Laser acupuncture for claudication symptoms in peripheral artery disease — Does it work? A randomized trial

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Background: Peripheral artery disease (PAD) receives little attention despite its clinical consequences. Intermittent claudication is the most disturbing symptom of the disease resulting in marked limitations to functional walking performance. Treadmill walking exercise is the first-line non-pharmacological treatment in PAD; however, older patients may be unable to exercise because of the functional disability of the disease itself or deconditioning.

Objective: In an attempt to seek an alternative intervention, this study aimed to assess the effect of laser acupuncture on patient-reported claudication symptoms and walk performance in PAD.

Methods: Thirty male patients with PAD were assigned randomly to a control group (n1 = 15, 64.5 ± 3.5 years old, 25.9 ± 2.6 kg/m²) or a study group (n2 = 15, 65.6 ± 3.3 years old, 25.44 ± 3.1 kg/m²). Inclusion criteria were mild-to-moderate PAD, Fontaine stage II, unilateral or bilateral claudications, and older men. Exclusion criteria were asymptomatic PAD, resting pain, severe or critical limb ischemia, ischemic ulcers, and patients contraindicated for laser therapy. Both groups received pharmacological treatment, but only the study group received gallium aluminum arsenide (GaAlAs) laser therapy at nine acupuncture points, namely, Liver 2 (LV2), Stomach 41 (ST41), Urinary bladder 40 (UB40), UB60, UB61, Gall bladder 30 (GB30), GB34, GB38, and GB40 for 2 days/week and five consecutive weeks. A pen-type laser device was used at a wavelength of 654.7 ± 2 nm, with a power output of 41 ± 3.65 mW, a spot size of 0.08 cm², and an energy density of 2 J/cm², for 60 s/point. The Edinburgh Claudication Questionnaire (ECQ) and the 6-min walk distance...
(6-MWD) were the endpoints of the study. The McNemar–Bowker Test and Generalized Estimating Equations Ordinal Logistic Regression Model were used for the within- and between-group statistical analyses of the categorical data of ECQ, respectively; and a mixed model MANOVA was used for the within- and between-group analyses of the 6-MWD data.

**Results:** There was a significant improvement in patients’ response to ECQ only in the study group compared to the baseline ($p = 0.002$) and the controls ($p < 0.001$) after the intervention. The 6-MWD increased significantly in the study group compared to the baseline ($318 \pm 77 \text{ m versus } 214 \pm 60 \text{ m, } p < 0.001$).

**Conclusion:** The GaAlAs laser acupuncture applied at selected acupoints may be a promising intervention complementary to drug therapy that could help relieve claudication symptoms and improve physical functional performance in older men with PAD (Fontaine stage II). Trials were conducted under the Trial Registration No. PACTR201912698539774.

**Keywords:** Laser acupuncture; peripheral artery disease; intermittent claudication; physical functional performance; 6-min walk distance.

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**Introduction**

The prevalence of peripheral artery disease (PAD) has increased dramatically in the last decade, with more than two-thirds of this global increase in PAD cases being found in low-income and middle-income countries.\(^1\) PAD is the third leading cause of morbidity in people with atherosclerotic vascular disorders after coronary heart disease and stroke; yet, it receives relatively less research attention than the other two morbidities.\(^1\) The most disabling symptom in PAD is the intermittent claudication in the ischemic limbs experienced during walking that leads to impairment in the functional performance of PAD patients and negatively affects their quality of life.\(^2\) The Edinburgh Claudication Questionnaire (ECQ) is a validated screening tool for intermittent claudication and has been used frequently in evaluating the patients with PAD.\(^3,4\) The 6-min walk test (6-MWT) represents one of the most commonly used functional tests and provides highly reliable results in the patients with PAD and intermittent claudication.\(^5,6\)

