Lasers in Surgery and Medicine 33:330–338 (2003)

Efficacy of Different Therapy Regimes of Low-Power Laser in Painful Osteoarthritis of the Knee: A Double-Blind and Randomized-Controlled Trial

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Background and Objectives: A prospective, double-blind, randomized, and controlled trial was conducted in patients with knee osteoarthritis (OA) to evaluate the efficacy of infrared low-power Gallium-Arsenide (Ga-As) laser therapy (LPLT) and compared two different laser therapy regimes.
Study Design/Materials and Methods: Ninety patients were randomly assigned to three treatment groups by one of the nontreating authors by drawing 1 of 90 envelopes labeled 'A' (Group I: actual LPLT consisted of 5 minutes, 3 J total dose + exercise; 30 patients), 'B' (Group II: actual LPLT consisted of 3 minutes, 2 J total dose + exercise; 30 patients), and 'C' (Group III: placebo laser group + exercise; 30 patients). All patients received a total of 10 treatments, and exercise therapy program was continued during study (14 weeks). Subjects, physician, and data analysts were unaware of the code for active or placebo laser until the data analysis was complete. All patients were evaluated with respect to pain, degree of active knee flexion, duration of morning stiffness, painless walking distance and duration, and the Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC) at week 0, 6, 10, and 14.
Results: Statistically significant improvements were indicated in respect to all parameters such as pain, function, and quality of life (QoL) measures in the post-therapy period compared to pre-therapy in both active laser groups ($P < 0.01$). Improvements in all parameters of the Group I and in parameters, such as pain and WOMAC of the Group II, were more statistically significant when compared with placebo laser group ($P < 0.05$).
Conclusions: Our study demonstrated that applications of LPLT in different dose and duration have not affected results and both therapy regimes were a safe and effective method in treatment of knee OA. Lasers Surg. Med. 33:330–338, 2003. © 2003 Wiley-Liss, Inc.

Key words: exercise; low-power laser therapy; knee osteoarthritis

INTRODUCTION

Low-power laser therapy (LPLT) was introduced as an alternative noninvasive treatment for osteoarthritis (OA) about 20 years ago, but its effectiveness is still controversial [1,2]. Recently, LPLT has become a popular modality, at least in some countries, in the physical therapy management of musculoskeletal disorders [3,4]. Frequently used lasers include the helium-neon-laser (He-Ne gas) and infrared lasers (with the diode gallium-arsenide (Ga-As) or gallium-aluminum-arsenide (Ga-Al-As)), or combination of both types [5]. Ga-As infrared laser is ideally suited for a blind study since the laser light is invisible and emits no heat or other physically detectable indication when it is activated.

LPLT have been shown to affect many subcellular and cellular processes, although the mechanisms have not been well defined [6]. However, it is important to note that LPLT does not produce significant tissue temperature changes, so any potential physiological effects appear to be nonthermal [7].

LPLT has been used experimentally to treat a wide variety of clinical conditions, but no consensus regarding indication or effectiveness has been established [8–11]. The equipment, experimental designs, and techniques used in the low-energy laser literature are highly variable, and close attention should be paid to therapy parameters when reviewing and comparing these studies. Still, the efficacy of this therapy method is controversial. Many authors have reported significant pain reduction with LPLT in acute and chronic painful conditions such as rheumatoid arthritis, OA, fibromyalgia, postoperative pain, and low-back pain [2,12–15]. However, some have failed to show such an effect in painful musculoskelatal pathologies [16,17].

Recently, in systematic review by Broussseau et al. [18], they stated that the results are conflicting in different studies and may depend on the method of application and

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Accepted 9 September 2003
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI 10.1002/lsm.10236

other features of the LPLT application in OA. Authors, in their review, stated that despite some positive findings, their meta-analysis lacked data on how LPLT effectiveness is affected by four important factors: wavelength, treatment duration of LPLT, dosage, and site of application over nerves instead of joints. In addition, they recommended that there is clearly a need to investigate the effects of these factors on LPLT effectiveness for OA in randomized-controlled clinical trials.

Therefore, a prospective, double blind, randomized, and controlled trial was conducted in patients with knee OA to evaluate the efficacy of infrared Ga-As laser therapy and two different laser therapy regimes employed were compared principally in terms of such parameters as power output, stimulation time, and pulsing frequency.

