Evaluation of the efficacy of gallium-aluminum-arsenide laser acupuncture in the management of knee osteoarthritis

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Background/aim
Knee osteoarthritis is a common degenerative disease affecting the joint, causing progressive loss of cartilage and inflammation. Its main symptoms are pain and stiffness. Medications such as NSAIDs have little benefit and are usually accompanied by serious adverse effects. The aim of this study was to evaluate the efficiency of laser acupuncture in the management of stage 2 or 3 knee osteoarthritis.

Patients and methods
The study was carried out on 30 patients (24 females and six males) diagnosed as having stage 2 or 3 knee osteoarthritis. The patients were recruited from the Complementary and Alternative Medicine Clinic at the Medical Centre of Excellence, National Research Centre, Cairo, Egypt. The patients were subjected to low-power laser (gallium-aluminum-arsenide 905 nm) with touch sensor guide light, power output of 100 mill watts, beam area of 1 cm^2, 1-min irradiation time, frequency 10 000 Hz, duty cycle 100%, total energy per point 6 J, energy density 6 J/cm^2, and irradiance 0.1 W/cm^2, for 3 days/week for a duration of 4 weeks (12 session), directed at various acupuncture points (ST 35, ST 36, Sp 9, Sp 10, GB 34, Sp 6, and liv3). Clinical and laboratory parameters were assessed before and after laser therapy.

Results
Pain on visual analog scale, number of tender points, tenderness score, angle of knee flexion, heel to hip distance, Western Ontario McMaster Universities Osteoarthritis Index scale score, and Lequesne Index showed significant improvement after treatment ($P<0.05$). Timed up and go test result was decreased after laser sessions, but its improvement was insignificant statistically. Significant improvement and increase of enkephalin and immunoglobulin (IL-4) were recorded after treatment.

Conclusion
Laser acupuncture showed efficacy in the management of stage 2 or 3 knee osteoarthritis.

Keywords:
acupuncture, knee osteoarthritis, laser, pain

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Introduction

Knee osteoarthritis is a common degenerative disease affecting the joint, causing progressive loss of cartilage and inflammation. Pain, stiffness, and restriction of range of flexion and extension are the main complaints of patients having the disease [1]. The pain increases by prolonged activity and is relieved by rest. Stiffness is common in the morning, mostly lasts less than 30 min and may return after periods of inactivity [2]. The symptoms deteriorate over the years ending up with disability [3].

Osteoarthritis may be primary, mostly related to variations in sex hormones as it is more common in postmenopausal women than among males of the same age. It may be secondary to obesity, diabetes, injury to ligaments, or joint infection [4]. Approximately 13% of females and 10% of males in the population aged more than or equal to 60 years have knee osteoarthritis in United States [5]. Many conventional medications such as NSAIDs and opioids are applied for pain management. Injection of the knee with corticosteroids and hyaluronic acid may improve the symptoms. However, these medications may have serious complications with little beneficial effects [6].

A meta-analysis study showed that the pain-decreasing effect of NSAIDs in knee osteoarthritis beyond placebo is small to moderate [7]. The pain-relieving effect of NSAIDs was indicated to be only 10.1 mm on the 0–100 mm visual analog scale (VAS) better than placebo [8].

In the last decade, it is highly recommended to consider nonpharmacological intervention to be the first line of treatment for patients with knee osteoarthritis. Many modalities of this intervention proved to be effective such as were physical therapy, weight loss, bracing, electrotherapy, and acupuncture [9,10].

Laser acupuncture is one of the nonpharmacological tools applied for the management of many medical conditions. It is defined as the stimulation of acupuncture points with low-power laser radiation. Laser acupuncture is considered safer than traditional needling as it is a noninvasive modality [11]. Therefore, it has been frequently used to control pain in various musculoskeletal diseases. Although the therapeutic evaluation of laser acupuncture is gaining popularity, objective assessment of its efficiency on knee osteoarthritis in literature is difficult because the dosages applied in different trials vary quite a lot [11].