Recent guidelines for the management of PAD recommend supervised treadmill walking exercise as the first-line treatment for PAD patients with intermittent claudication.\(^7\) However, older patients with PAD may be unable to engage in exercise training programs because of the functional disability from the disease itself or any co-existing cardiopulmonary limitations to exercise. For this reason, interventions other than exercise therapy are to be considered. Acupuncture treatment has shown physiological benefits for improving blood flow in peripheral arteries.\(^8,9\) Low-level laser therapy administered to acupuncture points, or laser acupuncture, is an innovative method of acupuncture, that is non-invasive, pain-free, shorter in duration, and safer than traditional acupuncture without the risks of needle trauma, bleeding, or infection.\(^10\) Low-level laser therapy could have favorable clinical outcomes owing to its vasodilator, anti-inflammatory, analgesic, and metabolic activating effects.\(^11\) In cardiovascular disease research, laser acupuncture has proved effective in reducing the systolic and diastolic blood pressure in hypertensive postmenopausal women\(^12\) and subjects with mild hypertension.\(^13\) Laser acupuncture has also managed to treat obesity, another cardiovascular disease risk factor, as evidenced by significant reductions in body mass index, waist circumference, and total fat percentage.\(^14\) In peripheral artery disease, it has been previously reported that laser acupuncture could increase the ankle-brachial index (ABI) and improve blood flow to the lower limbs,\(^15\) but these findings could be inconclusive as they have been reported from a conference proceeding. More recently, it has been shown that laser acupuncture was a successful intervention for improving the ABI and walking ability in patients with PAD.\(^16\) Yet, no previous study has investigated the potential effect of laser acupuncture on patients’ subjective perception of intermittent claudication in PAD. Therefore, the purpose of this study was to investigate the effects of laser acupuncture, using gallium aluminum arsenide (GaAlAs), in addition to pharmaceutical therapy, on patient-reported intermittent claudication assessed by the ECQ (i.e., as a primary outcome measure) and
the 6-min walk distance (6-MWD) attained during the 6-MWT (i.e., as a secondary outcome measure) in older men with PAD. The results of this study could provide new insights for the clinical application of laser acupuncture in the management of PAD patients, particularly the older population.

Methods

Design
This study was a randomized, controlled, parallel-group, interventional study with an allocation ratio of 1:1.

Ethical considerations
The Ethics Committee of Human Scientific Research of the Faculty of Physical Therapy at Cairo University approved the protocol of this study. This research followed the Declaration of Helsinki. The patients provided informed consent before participation in this study.

Subjects
Overall, 30 male patients with PAD aged between 60 years and 70 years were recruited for this study by referral from a vascular surgeon and a radiologist. The inclusion criteria were older men, mild-to-moderate PAD confirmed by an ABI from 0.5 to 0.9 in one or both legs, and Fontaine stage-II PAD with unilateral or bilateral claudication confirmed by a positive Edinburgh Claudication Questionnaire response (see Appendix). Patients with controlled diabetes or hypertension also were included. The exclusion criteria were asymptomatic PAD, severe PAD, resting pain, acute/critical limb ischemia, ischemic ulcers or gangrene, previous amputation, and patients contraindicated for laser therapy. Eligible participants were randomly assigned to either a control group \((n_1 = 15, 64.5 \pm 3.5 \text{ years old, } 25.9 \pm 2.6 \text{kg/m}^2)\) or a study group \((n_2 = 15, 65.6 \pm 3.3 \text{ years old, } 25.44 \pm 3.1 \text{kg/m}^2)\). Both groups received pharmacological therapy, but only the study group received laser acupuncture. There were no exercises or revascularization therapy received by the patients in both groups throughout the study period. The flow of participants in the two groups is shown in Fig. 1.

Measurements

Age and anthropometric measurements
The age, body weight, and height of the patients were recorded at baseline. Body mass index (BMI) was calculated as the body weight in kg divided by the height in \(m^2\).

Ankle-brachial index (ABI)
For the diagnosis of PAD, the ABI was measured at the baseline during rest using a hand-held 8-MHz Doppler probe. The ABI was measured as the highest systolic blood pressure in the foot (i.e., either in the dorsalis pedis or in the posterior tibial artery) divided by the highest systolic blood pressure in both arms.

Edinburgh claudication questionnaire (ECQ) (primary outcome measure)
The physiotherapist administered the ECQ to the patients at the baseline and after the end of the study (i.e., after five weeks) through face-to-face interview. According to Leng and Fowkes, the ECQ comprises six questions (as shown in Appendix). The ECQ was interpreted according to them as follows: A positive response was recorded if the patient’s answers were “Yes” to question no. (1), “No” to question no. (2), “Yes” to question no. (3), and “Usually disappears in 10 minutes or less” to question no. (5). The patient with a Grade-1 response had to answer “No” to question no. (4), and the patient with a Grade-2 response had to answer “Yes” to question no. (4).