SUBJECTS AND METHODS

Subjects

Of the total 276 patients referred for the first assessment, 177 did not meet the inclusion criteria and 9 subjects refused to participate; 90 patients were included in the trial. All patients had OA according to American College of Rheumatology criteria, and radiographic evidence of knee OA of Kelgreen–Lawrence Grade II, III, or IV. Outpatients with clinically and X-ray verified uni- or bilateral OA of the knee suffering from exercise-induced pain of at least 6 months duration were invited to participate in the study.

The following patients were excluded: patients with cancer, any acute diseases, uncontrolled diabetes mellitus, untreated hypertension, neurological deficits (motor or sensory), psychotic disorders, dementia, mental retardation, or other organic mental disorders. Patients already on treatment for more than 6 weeks continued their medication with drugs that could interfere with the intensity of pain, such as antidepressants, minor tranquillisers, or analgesics. Patients who had received intra-or periarticular injection therapy or physiotherapy during the 6 weeks were excluded. Patients with secondary OA due to inflammatory joint diseases and patients with routine medical examinations indicated other causes for knee-related pain (e.g., OA of the hip, arterial insufficiency, lumbar root compression) were also excluded.

Ninety patients of whom 18 were men and 72 were women, mean age was 59.43 ± 7.36 years (range 45–81), were included. No dropout was reported after inclusion and randomization due to complications.

Equipment

The active laser was a Ga-As infrared laser, class III b Laser Product, with a wavelength of 904 nm, Frank Line IR 30, Fysiomed Belgium. The same unit was used for the placebo treatment, for which no laser beam was emitted. Laser units were checked by the manufacturer just before the first patient started and after Patient no. 25 of the study. After Patient 50 and 70, the technical medical department at Dicle University checked the units.

Study Design, Randomization, and Blinding

All patients were especially evaluated in respect to age, body mass index, duration of disease, gender, educational level, smoking, pain localization, Heberden's nodules, radiological grade, and osteopenia (by dual Energy X-Ray Absorbtiometry measurements) before the therapy program. Patients were randomly assigned to three treatment groups by one of the nontreating authors by drawing 1 of 90 envelopes labeled A (Group I = actual laser therapies consisted of 5 minutes, 3 J total dose + exercise, 30 patients); B (Group II = actual laser therapies consisted of 3 minutes, 2 J total dose + exercise, 30 patients); and C (Group III = placebo laser group + exercise, 30 patients).

In all groups, the treatment was applied to two points at antero-lateral and antero-medial portals of the knee for 2 weeks, except weekends. Antero-lateral portal is located approximately 1 cm above the lateral joint line and approximately 1 cm lateral to the margin of the patellar tendon. Antero-medial portal is located in a manner similar to that of the antero-lateral portal, that is, 1 cm above the edge of the patellar tendon.

All patients received a total of 10 treatments with laser or placebo laser. In Group I, 5-minute stimulation time, 200-nanosecond maximum pulse duration, 2.5-kHz pulse frequency, 20-W maximum output per pulse, 10-mW average power, 1-cm^2 surface, 3-J total energy, and 30-J accumulated dose were applied. In Group II, 3-minute stimulation time, 200-nanosecond maximum pulse duration, 2.8-kHz pulse frequency, 20-W maximum output per pulse, 11.2-mW average power, 1-cm^2 surface, 2-J total energy, and 20-J accumulated dose were applied. In Group III, the placebo laser emitter was similar to the infrared emitter in appearance but did not emit light. The study was conducted in a double-blind fashion. Subjects and physician were unaware of the code for active or placebo laser until the data analysis was complete but therapist was aware of the code for active or placebo laser. The patients, who were eligible and willing to participate in the study, were assessed by an independent examiner.

In all treatment groups, patients were given exercise therapy program during 14 weeks. These exercises were to be started on the first day of the study. Each patient was questioned and repeatedly encouraged regarding compliance with the exercise program. A straight leg raising exercise was chosen as an isometric quadriceps exercise because it could be continued by elderly patients without difficulty at home. The patients were instructed to lie on their back with the affected leg to be kept straight and the opposite knee flexed. Then, the leg was raised straight, approximately 20 cm off the ground, and maintained for 10 seconds with attention paid to feeling quadriceps muscle contraction. This exercise was repeated 10 times for both legs and patients were instructed to exercise 90 times a day. The number of repetitions was counted and recorded daily in a form provided to the patients. Every follow-up, the patients were seen in the outpatient clinic, and whether they had performed the exercise correctly was checked. No special instructions were given to limit their daily

activities. Exercise treatment could be discontinued within the 14-week period. Compliance with home exercises was moderate to good: 69% of the patients reported exercising often or very often. The physical therapist estimated good compliance for 55% of the patients and moderate compliance for 34%.

