DOI 10.1515/plm-2012-0030 — Photon Lasers Med 2012; 1(4): 299–307

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Laser therapy applications for osteoarthritis and chronic joint pain – A randomized placebo-controlled clinical trial

Low-Level-Laser-Therapie in der Behandlung von Osteoarthritis und chronischen Schmerzen – Eine randomisierte, plazebokontrollierte klinische Studie

Abstract

Objective: A randomized placebo-controlled clinical trial to evaluate an adjunctive treatment modality for pain associated with knee disorders was conducted utilizing a therapeutic laser system (low energy, non-surgical).
Subjects and methods: The therapeutic laser system utilized a dual wavelength, multiple diode laser cluster probe with five super-pulsed 905 nm near-infrared (NIR) laser diodes, each emitting at 40 mW average power and four continuous wave 660 nm visible (VIS) red laser diodes, each emitting at 25 mW. It was used as an adjunctive modality providing 12 treatments, three times a week to a homogeneous patient population (n=126), in combination with standardized chiropractic techniques, to evaluate effectiveness on subjects presenting with osteoarthritis and knee pain. The primary endpoint was measured by the visual analog scale (VAS) to assess pain levels on a scale of 0–10. The success criteria for an individual patient in this study were identified as an improvement of 30% or more in the VAS from baseline to 12th treatment and/or an improvement of 20% or more in the VAS from baseline to 30-day follow-up evaluation.
Results: The data obtained in the study demonstrated that the present therapeutic laser system provided significant pain relief and osteoarthritic improvements in all primary evaluation criteria, with a statistical and clinical significance of $p<0.01$ in VAS from baseline to the 30-day follow-up.

Keywords: low-level laser therapy; osteoarthritis; osteoarthritic; inflammation; chronic pain; joint pain.

Zusammenfassung

Zielsetzung: Durchführung einer randomisierten, plazebokontrollierten klinischen Studie zur Evaluation einer begleitenden Schmerzbehandlung bei Knieerkrankungen mit einem nicht-chirurgischen therapeutischen Low-Power-Lasersystem.
Patienten und Methode: Zur begleitenden Schmerztherapie kam ein therapeutisches Lasersystem mit dualer Wellenlänge (660 nm/905 nm) zum Einsatz, welches über ein Handstück mit Diodenclustern bestehend aus 5 supergepulsten 905 nm nahinfraroten Laserdioden mit jeweils 40 mW mittlerer Leistung und 4 im sichtbaren Bereich kontinuierlich abstrahlenden 660 nm Laserdioden mit jeweils 25 mW Leistung verfügt. In die Studie eingeschlossen wurden 126 Patienten mit Osteoarthritis und Knieschmerzen, die die Schmerztherapie (12 Behandlungen pro Patient, 3x wöchentliche Anwendung) begleitend zu standardisierten chiropraktischen Techniken erhielten.
Primärer Endpunkt der Studie war der subjektive Schmerzlevel, der anhand der visuellen Analogskala (visual analog scale, VAS; von 1 bis 10) gemessen wurde. Als Erfolgskriterien wurden bestimmt entweder eine 30%-ige Verbesserung der VAS-Werte nach der 12. Behandlung oder eine 20%-ige Verbesserung der VAS-Werte innerhalb der Follow-up-Periode von 30 Tagen jeweils im Vergleich zu den Anfangswerten zu Beginn der Behandlung.
Ergebnisse: Die Studiendaten haben gezeigt, dass mit dem verwendeten therapeutischen Lasersystem eine Schmerzlinderung sowie eine Verbesserung der arthrotischen Beschwerden mit einer statistischen Signifikanz von $p<0.01$ erzielt werden konnte (Reduzierung der VAS-Werte vom Beginn der Therapie bis 30 Tage nach Behandlung).

Schlüsselwörter: Low-Level-Laser-Therapie; Osteoarthritis; arthrotisch; Entzündung; chronischer Schmerz; Gelenkschmerz.

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1 Introduction

Pain, especially its chronic form, is a complex process which deeply affects a person's life, forcing alterations in professional, private, social and other aspects of everyday activities [1]. Knee pain is the third most frequent ache reported today after low back pain and headache, and followed by neck pain, toothache and stomach ache. Osteoarthritis of the knee is the most common type of arthritis and the major cause of chronic musculoskeletal pain and mobility disability in the elderly, and therefore represents a significant burden on healthcare provision [2].