Six-minute walk test/distance (secondary outcome measure)
The physiotherapist conducted the six-minute walk test (6-MWT) for both groups at the baseline and at the end of five weeks. The 6-MWT is described in detail by McDermott et al. The patients were instructed to walk back and forth along a 30-m track as far as possible for 6 min at their own pace. They also were permitted to stop and rest if necessary and were encouraged to resume walking again as early as they could, but the stopwatch continued to run during rest periods. Upon the end of the test, the total distance covered during
6 min was measured in meters as the six-minute walk distance (6-MWD).6

**Interventions**

**Pharmaceutical treatment**

Patients in both groups have received pharmaceutical therapy to treat PAD and medications for co-existing conditions (i.e., Cilostazol, antiplatelet agents, antihypertensive drugs, antidiabetic medication, and lipid-lowering agents) throughout the study period. The pharmaceutical therapy in this study was administered under the direct supervision of a vascular surgeon.

**Laser acupuncture**

(*low-level laser therapy*)

The physiotherapist applied the laser acupuncture only to the study group using GaAlAs laser at specific acupuncture sites on the affected limb(s) with a treatment frequency of 2 days/week and a treatment total duration of five consecutive weeks.15 A laser pen-type device (laser irradiation diode pointer, manufactured in Egypt; S/N: WM 2017) was used for the application of GaAlAs laser at a wavelength of 654.7 ± 2 nm, with a power output of 41 ± 3.65 mW, an energy density of 2 J/cm², and a spot size of 0.08 cm². The application was carried out at nine acupuncture points separately for 60 s per point. The laser probe was held perpendicular to the treated point in direct contact with the skin. The acupoints were selected the same way as previously applied for improving blood flow to the lower extremities in PAD by Cunha et al.,15 as shown in Fig. 2 and Table 1. To be mentioned, there were no unintended effects or harms after the intervention.

**Statistical Analysis**

At baseline, the unpaired t-test was used to analyze the difference in the continuous variables between the two groups, and the Fisher’s exact test was
Table 1. Acupuncture points: locations and rationales.

| Acupuncture points | Location | Point rationale |
|--------------------|----------|-----------------|
| Liver 2 (LV2)      | Located on the dorsal surface of the foot between the first and second toes, and proximal to the margin of the web (at the junction of the red and white skin). | Useful in the case of lack of Qi flow (i.e., energy flow) to the lower limbs, and is a good point to calm the liver and eliminate the irritating liver wind. |
| Stomach 41 (ST41)  | Located on the dorsal surface of the foot at the middle of the transverse crease of the ankle joint, in the depression between the tendons of the extensor digitorum and the extensor hallucis longus, and approximately at the level of the tip of the lateral malleolus. | Useful for the pain of the lower limbs and muscle weakness/atrophy. |
| Urinary bladder 40 (UB40) | Located at the middle of the transverse crease of popliteal fossa between the tendons of the biceps femoris and semitendinosus muscles. | Useful for spasms and weakness of muscles of the lower limbs. |
| Urinary bladder 60 (UB60) | Located behind the lateral malleolus in the depression between the Achilles tendon and the tip of the lateral malleolus. | It is a focal point for ankle pain. |
| Urinary bladder 61 (UB61) | Located on the lateral aspect of the foot, and posterior and inferior to lateral malleolus directly below UB60 by 5 cm (at the junction of the red and white skin). | Pain and weakness of the lower limbs. |
| Gall bladder 30 (GB30) | Located on the lateral side of the buttock at the junction point of the lateral 1/3 and medial 2/3 of a line connecting the greater trochanter and the hiatus of the sacrum. | Weakness and pain of the legs. |
| Gall bladder 34 (GB34) | Located on the lateral aspect of the leg in a depression anterior and inferior to the head of fibula. | Influential point for muscles and is used for all problems in the locomotive system. |
| Gall bladder 38 (GB38) | Located slightly anterior to the anterior border of the fibula above the tip of lateral malleolus by 13 cm (4 cm). | Useful for muscle weakness and pain of the lower limbs. |
| Gall bladder 40 (GB40) | Located anterior and inferior to the external malleolus in a depression corresponding to the lateral aspect of the extensor digitorum longus tendon. | Useful for muscle weakness and pain of the lower limbs. |
used to assess the difference in the unpaired proportions of the nominal variables between the two groups. For the analysis of the ECQ post-intervention, the ECQ data were arranged into three categories: negative, Grade 1, and Grade 2. The McNemar–Bowker Test was used to analyze the difference between the multiple correlated categories of the ECQ within each group after the intervention. The Generalized Estimating Equations (GEE) Ordinal Logistic Regression Model was used to analyze the difference between the multiple correlated categories of the ECQ within each group after the intervention. The Generalized Estimating Equations (GEE) Ordinal Logistic Regression Model was used to analyze the difference in the multinominal (ordinal) categories of the ECQ between the two groups post-intervention. A mixed-design Multivariate Analysis of Variance (MANOVA) was used to compare the 6-MWD within and between the two groups post-intervention. The statistical analysis was conducted using the Statistical Package of Social Sciences (SPSS, Inc., Chicago, IL) software program version 25 for Windows.