The blind settings for patients and the physician were maintained until the last patient had completed the study. As a rule, the same therapist gave all the laser treatments for each patient and another therapist who was unaware of the code for active or placebo laser gave the exercise therapies for each patient. Upon arrival to the first and follow-up appointments, patient characteristics and health information and baseline measures such as demographic characteristics, functioning, pain, and quality of life (QoL) scores were recorded.

The Human Studies Research Committee of the University of Dicle, Diyarbakır approved all procedures, and written informed consent was obtained from each subject prior to inclusion in the study.

Follow-Up Measures

Active laser or placebo laser therapy continued for 2 weeks and exercise continued for 14 weeks. Follow-up measures were evaluated at baseline, 4, 8, and 12 weeks after the last therapy. Study was completed at 14 weeks. Pain at rest, pain at movement, and pain at flexion of the knee were evaluated by visual analog scale (VAS). Pain levels were labeled on a line of 10 categories, 10 points indicating unbearable pain and 0 no pain at all. Active flexion of the knee was measured with goniometry. Duration of morning stiffness in minutes, painless walking distance in meters (m), and duration in minutes were recorded. The health status and the QoL of the patients were measured via the Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC) [19].

Statistics

The data obtained were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). The results are expressed as means $\pm$ standard deviations. Statistical significance was tested using the two-way analysis of variance (ANOVA) for repeated measures of the same group and was tested one way-ANOVA and post hoc Bonferroni's test for multiple group comparisons. In addition, χ^2 or Fisher's exact test, when the cell number is small, were used for categorical variables. The level of statistical significance was set at a two-tailed P-value of 0.05.

RESULTS

Laser therapies continued daily for 2 weeks except weekends (10 treatments for each group) and exercise continued for 14 weeks. Follow-up measures were evaluated at baseline, 4, 8, and 12 weeks after the last laser therapy. Study was completed at 14 weeks.

The mean age of Groups I, II, and III were 58.64 ± 5.92, 59.80 ± 8.03, and 60.52 ± 6.91, respectively. Many of the patients had a low educational level and had Kelgreen–Lawrence Grade II and III. Group I consisted of 25 females and 5 males; there were 23 females and 7 males in Group II, and 24 females and 6 males in Group III. In all groups, mean body mass index and duration of OA were approximately the same. There was no statistically significant difference in any baseline characteristics among all the groups ($P > 0.05$) (Table 1). It was found that there was no statistically significant difference between any of the therapy groups with respect to all clinical outcomes such as pain, functions, and QoL scale scores before therapy (Table 2).

In both actual laser groups, statistically significant improvements were detected in all outcome measures such as pain levels at rest, movement, and flexion, painless walking duration and distance in the post-therapy period when compared to pre-therapy ($P < 0.01$). In the placebo laser group, statistically significant improvements in pain measures except painless walking duration and distance were detected at week 10 and 14 ($P < 0.01$), while statistically significant improvements were not detected in any pain measures at week 6. Improvements of pain measures, such as pain at movement, at rest, and movement in both actual laser groups during trial period, were statistically more significant when compared to placebo laser group ($P < 0.05$) (Fig. 1) whereas there was a statistically significant difference between Group I and placebo laser with respect to painless walking duration and distance (Fig. 2A,B).

There was a statistically significant improvement in the flexion of the knee in all groups except placebo laser group in the post-therapy period compared to the pre-therapy ($P < 0.01$) and a statistically significant improvement in the flexion of the knee in Group I during the study period compared to placebo laser ($P < 0.05$) (Fig. 2C). There were statistically significant improvements in WOMAC score in all groups, except placebo laser at week 6 during the study period, compared to the pre-therapy ($P < 0.01$), and the improvements in the WOMAC score in both of the actual laser groups were statistically significant compared to placebo laser ($P < 0.05$) (Fig. 3A). Statistically significant improvements were detected in morning stiffness scores in three of the groups during the trial period and improvements in morning stiffness in Group I, which consisted of 5 minutes 3 J during the study period, were statistically more significant than that of the placebo laser group ($P < 0.05$) (Fig. 3C) (Table 3).