The prevalence, disability and associated costs of knee osteoarthritis are expected to steadily increase over the next 25 years due to aging in the population [3] and concerns about the increasing obesity in developed economies. Although pain and dysfunction from osteoarthritic pain trouble 40% of the adults in the Western world [4, 5], no successful cure for osteoarthritis has been found to date. Common methods of treatment for osteoarthritis of the knee include joint surgery, medication, electrotherapy, muscle strengthening and external mechanical load reducing devices. None of these treatment options has proven consistently successful in clinical practice, although they have all shown varying degrees of success [6].

The impact of a successful clinical trial in the treatment of chronic knee pain using non-invasive therapeutic means that are effective and with no side effects is quite significant [7].

The objective of this randomized placebo-controlled clinical research study was to assess the effectiveness of low-level laser therapy (LLLT) in the treatment of chronic knee pain. In particular, the research study was focused on measuring the effectiveness of LLLT using a combination of super-pulsed and continuous wave (cw) laser diodes. Specifically, the present study was designed to evaluate the usefulness of a multiwavelength diode laser system as an adjunctive modality in the reduction of chronic knee-joint pain.

2 Subjects and methods

2.1 Study design and objectives

The research study consisted of a multi-site placebo-controlled randomized clinical trial. Three private clinics in the cities of Richmond and Charlottesville, Virginia, were used to conduct the treatments. The clinical study protocol was approved by the Texas Applied Biomedical Services (TABS) Institutional Review Board (IRB). After a mandatory 3-month "washout" period for any immunosuppressive drugs, the 126 patients who represented a homogeneous population 21 years of age or older (78 male and 48 female) with chronic knee pain, were randomly assigned to either the "active laser" (group A) or "sham laser" group (group B) as is further described below.

Subjects who presented with the following underlying conditions were excluded from the study:

- Pregnancy
- Pacemakers
- Benign or malignant tumors
- Any subject currently undergoing any systemic medical or surgical treatment or physical therapy for the knee joint.

Patients with pacemakers were excluded from the study largely because of extreme caution of the TABS IRB, as well as safety and liability concerns of the clinical (investigational) sites which are private clinics in Richmond and Charlottesville, Virgina, USA.

The therapeutic laser system was used as an adjunctive modality to standard treatment for knee pain using chiropractic techniques [8]. The chiropractic treatment techniques were consistently applied as a baseline therapy to all participants regardless of their laser assignment in either group A or B. The baseline chiropractic treatment consisted of adjustments as taught in Council of Chiropractic Education accredited schools of chiropractic [8].

The main objectives of the study were to evaluate the safety and efficacy of LLLT in the therapeutic treatment of knee pain. The safety aspect of the study was evaluated in terms of reported clinical complications and/or unanticipated adverse effects associated with generally accepted clinical modalities of treating knee pain. The efficacy of the study was evaluated by the assessment of pain levels via the visual analog scale (VAS) measurement. The VAS has been validated worldwide and is reproducible and accepted by the medical community, especially, neurology and orthopedic specialists [9–12].

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2.2 Low-level laser therapy

The treatment was conducted using a Theralase TLC-1000 therapeutic laser system (Figure 1), a Class 3B medical laser system (Theralase Inc., Toronto, Canada). The system has been formally approved for use by the FDA for the United States of America, Health Canada for Canada, CE marked for use in all 30 member European countries and by various countries throughout South America, the Middle East and Asia-Pacific.

The therapeutic laser system has a dual wavelength, TLC-900 multiple diode laser cluster probe that consists of a cluster of five 905 nm super-pulsed near-infrared (NIR) laser diodes (50,000 mW peak power, up to 100 mW average power, 200 ns pulse width, up to 10,000 Hz frequency) and four 660 nm visible (VIS) red laser diodes (25 mW average power).

The system is used in direct contact with the tissue in order to emit photons non-invasively into the tissue according to a pre-programmed clinical protocol. The characteristics of the therapeutic laser system can be seen in Table 1.

The sham laser (group B) which was used as a control in the clinical study was identical to the therapeutic laser system except it had no NIR optical output and 660 nm 1 mW light emitting diodes (LEDs) were used instead of 660 nm VIS red laser diodes.

