis test was conducted to compare if there is a statistically significant difference between age groups in the measurements. According to the results, no statistically significant difference was found in the NRS, 5xSST, and WOMAC scale between age groups, both before and after treatment (p>0.05).

Table 2. Paired Wilcoxon Signed-Rank Test for comparison of tests pre- and post-treatment.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Variables</th>
<th>Mean ± SD (N=50)</th>
<th>M (Min - Max)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS (score)</td>
<td>Pre-treatment</td>
<td>7.14 ± 1.70</td>
<td>7.00 (1.00-10.00)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>3.06 ± 2.16</td>
<td>3.00 (0.00-7.00)</td>
<td></td>
</tr>
<tr>
<td>5 Times Sit-to-Stand (sec)</td>
<td>Pre-treatment</td>
<td>14.59 ± 3.36</td>
<td>13.96 (6.16-22.66)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>11.75 ± 2.30</td>
<td>11.72 (5.37-20.41)</td>
<td></td>
</tr>
<tr>
<td>WOMAC (%)</td>
<td>Pre-treatment</td>
<td>41.91 ± 18.07</td>
<td>40.10 (2.08-73.87)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>15.57 ± 15.14</td>
<td>8.33 (0.00-57.29)</td>
<td></td>
</tr>
</tbody>
</table>

N: sample size, SD: standard deviation, M: median, Min: minimum value, Max: maximum value *p<0.05
A Wilcoxon signed-rank test was conducted to compare if there is a statistically significant difference between the tests before and after treatment. Based on the findings, a statistically significant disparity was noted in the NRS, 5 Times Sit-to-Stand scale, and WOMAC scale scores for patients within the 41-50 age bracket, both prior to and following treatment (p<0.05). Similarly, for patients in the 51-60 age group, a statistically significant difference was found in the NRS, 5xSST, and WOMAC scale, both before and after treatment (p<0.05).

Likewise, for patients in the 61-70 age group, a statistically significant difference was observed in the NRS, 5xSST, and WOMAC scale, both before and after treatment (p<0.05). A Wilcoxon signed-rank test was conducted to compare if there is a statistically significant difference between the tests before and after treatment (Table 5).

The bee sting application was found to be painful for the first minute, as well as some minimal local reactions such as itching for a while. No severe adverse events were observed.

Table 3. Results of inter-rater reliability assessment.

<table>
<thead>
<tr>
<th>Tests</th>
<th>ICC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS (score)</td>
<td>0.580</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>5 Times Sit-to-Stand (sec)</td>
<td>0.822</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>WOMAC (%)</td>
<td>0.652</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

ICC: Intraclass Correlation Coefficient

Table 4. Paired Wilcoxon Signed-Rank Test for comparison of tests pre- and post-treatment according to stages.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Variables</th>
<th>Stage 2 (N=17)</th>
<th>Stage 3 (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>M (Min - Max)</td>
</tr>
<tr>
<td>NRS (score)</td>
<td>Pre-treatment</td>
<td>6.29 ± 2.17</td>
<td>6.00 (1.00-10.00)</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>2.41 ± 2.15</td>
<td>2.00 (0.00-6.00)</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>5 Times Sit-to-Stand (sec)</td>
<td>Pre-treatment</td>
<td>14.81 ± 4.41</td>
<td>14.83 (6.16-22.66)</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>11.73 ± 2.90</td>
<td>12.2 (5.37-16.80)</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>WOMAC (%)</td>
<td>Pre-treatment</td>
<td>37.44 ± 19.48</td>
<td>37.5 (2.08-70.83)</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>13.28 ± 15.26</td>
<td>5.20 (0.00-42.70)</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

N: sample size, SD: standard deviation, M: median, Min: minimum value, Max: maximum value *p<0.05

Table 5. Paired Wilcoxon Signed-Rank Test for comparison of tests pre- and post-treatment according to age groups.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Variables</th>
<th>41-50 years (N=15)</th>
<th>51-60 years (N=21)</th>
<th>61-70 years (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>M (Min - Max)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>NRS (score)</td>
<td>Pre-treatment</td>
<td>7.67 ± 1.11</td>
<td>7.00 (6.00-10.00)</td>
<td>6.81 ± 2.27</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>3.07 ± 1.83</td>
<td>3.00 (0.00-7.00)</td>
<td>3.14 ± 2.41</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>2.93 ± 2.24</td>
</tr>
<tr>
<td>5 Times Sit-to-Stand (sec)</td>
<td>Pre-treatment</td>
<td>14.76 ± 2.57</td>
<td>14.15 (10.30-18.76)</td>
<td>14.57 ± 3.60</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>11.60 ± 2.01</td>
<td>11.10 (8.96-16.80)</td>
<td>11.91 ± 2.80</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>11.67 ± 1.87</td>
</tr>
<tr>
<td>WOMAC (%)</td>
<td>Pre-treatment</td>
<td>39.51 ± 15.19</td>
<td>38.50 (20.80-73.90)</td>
<td>46.82 ± 19.17</td>
</tr>
<tr>
<td></td>
<td>Post-treatment</td>
<td>14.77 ± 13.54</td>
<td>8.33 (0.00-38.50)</td>
<td>15.37 ± 16.79</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td>16.74 ± 15.19</td>
</tr>
</tbody>
</table>

N: sample size, SD: standard deviation, M: median, Min: minimum value, Max: maximum value *p<0.05

DISCUSSION

Bee venom treatment, an age-old therapy in traditional and complementary medicine (T&CM), has historically been applied to address diverse ailments (18). Particularly, it has gained popularity as an alternative approach to manage joint discomfort (18).