A statistically significant difference was observed in only pain at flexion at week 6 in favor of Group 2, which consisted of 3 minutes 2 J compared to Group I, which consisted of 5 minutes 3 J ($P < 0.05$).

DISCUSSION

We found significant improvements in patients within the two active therapy groups with respect to all of the parameters such as pain, functioning, and QoL measures, whereas there were significant improvements in patients in the placebo laser group with respect to morning stiffness, pain at movement, pain at rest, pain at flexion, and WOMAC at the end of 14 weeks. Additionally, we did not find any significant differences in placebo laser group with

TABLE 1. Baseline Characteristics of All Subjects With Knee Osteoarthritis Who Received Therapy (Group I = Actual Laser Therapies Consisted of 5 Minutes, 3 J Total Dose + Exercise; Group II = Actual Laser Therapies Consisted of 3 Minutes, 2 J Total Dose + Exercise; Group III = Placebo Laser Group + Exercise)

	Group I (30 patients)	Group II (30 patients)	Group III (30 patients)
Age (year)	58.64 ± 5.92	59.80 ± 8.03	60.52 ± 6.91
Body mass index	31.17 ± 3.77	28.49 ± 3.02	30.27 ± 311
Duration of disease (month)	55.72 ± 50.22	53.12 ± 50.63	62.08 ± 30.64
Sex			
Male	5	7	6
Female	25	23	24
Educational level			
Illiterate	11	12	12
Elementary	13	11	10
High school	3	4	4
University	3	3	4
Smoking (year)			
Never	21	20	18
0–5	3	5	3
6–10	3	2	6
11–19	2	2	2
> 20	1	1	1
Sport activity			
Never	20	22	25
Rarely	7	5	4
Usually	3	3	1
Pain localization			
Medial	6	8	8
Lateral	9	8	7
Patellofemorale	6	4	6
Combination	9	10	9
Systemic disease, yes	16	14	13
Crepitation, yes	23	24	24
Effusion, yes	12	9	11
Involved knee			
Right	3	5	5
Left	4	3	5
Bilaterally	23	22	20
Heberden's nodules, yes	11	10	7
Osteopenia, yes	15	12	13
History, yes	15	12	12
Radiological grade			
Grade II	14	13	13
Grade III	10	12	11
Grade IV	6	5	6

Figures represented mean (and standard deviations), unless stated to be number of cases of the group.
No significant difference between groups (one-way ANOVA for means, and χ^2 or Fisher's exact test for categorical variables).

respect to any outcome measures except morning stiffness at week 6. This finding was one of the most important results of our study. This finding suggests that significant improvements in some outcome measures starting from week 10 in the placebo laser group may rise from the exercise therapy applied rather than the placebo laser therapy.

Treatment guidelines for OA of the knee have considered exercise as an important nonpharmacologic approach. In addition, it directly reduces disability and corrects walking. Quadriceps muscle weakness is usually present in knee OA patients, although this weakness is not directly related to the degree of pain [20]. Muscle exercise therapy has been a

TABLE 2. Comparisons of Clinical Outcomes of All Groups Before Therapy (Group I = Actual Laser Therapies Consisted of 5 Minutes, 3 J Total Dose + Exercise, 30 Patients; Group II = Actual Laser Therapies Consisted of 3 Minutes, 2 J Total Dose + Exercise, 30 Patients; and Group III = Placebo Laser Group + Exercise, 30 Patients)

	Group I	Group II	Group III
Flexion			
Left (degree)	115.80 ± 11.15	119.12 ± 5.89	117.60 ± 5.79
Right (degree)	122.2 ± 05.41	118.60 ± 7.43	118.80 ± 5.45
Morning stiffness (minute)	11.32 ± 6.31	10.60 ± 6.46	11.56 ± 6.75
Painless walking duration (minute)	13.98 ± 15.81	14.56 ± 10.22	14.80 ± 9.71
Painless walking distance (m)	234.8 ± 318.5	254.0 ± 325.6	272.0 ± 276.9
Pain at movement (VAS)	7.32 ± 2.37	7.44 ± 1.38	6.74 ± 1.73
Pain at rest (VAS)	2.70 ± 2.61	2.84 ± 1.31	2.54 ± 1.59
Pain at flexion (VAS)	6.80 ± 2.59	7.08 ± 1.28	6.98 ± 1.41
WOMAC	54.56 ± 13.37	49.52 ± 13.03	50.76 ± 15.42