The laser probe was positioned for 1 min over each of seven specific locations around the knee joint of the subject encompassing three locations on the lateral aspect of the knee, three locations on the medial aspect of the knee and one location on the posterior aspect of the knee at the midline of the popliteal fossa, and both inferior and superior to the midline of the popliteal fossa. The therapeutic laser system was set to an average power of 60 mW with a treatment time of 60 s per location to produce a dose or energy density of 3.6 J/cm^2 at the skin surface per 905 nm laser diode. The total optical output of the laser probe was therefore 5×60 mW @ 905 nm + 4×25 mW @ 660 nm =400 mW for 60 s or 24 J/cm^2 per location.

All subjects were expected to complete the study program of 12 treatments over a 4-week period at a frequency of three treatments per week. The intervals between treatments were not allowed to be >3 days without dismissal from the randomized controlled trial. Furthermore, patients who were absent for more than two treatments during the 4-week treatment phase were excluded from the clinical study.

2.3 Statistical analysis

For the purposes of statistical analysis, assumptions were made that the missing observations were “missing at random” or were “random dropouts”, which suggests that any missing observations in the clinical data set depend on those observations that have already been observed in the past evaluations, prior to dropping out. Using this methodology, this inferred data set information is conditionally independent of all future

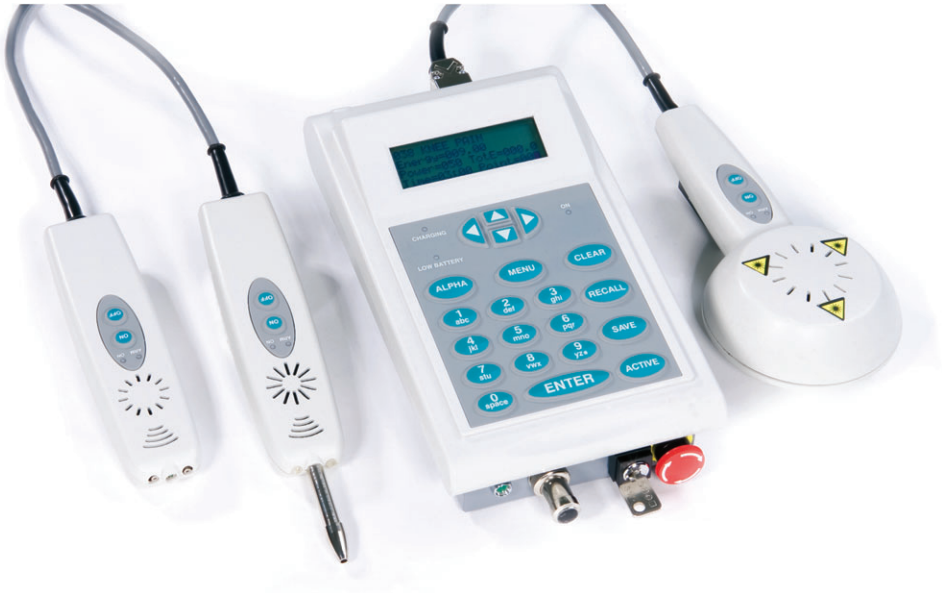

Figure 1 The complete Theralase TLC-1000 therapeutic laser system.

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Input	
Input power	110–120 VAC
Frequency	50/60 Hz
Output	
Maximum average power	100 mW per NIR laser diode, 25 mW per VIS laser diode
Frequency	0–10,000 Hz
Wavelength	905 nm for NIR diodes, 660 nm for VIS diodes
Beam spot size	0.01 cm^2
Pulse duration	200 ns
Energy density	360 J/cm^2/min per TLC-900 multiple laser probe
Class	3B laser diodes
Weight	2 kg
Dimensions	23.3 cm×13.4 cm×8.8 cm

Table 1 Equipment specifications of the Theralase TLC-1000 therapeutic medical laser system and the TLC-900 multiple laser probe.

unobserved/ unrecorded measurements on the outcome of interest [13].

Two strategies of accounting for missing data are used in this analysis:

- *Last observation carried forward:* a method of replacing the missing values or measurements for subjects in the clinical data set, with the subject's last available assessment or evaluation [14]. For this analysis, patients who had baseline evaluations only were excluded, as no inference could be drawn from a subject who was not treated clinically.
- *Imputation using the group mean:* this method replaces the missing values or measurements for subjects in the clinical data set with the mean of the subject's group at a particular point in time [15].