Studies that use inadequate dosages get negative results [12]. Recently, there has been an increased number of randomized controlled trials, performed according to World Association of the Laser Therapy (WALT), evaluating the therapeutic effect of laser acupuncture on patients complaining of knee osteoarthritis [13].

The aim of this study was to evaluate the efficiency of laser acupuncture as a complementary modality for management of stage 2 or 3 knee osteoarthritis and its consequence on physical and daily activities of osteoarthritic patients as well as its effect on biochemical markers.

Patients and methods

Patients

In this single-case interventional study, 30 patients (24 females, six males) diagnosed as having stage 2 or 3 knee osteoarthritis were included. Their ages ranged between 38 and 60 years. The patients were selected from the Complementary and Alternative Medicine Clinic at the Medical Centre of Excellence, National Research Centre, Cairo, Egypt, from February 2020 to November 2020. The present study started with 50 patients. Some cases (n=10) did not fulfill the inclusion criteria and were excluded from the study. Overall, four patients were diagnosed as having stage 4, and they needed knee surgical replacement. Other cases (n=6) were irregular in attending laser sessions.

Inclusion criteria

The following were the inclusion criteria:

(1) Knee osteoarthritis of Kellgren stage 2 or 3 diagnosed by plain radiograph and free from any sign of inflammation.
(2) Weaning of all conventional medications 2 weeks before the start of the first laser session.

Exclusion criteria

The following were the exclusion criteria:

(1) Patients with renal or hepatic impairment.
(2) Recent heart attack or stroke.
(3) Patients under treatment with antibiotics or corticosteroid.
(4) Patients having cardiac pacemaker.
(5) Epileptic patients.
(6) Pregnancy.
(7) Malignancy.

Ethical consideration

Before the start of the study, informed consents were obtained from all patients in accordance with Helsinki Declaration 1964. This study was approved by the Medical Research Ethics committee of the National Research Centre, Cairo, Egypt, with approval number 16/337.

Clinical examination

Each patient was subjected to general clinical examination. Pain intensity on VAS, morning stiffness time, tenderness score (TS), range of knee flexion and extension (by Goniometer), Western Ontario McMaster Universities Osteoarthritis Index scale (WOMAC), sequence index, distance between the hip and heel, and timed up and go test were performed in all of the patients before and after treatment.

Pain intensity on visual analog scale

The linear scale is the visual representation of the range of pain that a patient believes he or she might experience. The range is represented by a line, usually 10 cm in length, with or without marks at each centimeter. One end represents 'no pain,' whereas the other represents the worst pain the patient could imagine. The scale is scored by the patient, who is asked to draw a mark on the line that represents the level of pain being experienced [14].

Tenderness score

Tenderness is tested by applying firm pressure to the knee, and it is recorded according to the following score:

Score 0: the patient feels no pain.

Score 1: the patient says it is painful.

Score 2: the patient says it is painful and winces.

Score 3: the patient says it is painful, winces, and withdraws the limb.

This is applied to each of the following sites: suprapatellar, infrapatellar, medial collateral ligament, lateral collateral ligament, and popliteal fossa; thereafter, the mean TS of these areas is calculated. Tenderness to palpation can be scored on a scale from 0 to 3, where 0 represented no pain, and 1, 2, and 3 represented mild, moderate, and severe tenderness, respectively [15].

Goniometry of knee range of motion

Knee range of motion was measured with a universal goniometer from the manufacturer CARCI. Active extension was measured with the participant in a supine position with extended legs. For goniometry of active flexion, the participant was in the prone position with the contralateral lower limb in extension [16]. Range of painless movement (flexion) measures the range of flexion in degrees starting from the zero position of normal full extension. Flexion of 135 and over is regarded as normal.