Values are mean ± standard deviation for all variables. WOMAC, Western Ontario and Mc Master Universities Osteoarthritis Index, HAQ, Health Assessment Questionnaire.
No significant difference between groups (one-way ANOVA).

useful treatment option for the majority of knee OA patients. Although many studies have been published on the effect of muscle exercise on muscle strength and functional ability [21–23], the mechanisms of its effects remains uncertain. Efficacy of home exercises has been demonstrated by several studies [24–26] and the benefits were comparable to the same program performed in hospital [27].

Recent guidelines have advocated the inclusion of exercise in the treatment of OA of the knee. Past reports of exercise as a cause of OA of weight-bearing joints, however, may have reduced implementation among physicians. Lack of standard protocols, outcome measures, and maintenance strategies may also have contributed to poor implementation of exercise [28].

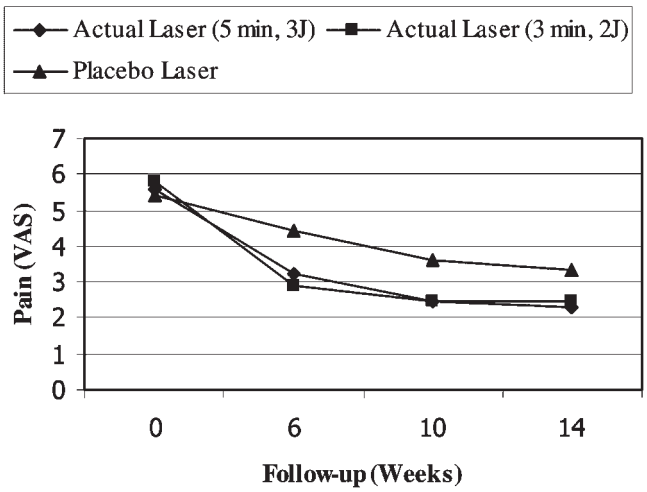

Fig. 1. Change from baseline in total mean scores of pain at movement, at rest, and at knee flexion in patients treated with actual laser or placebo laser. All assessments were made at baseline (0) and at week 6, 10, and 14.

Patients treated with LPLT reported more than 50% pain relief after 4 weeks of 10 sessions treatment. Pain relief continued for an average of 12 weeks after the treatment and patients reported more than 65–70% pain relief after 12 weeks of treatment. Our results are similar to those reported by Trelles et al. [29] and Stelian et al.[30]. Trelles et al.[29] studied the impact of infrared laser on pain, inflammation, joint mobility, and treatment tolerance in patients with OA. Their study showed significant improvement immediately after 4 weeks of twice-weekly treatment and 4 months later. Stelian et al.[30] suggested that in their study patients treated with red or infrared light emitters reported more than 50% pain relief after 10 days of treatment and pain relief continued for an average of 4–6 months after the treatment.

Interestingly, although we observed significant differences with respect to all parameters in favor of both active laser groups, compared to placebo laser group, we observed the same degree of improvement in patients within the two active therapy groups with respect to all outcome parameters except pain during flexion. Thus, our study suggests that variations of the total dose and duration of the application of the same laser equipment have not significantly changed results in painful knee OA and indicates that effects of LPL therapy may be independent from dosage and duration of application. But, this finding should be supported with further clinical investigations

LPLT was introduced as an alternative noninvasive treatment for OA about 20 years ago. Marks et al.[31] reported that LPLT seemed to be an extremely successful method of relieving symptoms in OA and related disability in Russia and Eastern Europe. Similarly, excellent results have been reported for cervical OA, parallel to Walker