The results are reported by treatment group for each outcome, summarized using descriptive summary measures: expressed as mean with standard deviations (SD) for continuous variables and number (per cent) for categorical variables. The repeated measures of ANalysis Of VAriance (ANOVA) and Student's *t*-test were used to assess the efficacy of the therapeutic laser system based on the VAS pain measures. All statistical tests were performed using two-sided tests at the 0.05 confidence level. In order to be consistent with previous reports, *p*-values are reported to two or three decimal places with values <0.01 reported as $p<0.01$. All statistical analyses were performed using SAS, version 8 (SAS Institute Inc., Cary, NC, USA). The data sets were analyzed to determine both the differences and whether a significant difference exists between the pre-laser treatment and post-laser treatment data for the mean values of these parameters.

The primary endpoint was evaluated by the VAS assessment of pain levels on a scale of 0–10. The success criteria for an individual subject in this study was an improvement of 30% or more in the VAS from baseline to 12th treatment or an improvement of 20% or more in the VAS from baseline to 30-day follow-up evaluation. The success criteria for the study as a whole was that the responder rate for VAS (≥30% improvement at 12th treatment or ≥20% improvement at 30-day follow-up) would be significantly greater in the active therapeutic laser system group (group A) vs. the sham laser group (group B).

The VAS was used to record the subject's current pain level without influencing their response by using descriptive terms of pain severity. The scale is a vertical line. At the bottom end of the scale are the words "No pain" corresponding to a VAS of 0. The words at the top end of the scale are "Worst pain possible" corresponding to a VAS of 10.

The participant was instructed to place a line between the top and bottom ends of the line to indicate their level of pain. A linear scale of 10 equal divisions was placed over the vertical line by the biostatistician to quantify the patient response. Serial responses were compared using the results from the numerical overlay.

The study was designed to include a total of 126 (25–80 years old) subjects equally divided into two groups at three independent study sites. Each study site was allocated 42 sealed coded envelopes containing the coded laser designation to be assigned in a sequential order as eligible subjects were enrolled in the study. At the end of the study four coded envelopes (1A and 3B) were not used, thus ending the study with a total subject enrollment of 122 subjects.

3 Results

Of the 122 subjects enrolled, 82.8% (101/122) completed the study with the 30-day post treatment follow-up

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evaluation. The drop-out rate for this study was 10.7% (13/122) with the "lost to follow-up" rate being 4.9% (6/122). Two of the 122 subject files (1.6%) were not included in the final data analyses due to discrepant/conflicting case report forms. Accountability for the total subject enrollment by individual investigative site is shown in Table 2.

Of the 122 subjects enrolled, 101 subjects completed the 30-day follow-up evaluation. Table 3 shows the breakdown of the subjects from initial enrollment, treatment sessions 1, 3, 6, 9, and 12 and the 30-day post-treatment follow-up evaluation.

A summary of the demographics and baseline values for subjects that completed the study through the 30-day follow-up evaluation is provided in Table 4. The results include the number of subjects in each treatment group, mean baseline values, gender and age range.

A comparison of the endpoint criteria characteristics was analyzed utilizing patient data for all patients completing the 30-day follow-up evaluation. The data as seen in Table 5 show the per cent improvement in the pain level for the active laser group (group A) of 56.8% as compared to 31.3% for the sham laser group (group B), $p<0.01$. The repeat analysis of the mean VAS scores of the two groups (active laser group vs. sham laser group) at the 12th treatment visit (2.9±2.0 vs. 3.9±2.8, $p<0.05$), as well as the differences in the mean VAS scores between the active and sham treatments at the 30-day follow-up evaluation (2.8±2.4 vs. 4.6±2.6, $p<0.01$) is demonstrated in Table 6.

In addition, the successful responder rates for all patients that completed the full 12 laser treatments and the 30-day follow-up evaluations for the end-point parameter for the active laser group (group A) and the sham laser group (group B) are shown in Figure 2.

A set of *t*-tests (ANOVA) for independent samples and repeated measures were used to assess the efficacy of LLLT treatment for subjects with completed data through the 30-day follow-up evaluation. The *t*-tests were performed to assess differences between the active laser and sham laser groups at baseline, at each of the 1st, 3rd, 6th, 9th and 12th treatment and at the 30-day follow-up intervals.

Number of subjects	Total	Site 101	Site 102	Site 103
Allocated	126	42	42	42
Not used	4	0	4	0
Enrolled	122	42	38	42
Drop-outs	13	9	2	2
Discrepant files	2	0	2	0
Lost to follow-up	6	0	4	2
Completed study	101	33	30	38

Table 2 Subject accountability.

The repeated measures assessed longitudinally the treatment sessions and 30-day follow-up intervals. Repeated measure analysis *p*-values=0.04 shows that the differences of VAS scores between the active laser group (group A) and the sham laser group (group B) subjects over time are statistically significant (Figure 3).