Results

The anthropometric and clinical characteristics of the patients in the two groups are shown in Table 2. At the baseline, non-significant differences were present between the two groups in the anthropometric, clinical data, ECQ outcome, or 6-MWD \((p > 0.05)\), as shown in Table 2. In the control group, no significant change was found in any of the measured variables compared to baseline \((p > 0.05)\), as shown in Table 3. In the study group, there were significant improvements in patients’ response to the ECQ \((p = 0.003)\) and the 6-MWD \((p < 0.001)\) compared to baseline after the intervention, as shown in Table 3. Upon comparison of the two groups post-intervention, there was a significant difference only in the patients’ response to the ECQ \((p < 0.001)\) in favor of the study group, as shown in Table 3.

**Discussion**

Our study aimed to investigate the effect of GaAlAs laser acupuncture on patient-reported claudication symptoms and functional walking performance in older patients with PAD using the ECQ and 6-MWT. The main findings of this study...
were as follows: (a) Laser acupuncture in conjunction with pharmaceutical treatment has significantly improved the patient-reported symptoms of the intermittent claudication compared to the pharmaceutical treatment alone in older men with PAD, as evidenced by the significant improvement in patients’ response to the ECQ compared to the baseline values and the controls. (b) Also, walking functional performance/ability has been significantly improved in patients treated by laser acupuncture and pharmaceutical therapy, as evidenced by a significant increase in the 6-MWD compared to the baseline. Our findings could be attributed to a synergistic effect of the low-level laser therapy and the stimulation of the acupoints, both of which can induce their therapeutic benefits by working through different mechanisms. To better understand the underlying mechanisms by which laser acupuncture could relieve claudication symptoms and improve functional walking performance in PAD patients, it is necessary first to address the pathophysiology of the disease responsible for limb claudication and functional disability. The underlying pathophysiology in PAD can be summarized as follows: reduced muscle perfusion during walking because of atherosclerotic occlusion, reduced microcirculation, vascular dysfunction, impaired angiogenesis, muscular metabolic alterations, mitochondrial dysfunction within muscle cells, and local inflammatory activation within the muscles.23

The aforementioned pathophysiological changes can be altered by the low-level laser therapy as explained by the following: (a) For the impaired muscle perfusion and microcirculation in PAD, it has been shown that laser therapy has the advantage of improving blood circulation to the soft tissue.24 Laser acupuncture using GaAlAs at acupuncture points similar to those used in our protocol significantly increased peripheral circulation and lower limb muscle perfusion in PAD patients, as evidenced by a significant improvement in the ankle-brachial index.15,16 Besides, GaAlAs laser therapy produced an enhancement in the microcirculation with marked increases in the diameters of the original blood vessels.24 The physiologic mechanism for improved limb circulation can be laser-induced nitric oxide (NO) release,25 which has a potent vasodilator effect. The vasodilation results in an increase in blood supply, an enhanced bioavailability of nutrients and oxygen to the ischemic muscles, and an accelerated removal of CO2, catabolites, and waste products, resulting in an improvement in muscle contraction. (b) For the metabolic alterations in the ischemic muscles of PAD patients, low-level laser therapy has been found to increase the resistance to fatigue and delay the exhaustion in skeletal muscles,26 which could be attributed to modulation of the redox system within muscle cells.27 Besides, low-level laser therapy has been found to decrease oxidative stress within skeletal muscles induced by exercise27 and reduce the biochemical markers related to skeletal muscle damage.28 (c) Regarding vascular dysfunction involved in the pathophysiology of PAD, low-level laser therapy has been shown to protect the vascular endothelium from the damage induced by continued exposure to inflammatory cytokines.29 These physiological effects could help improve blood flow and metabolic functions within the ischemic muscles resulting in more resistance to fatigue and less perception of limb discomfort during activities.

Apart from the therapeutic effects of low-level laser therapy, our findings could also be attributed to the effect resulting from acupuncture stimulation itself, as mentioned earlier in this section. Acupoints are specific sites where the meridian energy (Jing-Qi in Chinese) radiates onto the superficial tissues and flows into the deeper tissues and visceral organs.30 Evidence showed that the level of NO is elevated in the acupoints/meridians resulting in vasodilatation and an increase in local blood supply rich in substances helping in pain relief.31 Also, it has been proposed that the increased blood perfusion induced by acupuncture stimulation may be related to the inhibition of the sympathetic nerve activity with consequent vasodilation in local microvascular beds.9 This vasodilator response could explain the reduction of the severity in claudication symptoms perceived by our patients treated by laser acupuncture.