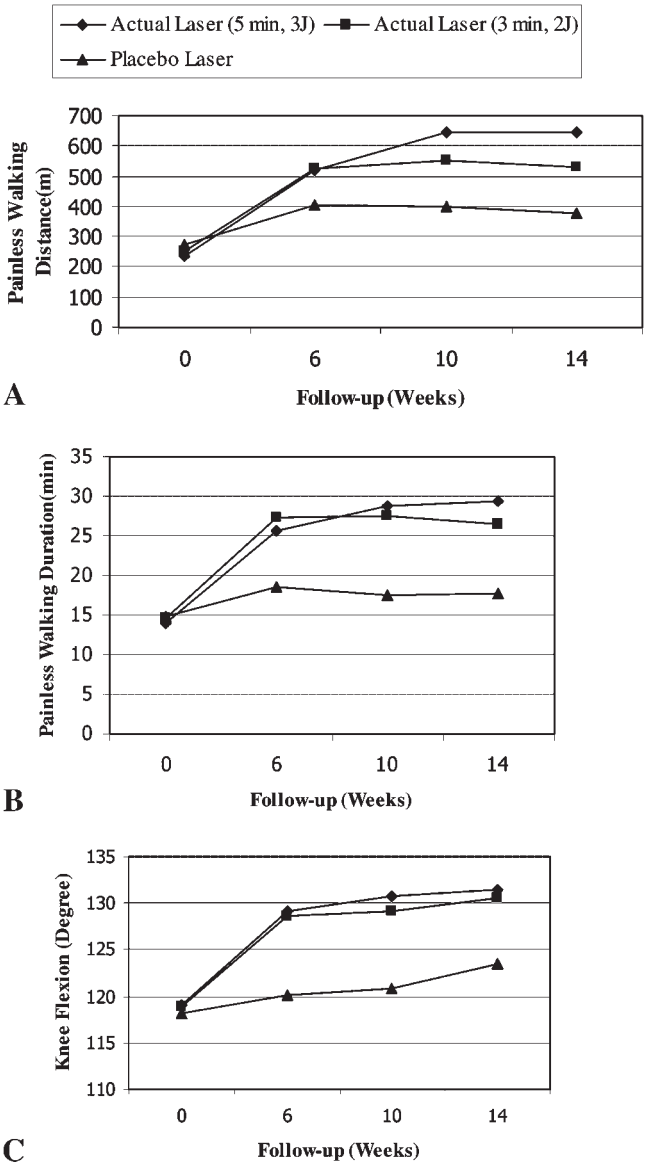

Fig. 2. Mean change from baseline for (**A**) painless walking distance, (**B**) painless walking duration, and (**C**) knee flexion in patients treated with actual laser or placebo laser. All assessments were made at baseline (0) and at week 6, 10, and 14.

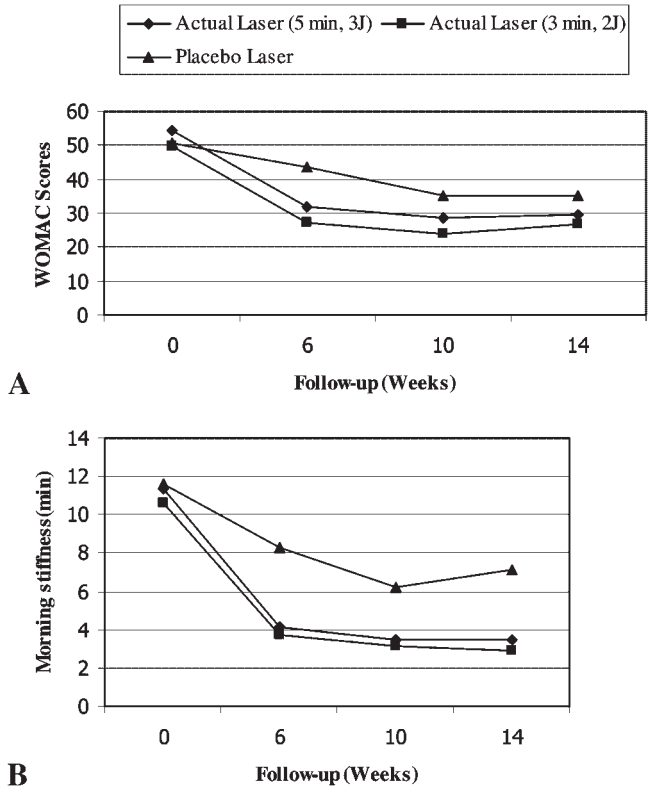

Fig. 3. Mean change from baseline for (**A**) WOMAC scores and for (**B**) morning stiffness in patients treated with actual laser or placebo laser. All assessments were made at baseline (0) and at week 6, 10, and 14.

et al.'s findings on the analgesic effect of LPLT in sciatica and OA [32,33].