The *t*-tests for independent samples and repeated measures analyses of variance (ANOVA) demonstrated statistically significant differences and non-significant trends between subjects treated with the therapeutic laser system (group A) and subjects treated with the sham laser (group B). Table 6 reflects the statistical evidence in support of the efficacy of the therapeutic laser system in the management of pain associated with knee disorders.

Means, SDs, and *t*-test *p*-values for baseline, treatment and follow-up sessions are presented in Table 6. There were statistically significant differences between the active laser and sham laser groups at treatment visit 12 and 30-day follow-up. In addition, there were non-significant trends at baseline and treatment visits 1, 3, 6 and 9. For each of these results, the active laser groups mean VAS scores were lower than the sham laser group mean score.

4 Discussion

The resulting outcome measures obtained from the randomized control clinical trial demonstrate that the therapeutic laser system used in the study provided significant pain relief and improvements in the primary evaluation criteria. The system passed both primary endpoints based on the VAS scores.

The treatment clearly improved the pain level by reducing the VAS scores by 56.8% at the 30-day follow-up evaluation. Utilizing the *t*-test and repeated measures analysis techniques, the *p*-values at the 12th treatment visit and the 30-day follow-up for the VAS showed a statistically significant difference at the 0.05 level between the active laser group (group A) and the sham laser group (group B). The *p*-values between the two groups were <0.05 at 12th visit and <0.01 at the 30-day follow-up evaluation. The reported clinical data clearly demonstrate that the present therapeutic laser system provides significant pain relief from chronic knee pain in this subject population.

Osteoarthritis (OA) is a chronic arthritic disease characterized by pain, local tissue damage and incomplete tissue repair. Historically, cartilage damage was believed to be the hallmark of OA; however, since cartilage is an avascular, aneural tissue, the mechanisms of pain are likely to be more complex and are thus influenced by

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	Laser A (active)		Laser B (sham)		Total (group A+B)	
	Number	%	Number	%	Number	%
Randomized enrollment	62	100.0	60	100.0	122	100.0
Completed treatment 1	62	100.0	57	95.0	119	97.5
Completed treatment 3	59	95.2	55	91.2	114	93.4
Completed treatment 6	55	88.7	49	81.2	104	85.2
Completed treatment 9	55	88.7	50	88.3	105	86.1
Completed treatment 12	55	88.7	50	88.3	105	86.1
30 Day follow-up	53	85.5	48	80.0	101	82.8
Drop-out/terminations	6	9.6	7	11.7	13	10.7
Lost to follow-up	3	4.8	3	5.0	6	4.9
Discrepant data files	0	0	2	3.3	2	1.6

Table 3 Multi-center patient accountability (with respect to enrollment, treatment and follow-up attendance).

non-cartilaginous structures in the joint including the synovium, bone and soft tissue. Imaging studies reveal the presence of synovitis and bone marrow lesions that may help mediate pain relief. The presence of local joint inflammation, altered cartilage and bone turnover in OA implicates a potential role for a range of molecular mediators in OA pain. Mechanisms of pain perception may include the activation and release of local proinflammatory mediators such as prostaglandins and cytokines accompanied by the destruction of tissue, which is mediated by proteases [16].

There is abundant strong evidence that supports these clinical results. The scientific literature strongly suggests that LLLT acts on the cellular mitochondria to amplify its biological effect via increased adenosine triphosphate (ATP) production and the induction of key regulatory transcription factors, as well as anti-apoptosis and pro-survival genes [17, 18]. In tissues, these biological events induce protein synthesis that triggers further effects downstream, such as increased cell proliferation and migration, modulation in the levels of regulatory cytokines, growth factors, modulation of inflammatory mediators, increased tissue oxygenation and remodeling [19–21]. Therefore, inflammation and tissue degeneration, in particular, appear to be strong clinical targets for LLLT.

OA is the most common and most enduring physical impairment of patients in the Western world and age is known to be one of the most important risk factors for this disease. It affects approximately 10% of all people over 60 years of age, with consequent estimated socioeconomic costs of over 60 billion dollars per year in the US alone [22].