Western Ontario and McMaster Universities Arthritis Index

The questionnaire contains 24 questions, of which five evaluate pain, two joint stiffness, and 17 function. Each question is graded qualitatively, with the response options none, low, moderate, severe, and very severe. The equivalent scores are 0, 1, 2, 3, and 4. Higher scores indicate greater effect on quality of life [17].

Lequesne Index: this index is composed of 11 questions about pain, discomfort, and function. Each answer has an equivalent score. The total score ranges from 0 to 24 and is divided into five categories of functional impairment: no=0, bit=1–4, moderate=5–7, severe=8–10, very severe=11–13, and extremely severe more than or equal to 14. In conclusion, the higher the score, the greater the impairment of function [18,19].

Timed up and go test: this test has been shown to be reliable, reproducible, and responsive to change. Participants were asked to rise from a standard armchair, walk at a safe and comfortable pace to a mark 3 m away, and then return to a sitting position in the chair, using gait aids and chair armrests to assist with sit to stand as needed. The outcome measured was the time to complete the task. The longer the time spent, the worse their mobility [20].

Radiological examination: plain radiography was performed before laser sessions to verify the stage of osteoarthritis.

Laboratory analysis

Blood samples (5 ml) were withdrawn from each patient. They were left to coagulate and then centrifuged at 300 rpm. The sera were separated into aliquots and stored at −80°C till the determination of serum interleukin-4 (IL-4) and enkephalin levels. Serum IL-4 and enkephalin levels were determined using human ELISA reagent kits of Assaypro (Charles, Missouri, USA), according to the instruction provided in each kit.

Laser apparatus: gallium-aluminum-arsenide 905-nm laser with touch sensor guide light, power output of 100 mill watts, beam area of 1 cm^2, 1-min irradiation time, frequency 10 000 Hz, duty cycle 100%, total energy per point 6 J, energy density 6 J/cm^2, irradiance 0.1 W/cm^2, for 3 days/week for duration of 4 weeks (12 session), was directed to various acupuncture points (ST 35, ST 36, Sp 9, Sp 10, GB 34, Sp 6, and liv3), which were selected according to the traditional Chinese medicine guidelines [21]. Gallium-aluminum-arsenide laser energy was calculated according to the recommendations of WALT [22].

Statistical analysis

The significance of association of qualitative data was tested applying the χ^2 test or Fisher's exact test, as indicated. The distribution of quantitative data across the two groups was evaluated using the Mann–Whitney test. The Wilcoxon signed-rank test was used to compare mean of the differences of paired quantitative data. All tests were bilateral, and a P value less than or equal to 0.05 indicated statistical significance. Statistical calculations were carried using a statistical analysis system (SAS) program software (copyright (c) 1998 by SAS Institute Inc., Chicago, Illinois, USA).

Results

This single-case interventional study included 30 patients with knee osteoarthritis (24 females and six

males), with ages ranged from 38 to 60 years. All of them completed the study period. The baseline demographic characteristics of the patients of our study recorded a mean age of 49.2 years. The disease duration was from 0.5 to 5 years, with a mean of 2.63 years. The weights of those patients ranged between 50 and 111.6 kg, with an average of 83.4 kg. Their heights were between 148 and 175 cm, with an average of 156.1 cm, and their BMI ranged between 26.8 and 51.8, with an average value of 35.37 (Table 1).

Table 1 Demographic characteristics of patients

	Mean (minimum–maximum)
Sex	
Female	24
Male	6
Age (year)	49.2 (38/60)
Weight (kg)	83.4 (50/111.6)
Height (cm)	156.1 (148/175)
BMI (kg/m^2)	35.37 (26.8/51.8)
Duration (year)	2.63 (0.5/5)