The exact mechanism of pain reduction by LPLT is not completely understood. Broussseau et al. [34], in their review, expressed that the success of LPLT in OA may be due to several mechanisms and there has been increasing recognition that LPLT may have physiologic effects mediated by photochemical actions at the cellular level in animal and human tissues. LPLT upregulates cartilage proteoglycan, collagen, noncollagen protein, and DNA synthesis in the absence of histologic or biochemical evidence of enhanced matrix catabolism in animal studies [35,36]. Bassleer et al. [37] concluded that LPLT also has cartilage stimulatory properties in humans. Proteoglycan synthesis, quantified by radioimmunoassay, was significantly increased using an infrared laser (904 nm) [38]. LPLT may possibly be through its positive effects on chondrocyte proliferation and matrix synthesis [31,38,39].

Some investigators believe that OA has an inflammatory component and many investigators have observed an anti-inflammatory effect of LPLT in studies conducted in patients with rheumatoid arthritis [40,41]. A histochemical study has shown a marked increase of prostaglandin I_2 following LPLT, and consequently inhibition of platelet aggregation and vasodilatation [42]. Improvement of local circulation leads to reduction of edema and better oxygenation of tissues and thus may result in reduction of pain. Lack of Na-K-ATPase activity seems to increase nociceptive impulse transmission; an increase in Na-K-ATPase following LPLT may be a factor in pain attenuation [33,43–45]. Kudoh et al. [43] reported a charge of Na-K-ATPase in rat saphenous nerve alter LPLT treatment. Synder-Mackler and Bork [46] reported a statistically significant increase in the latency of the superficial radial nerve in healthy subjects that corresponded to a decrease in sensory nerve conduction velocity after application of LPLT.

TABLE 3. Comparisons of All Groups Clinical Outcomes After Therapy at Week 4, 8, and 12 (Group I = Actual Laser Therapies Consisted of 5 Minutes, 3 J Total Dose + Exercise, 30 Patients; Group II = Actual Laser Therapies Consisted of 3 Minutes, 2 J Total Dose + Exercise, 30 Patients; and Group III = Placebo Laser Group + Exercise; 30 Patients)

	Group I			Group II			Group III		
Variables	4th week	8th week	12th week	4th week	8th week	12th week	4th week	8th week	12th week
Flexion									
Left (degree)	$129.20 \pm 7.17^{a,j}$	$130.00 \pm 9.01^{b,j}$	$131.40 \pm 6.04^{c,j}$	129.40 ± 5.06^{d}	130.00 ± 5.20^{e}	130.80 ± 3.44^{f}	120.40 ± 4.50	119.38 ± 3.45	125.80 ± 3.31
Right (degree)	$129.60 \pm 5.75^{a,j}$	$131.60 \pm 5.90^{b,j}$	$131.60 \pm 4.72^{c,j}$	127.80 ± 5.22^{d}	128.40 ± 5.72^{e}	129.80 ± 4.67^{f}	119.80 ± 3.94	122.40 ± 3.20	121.00 ± 3.53
Morning stiffness (minute)	$4.16 \pm 2.80^{a,j}$	$3.48 \pm 2.85^{b,j}$	$3.44 \pm 2.87^{c,j}$	3.76 ± 3.84^{d}	3.16 ± 2.93^{e}	2.92 ± 3.32^{f}	8.32 ± 4.74^{g}	6.20 ± 5.25^{h}	7.09 ± 4.18^{i}
Painless walking duration (minute)	$25.68 \pm 29.89^{a,j}$	$28.80 \pm 28.90^{b,j}$	$29.40 \pm 28.23^{c,j}$	27.20 ± 10.51^{d}	27.40 ± 10.01^{e}	26.40 ± 10.05^{f}	18.64 ± 11.69	17.40 ± 10.44	17.72 ± 10.17
Painless walking distance (m)	520.0 ± 506.6^{a}	$644.0 \pm 602.1^{b,j}$	$644.0 \pm 449.1^{c,j}$	526.03 ± 49.4^{d}	552.0 ± 213.3^{e}	532.0 ± 229.9^{f}	402.1 ± 310.3	398.1 ± 317.2	380.0 ± 284.3
Pain at movement (VAS)	$4.42 \pm 1.76^{a,j}$	$3.61 \pm 1.42^{b,j}$	3.58 ± 1.12^{c}	$4.36 \pm 0.81^{d,k}$	3.72 ± 0.61^{e}	3.80 ± 0.86^{f}	5.58 ± 1.62	4.58 ± 1.36^{h}	4.30 ± 1.38^{i}
Pain at rest (VAS)	$1.08 \pm 1.41^{a,j}$	$0.54 \pm 0.93^{b,j}$	$0.71 \pm 0.650^{c,j}$	$0.76 \pm 0.72^{d,k}$	$0.64 \pm 0.63^{e,k}$	$0.84 \pm 0.55^{f,k}$	2.30 ± 1.52	1.86 ± 1.22	1.58 ± 0.97
Pain at flexion (VAS)	$4.20 \pm 2.30^{a,j}$	$3.24 \pm 1.63^{b,j}$	$2.68 \pm 1.21^{c,j}$	$3.64 \pm 1.11^{d,k,l}$	$2.96 \pm 0.93^{e,k}$	$2.72 \pm 0.84^{f,k}$	5.42 ± 1.52^{g}	4.34 ± 1.21^{h}	4.02 ± 1.29^{i}
WOMAC	$31.88 \pm 12.82^{a,j}$	$28.60 \pm 9.75^{b,j}$	29.56 ± 8.81^{c}	$27.20 \pm 9.43^{d,k}$	$24.00 \pm 6.52^{e,k}$	$26.68 \pm 9.36^{f,k}$	43.64 ± 11.64	35.32 ± 9.77^{h}	34.96 ± 7.19^{i}