In the present investigation, which delves into the immediate safety and effectiveness of acupuncture using live bees for knee osteoarthritis, noteworthy reductions in mean NRS, 5xSST, and WOMAC scale values were observed post-treatment. Notably, apart from localized pain and itching, no significant systemic adverse effects were recorded during this study. Several studies have investigated the use of bee venom in the treatment of pain (9,15). Kim et al. (2016) studied the combined effects of BVA and morphine on oxaliplatin-induced neuropathic pain in mice. The study found that the combined use of BVA and morphine had a greater and longer-lasting anti-allodynic effect compared to either treatment alone. This suggests that BVA may have additive effects when used in combination with conventional pain medications (15).
Furthermore, a recent systematic review and meta-analysis found that bee venom treatment has a significant potential in the management of knee osteoarthritis (29).

Hye et al. (2004) investigated the molecular mechanisms of the antiarthritic effects of bee venom in a rat model of carrageenan-induced acute edema and a rat model of chronic adjuvant-induced arthritis. They found that bee venom reduced the effects of carrageenan- and adjuvant-induced arthritis, which was consistent with bee venom's inhibitory effects on inflammatory gene expression (13).

Chronic inflammation contributes to the development of several diseases (30). The potential mechanisms of action of bee venom in arthritis include its anti-inflammatory effects and modulation of intracellular signal transduction (31,32). Bee venom has been shown to inhibit the NF-kB pathway, reduce inflammation, and have antinociceptive activity (32). It may also interact with the spinal alpha2-adrenergic activity and inhibit beta-tyrosine phosphorylation of PDGF receptors (32). It was reported that bee venom and melittin can inhibit the generation of proinflammatory mediators in lipopolysaccharide-stimulated microglia, suggesting their potential therapeutic use in the treatment of neurodegenerative diseases accompanied by microglial activation (33). Melittin, a compound found in bee venom, has shown anti-inflammatory effects at lower doses. Studies have explored the mechanisms by which melittin inhibits inflammatory cytokines and reduces inflammation in different tissues (13,34).

While bee venom therapy has been reported to have therapeutic effects, it is important to note that bee venom stings are painful (35), and can also cause adverse effects, including anaphylactic shock (14). The treatment with whole bee venom or its specific components is still a matter of debate and studies are needed to make firm conclusions (16). Therefore, further research is needed to fully understand the action mechanisms and determine the optimal dosage and delivery methods (14). Efforts have to be made to increase the efficacy and minimize the adverse events (14,33).

This study has some limitations. It is designed as a single arm study to evaluate the short-term data as mentioned in the title. Further studies are needed to investigate the long-term data with various groups in comparison with appuncture.

The current study incorporated live bee stings as a facet of the intervention strategy. However, it is crucial to recognize that the utilization of live bee stings entails certain limitations. Primarily, the use of live bee stings exposes patients to a notably higher frequency of stings. This increased exposure to bee stings can lead to more discomfort. Furthermore, using living bee stings can pose risks and adverse events, which can vary depending on the dosage, method, route of administration, and individual factors (17). However, using living bee stings may not be as precise or controlled as venom injections which may allow for a more accurate and controlled dosage of venom to be administered (36). This precision is important for ensuring the safety and effectiveness of the therapy. Earlier research endeavors have encompassed a variety of dosages, encompassing both fixed quantities of bee venom per needle and total bee venom quantities per session (37).

There is a necessity for a novel approach to apply bee venom, aiming to achieve a safer and more precise delivery method. Such an innovative technique could reduce unwanted effects and improve the effectiveness of the treatment (38).

The aim is to harness the beneficial aspects of bee venom while minimizing potential side effects or allergic reactions. By imitating nature's design and mechanisms, biomimetic bee venom treatments may offer safer and more targeted therapies for various medical conditions.

**CONCLUSION**

Management of knee osteoarthritis involves an integrative, and multidisciplinary approach, including traditional therapies. While bee venom therapy has shown promise in the treatment of knee osteoarthritis, it is important to consider the potential risks associated with its use. It is crucial to carefully evaluate the risks and benefits of bee venom therapy on a case-by-case basis and to ensure that it is administered by trained professionals with necessary precautions like in any treatment. Further research is needed to fully understand the mechanisms underlying the therapeutic effects of bee venom and its components. The concept of biomimicry in bee venom treatment highlights the potential of nature-inspired solutions in modern medicine, paving the way for innovative and effective therapeutic approaches.

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**Ethical approval:** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Written consent was obtained from each patient to use their hospital data.
The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Istanbul Medipol University, Istanbul, Turkey (Date: 11/05/2023, No:14).

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