After laser therapy, there was a decrease in the mean value of VAS from 7.66±2.06 to 3.33±2.16, there was a decreased in the mean value of number of tender point (NTP) from 4.8±2.1 to 1.09±0.93, there was a decrease in the mean value of timed up and go test from 63.2±25 to 51.4±16.4, there was a decrease in the mean value of TS from 2.67±0.49 to 0.72±0.67, there was a decrease in the mean value of angle of flexion from 84±25 to 117.3±16.13, there was a decrease in the mean value of distance between hip and heel (cm) from 35.87±8.3 to 22.67±6.39, there was a decrease in the mean value of WOMAC from 58.13±19 to 21.93±13.47, and finally, there was a decrease in the mean value of Liquesce Index from 12.56±3.27 to 5.473±3.13. Pain on VAS, NTPs, TS, angle of knee flexion, heel to hip distance, WOMAC score, and Liquesce Index showed significant improvement after treatment ($P<0.05$). Timed up and go test was decreased after laser sessions, but its improvement was insignificant statistically (Table 2).

Table 2 Clinical characteristics of patients with knee osteoarthritis before and after treatment

	Before treatment	After treatment
VAS	7.66±2.06	3.33±2.16*
NTP	4.8±2.1	1.09±0.93*
Timed up and go test (s)	63.2±25	51.4±16.4
TS	2.67±0.49	0.72±0.67*
Angle of flexion	84±25	117.3±16.13*
Distance between hip and heel (cm)	35.87±8.3	22.67±6.39*
WOMAC	58.13±19	21.93±13.47*
Lequesne Index	12.56±3.27	5.473±3.13*

All data are presented as mean±SD. NTP, number of tender points; TS, tenderness score; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.
*Significant difference than before treatment at *P* value less than or equal to 0.05, using Wilcoxon signed-rank test.

In addition, laser resulted in an improvement in the immunological status, which achieved an elevation of the mean value of enkephalin from 398±87 to 510±194, and there was an elevation of the mean value of anti-inflammatory cytokines (IL-4) from 201±66 to 314 ±121. Laser showed significant improvement after treatment ($P<0.05$) (Table 3).

Table 3 Laboratory parameters of patients with knee osteoarthritis before and after treatment with laser

	Before treatment	After treatment
Serum enkephalin (pg/ml)	87±396	194±510*
Serum IL-4 (ng/l)	66±201	121±314*

All data are presented as mean±SD. IL-4, interleukin 4.
*Significant difference than before treatment at *P* value less than or equal to 0.05, using Wilcoxon signed-rank test.

Low-level laser therapy gave improvement regarding pain intensity, disability, and quality of life. Laboratory parameter measurement gave an idea about mechanism of action and chemical changes occurring with laser.

Discussion

In our single-case interventional study, 30 patients diagnosed with stage 2 or 3 knee osteoarthritis had been treated with laser acupuncture for 12 sessions (three sessions per week). Low-level power laser (wavelength 905 nm) with an energy of 6 J was directed to each of the seven acupuncture points: ST 35, ST 36, Sp 9, Sp 10, Sp 6, GB 34, and liv3.

Pain on VAS, NTP, TS, angle of knee flexion, heel to hip distance, WOMAC score, and Lequesne Index showed a significant improvement in 30 patients just after the end of the last session of laser acupuncture. A meta-analysis of randomized placebo controlled trials assessed the clinical efficiency of laser acupuncture in knee osteoarthritis and showed that improvement of pain on VAS does not last more than 2 to 3 weeks after the end of the therapy [23]. On the contrary, Law *et al.* [11] reported in their meta-analysis study that a positive laser acupuncture effect on pain (VAS) was more significant 6 months after termination of laser sessions.

Laser acupuncture has an anti-inflammatory effect that helps decrease pain in patients with knee osteoarthritis. This is achieved by reducing metalloproteinase 3 and

13 enzymes, pro-inflammatory IL-1b, IL-6, tumor necrosis factor alpha, and prostaglandin E2 [24]. Laser acupuncture increased collagen II, growth factor beta, and aggrecan, enhancing cartilage regeneration. It increases serum levels of nitric oxide leading to vasodilation, enriching blood circulation in the knee joint [1].