Values are mean ± standard deviation for all variables; where no superscript appears, there is no significant difference.

[a]4th week, [b]8th week, and [c]12th week values of Group I are significantly different from values before therapy of the same group by two-way ANOVA test ($P < 0.01$).

[d]4th week, [e]8th week, and [f]12th week values of Group II are significantly different from values before therapy of the same group by two-way ANOVA test ($P < 0.01$).

[g]4th week, [h]8th week, and [i]12th week values of Group III are significantly different from values before therapy of the same group by two-way ANOVA test ($P < 0.01$).

[j]Follow-up values of Group I are significantly different from the values in the corresponding week of the Group III by one-way ANOVA test ($P < 0.05$).

[k]Follow-up values of Group II are significantly different from the values in the corresponding week of the Group III by one-way ANOVA test ($P < 0.05$).

[l]Follow-up values of Group II are significantly different from the values in the corresponding week of the Group I by one-way ANOVA test ($P < 0.05$).

It has also been suggested that LPLT has effects on peripheral nerve stimulation and microcirculation regulation, interrupting the pain mechanisms and thereby providing analgesia [47]. In some experimental studies, pain thresholds have been shown to increase owing to laser application [48]. Thus, LPLT could produce pain relief by one or a combination of these mechanisms: chondrocyte proliferation, anti-inflammatory effect, circulation enhancement, peripheral nerve stimulation, and analgesic effect.

In the planning stage of this study, we had difficulty in finding readings in the literature related to the use of laser therapy in OA. We found that there were no standard therapy programmes regarding the dose and duration of the laser, and the current publications revealed various results. These varieties in the literature may have arisen from the selection of patients, application of the therapy, and dose, period, and type of laser. In order to get over these problems, we need controlled studies that involve increased patient populations and various therapy alternatives. Hence, in this study, we applied two different therapy regimes with different doses and durations applied with the same laser equipment, and we compared the results of these therapies.

There are many open questions. What is the real mechanism of the therapy? What is the correct dosage per point? We know that the penetration of the skin differed between Ga-As and He-Ne lasers. Most of the energy is absorbed in the first two millimeters. Also there are differences in the technology and in the devices, and differences between the geometry of the laser beam, the divergence of the beam, and the system of collimation of the diode laser equipment. Because of the large number of positive reports and the innocuous nature of the therapies, further clinical evaluation of laser therapy is warranted.

In conclusion, this study revealed that short-period application of LPLT plus exercise is more effective in pain relief and in the improvement of functional ability and QoL than that of placebo laser plus exercise in patients with knee OA. In addition, our study demonstrated that application of LPLT in different doses and durations did not significantly influence the findings and both therapy regimes were safe and effective methods in the treatment of knee OA. Thus, LPLT can be an important adjunct with exercise in the treatment of knee OA, especially in patients with adverse side effects to drug treatment.

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