Of interest, the acupoints selected for laser acupuncture in our study (i.e., ST41, UB40, UB60, UB61, GB30, GB34, GB38, and GB40) have been reported to be clinically useful in the cases of muscle pain/spasm or weakness of the lower extremities,21,22 shown in Table 1. Thus, we can assume that the reduction in the limb discomfort/intermittent claudication perceived by the patients treated by laser acupuncture and the related increase in the 6-MWD could be explained by laser-induced stimulating/analgesic effect on these points. To add, another point selected for stimulation by laser acupuncture in our study was LV2. This point has been used for the conditions in which there is a lack of
energy flow to the lower extremities.\textsuperscript{20} It has been suggested that the lack of energy flow could be a consequence of an underlying pathology in deeper tissues causing energy restriction and that the stimulation of the acupoints can be beneficial for releasing this energy and regaining energy balance in the body.\textsuperscript{30} Notably, the LV2 has also been used for calming the liver and restoring its homeostasis.\textsuperscript{21}

The liver has an important role in modulating blood volume, restoring a large amount of blood during rest and releasing it during activities to meet the increased demands; besides, the liver has been considered as a source of endurance (i.e., an enhanced function of the liver is manifested by a good endurance and vice versa).\textsuperscript{32}

Finally, as with other studies, our findings should be viewed in light of some limitations. The major limitation in our study was that neither the physiotherapist conducting the research nor the patients receiving the intervention were blinded to the intervention allocation. This was due to the lack of application of sham laser therapy to the controls. There was a difficulty in inducing sham laser acupuncture with visible light radiation. Also, the assessor was not blinded to patient allocation. We do think that the outcomes of this study would have been better interpreted with less probability of bias or psychological conditioning if the study design was double-blinded with a “real” control group receiving the same treatment procedure but without the application of laser stimulus (sham laser therapy). Further, the small number of outcome measures represents another limitation for this study.

Conclusion

We can suggest that the low-level laser therapy using GaAlAs laser applied at specific acupoints could be a promising intervention complementary to pharmaceutical treatment, that could help relieve perceived intermittent claudication symptoms and improve walking performance in older men with PAD (Fontaine stage II), presumably through synergistic physiological mechanisms. Our suggestion may get the attention of other researchers or healthcare professionals interested in complementary or alternative therapy for PAD patients, particularly the older patients who may be unable to engage in physical exercise training because of the functional disability from the disease itself or other co-existing health issues. Nevertheless, future well-designed studies are needed to confirm our findings.

Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

Ahmad Mahdi contributed to the concept and design of the research work, the supervision of research work, the analysis of the data and interpretation of the findings, writing the research paper and revising it critically for important intellectual content, and the final approval of the manuscript to be published. Hasnaa Abdel-Aziz contributed to the concept and design of the research work, the application of laser acupuncture, the evaluation of outcome measures, data collection and acquisition, and the final approval of the manuscript to be published.

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Appendix

The Edinburgh Claudication Questionnaire\textsuperscript{3}

(1) Do you get a pain or discomfort in your leg(s) when you walk? Yes No

If you answered “Yes” to question (1), please answer the following questions. Otherwise you need not continue.

(2) Does this pain ever begin when you are standing still or sitting? Yes No

(3) Do you get it if you walk uphill or hurry? Yes No

(4) Do you get it if you walk at an ordinary pace on the level? Yes No

(5) What happens to it if you stand still?

(a) Usually continues for more than 10 min?
(b) Usually disappears in 10 min or less?

(6) Where do you get this pain or discomfort?

Mark the place(s) with an “X” on the following diagrams:

Definition of positive classification requires all of the following responses: “Yes” to (1), “No” to (2), “Yes” to (3), Grade 1 “No” to (4), and Grade 2 “Yes” to (4). If these criteria are met, a typical claudicant is one who indicates the pain is in the calf, regardless of whether pain is also marked at other sites; a diagnosis of atypical claudication is made when the pain is marked in the thigh or buttock, in the absence of any calf pain. Subjects should not be diagnosed to have claudication if pain is indicated in the hamstrings, feet, shins, joints, or radiates in the absence of any calf pain.

Source: Ref. 33.

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