Pallotta *et al.* [25] performed a study evaluating the effect of laser acupuncture (wavelength 810 nm) in rats having knee osteoarthritis with signs of inflammation. They concluded that the laser significantly increases cyclooxygenase 1 and 2, which inhibit and decrease many inflammatory makers such as myeloperoxidase and IL-1 and IL-6.

Low-power laser inhibits the neural fibers A and C leading to an increase in the pain threshold. It also enhances the secretion of histamine and bradykinin, which depolarize many nociceptors in the joint. Signals are transmitted to the brain, which increases the productions of opioid neurotransmitters helping reducing pain sensation [26].

Many clinical trials have proven the effectiveness of laser acupuncture in knee osteoarthritis. Helianthi *et al.* [27] conducted a study which concluded that low-power laser significantly alleviates pain on VAS in patients with knee osteoarthritis (grades 2 and 3) more than the control group receiving sham laser. They used gallium-aluminum-arsenide laser with wavelength less than that applied in our study (785 nm). However, the energy used was according to the recommendations of WALT (4 J/point). WALT recommends 4 J/acupoint at least when using 780–860 nm and a minimum of 1 J/point with 905-nm wavelength [13].

Another study showed the efficiency of laser acupuncture in reducing pain on VAS in cases having knee osteoarthritis grades 2, 3, and 4. WOMAC and Lequesne indices were significantly improved for 6 months after cessation of the therapy. GAALAS (904 nm) was used, and 3 J/point was applied [28].

Many studies have proven to be beneficial in pain management of patients with knee osteoarthritis even with energy dosages less than the minimum required by WALT. However, disability has significantly improved in cases receiving the minimum joules recommended by WALT [29–31].

This study recorded significant improvement and increase of enkephalin and immunoglobulin (IL-4) just after the last session of laser therapy. Thirty years ago, IL-4 was found to reduce inflammation by suppressing the production of tumor necrosis factor-α and IL-1beta. IL-4 is produced by T cells, basophils, eosinophils, mast cells, and natural killer T cells. IL-4 also stimulates the production of IL-1 receptor antagonist enhancing cartilage repair and preventing bone erosion. IL-4 activates macrophages and counteracts inflammation through releasing IL-10 and transforming growth factor-β, promoting wound healing and cell repair [32]. In literature, we found many studies showing that laser acupuncture inhibits pro-inflammatory cytokines such as IL-6 and IL-1beta [24,33]. To our knowledge, this may be the first trial revealing the increase of the anti-inflammatory IL-4 in patients with knee osteoarthritis treated by laser acupuncture.Enkephalin was the first endogenous opioid compound to be discovered in 1975. It has been detected in brainstem, midbrain, globus pallidus, hypothalamus, gray area, amygdala, spinal cord, pituitary gland, and adrenal gland. Activation of opioid receptors, located in the midbrain, by enkephalins inhibits the pain sensation in the gray matter and the reticular paragigantocellularis. The inhibitory signal is propagated to 5-hydroxytryptamine-containing neurons, thus reducing the propagation of pain stimulus to the central nervous system [34,35]. It had been proved that enkephalins inhibit the release of acetylcholine when cholinergic nerves are stimulated, thus decreasing their excitability and helping attenuation of pain sensation [34]. Moreover, enkephalin alleviates pain and reduces inflammation by inhibiting the release of substance P [36]. Substance P is a neuropeptide detected in the brain and spinal cord. Its serum levels tend to increase in conditions causing pain and inflammation [37]. Laser acupuncture was proved to decrease significantly serum level of substance P [26].

Conclusion

According to the results obtained from this study, we can conclude that laser acupuncture is effective in the management of inflammatory grades 2 and 3 knee osteoarthritis associated with improvement of quality of life supported by elevation of endogenous opioid and anti-inflammatory cytokines. Follow-up of cases must be done to be acquainted with the duration during which pain alleviation will persist.

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Conflicts of interest

There are no conflicts of interest.

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