Due to the complex pathogenesis of OA, we have utilized dual 660 nm cw and 905 nm super-pulsed wavelengths in this randomized, controlled clinical study. These particular wavelengths have been identified in previous clinical and scientific investigations to activate differing cellular pathways [23–25]. Six hundred and sixty nanometer laser light has been shown to achieve an electronic excitation in most biomolecules, including cytochrome c oxidase [26–28] whereas super-pulsed 905 nm laser light has been shown to induce micro-thermal gradients and selective photothermolysis within mitochondrial structures. The 660 and 905 nm wavelengths used in this clinical study therefore correspond to the absorption and the action spectra optical windows of the key cellular chromophores [17, 18].

Moreover, it is apparent that 660 nm (1.9 eV per photon) and 905 nm (1.3 eV per photon) will have an impact on the mitochondrial chromophores via independent mechanisms, including primary photochemical

Parameter	Laser A (active)	Laser B (sham)
Patients (number)	53	48
Baseline value VAS (mean±SD)	6.16±2.05	6.04±1.89
Male (number)	31	33
Female (number)	22	15
Age range (years)	30–80	25–80

Table 4 Demographic characteristics for subjects completing the 30-day follow-up.

End-point parameter	Laser A (active)		Laser B (sham)	
	Total (number)	Passed (number/%)	Total (number)	Passed (number/%)
VAS	53	30 (56.8)	48	15 (31.3)

Table 5 Successful responder rate. Active laser group (group A) vs. sham laser group (group B), $p<0.01$.

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Time interval	Laser A (active) (n=53) (mean±SD)	Laser B (sham) (n=48) (mean±SD)	*p*-Value
Baseline	6.32±1.43	6.61±1.45	
Treatment visit 1	6.2±2.0	6.0±1.9	0.77
Treatment visit 3	4.9±2.2	5.4±2.1	0.32
Treatment visit 6	4.3±2.1	5.0±2.6	0.10
Treatment visit 9	3.8±2.3	4.5±2.3	0.12
Treatment visit 12	2.9±2.0	3.9±2.8	<0.05
Follow-up 30 day post treatment	2.8±2.4	4.6±2.6	<0.01

Table 6 Summary of VAS. Results of repeat measures analyses.

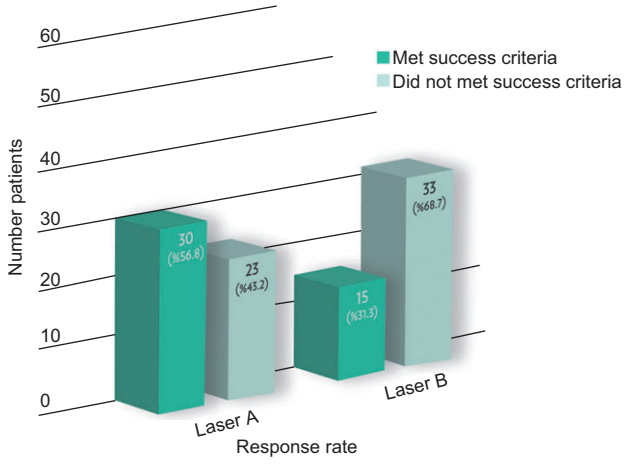

Figure 2 Comparison of responder rate for VAS. Active laser group (group A) vs. sham laser group (group B). The success criteria for an individual patient in this study was identified as an improvement of 30% or more in the VAS from baseline to 12th treatment and/or an improvement of 20% or more in the VAS from baseline to 30-day follow-up evaluation.

reactions and photophysical reactions, respectively [18]. Hence, the combination of 660 and 905 nm light is considered to have a high probability of inducing additive or even synergistic biologic effects, as compared to the wavelengths utilized independently.

Lievens and van der Veen [29] have verified an increase in the fibroblastic proliferation of injuries by using a combination of HeNe (632.8 nm, 5 mW) and GaAs (904 nm, 68.8 mW) lasers. This suggests that the combination of lasers with different wavelengths may achieve better results for the conjunctive tissue recovery. Gigo-Benato et al. [30] have described a possible synergetic effect while using two distinct wavelengths at cw and pulse regimes in the treatment of peripheral nervous injury.

Therefore, one may postulate that wavelength is one of the most important features of laser therapy, since it determines which bio-molecular pathway will trigger the biological responses. Visible radiation at 660 nm triggers a mitochondrial cytochrome c oxidase pathway due to photochemical mechanisms, and invisible 905 nm infrared light will most probably initiate the photophysical reactions at the level of mitochondrial membrane lipids. Therefore, there is a possibility of using both wavelengths in combination with the objective of improving the outcomes of LLLT. However, because it is a relatively new technology, its real effects, effective

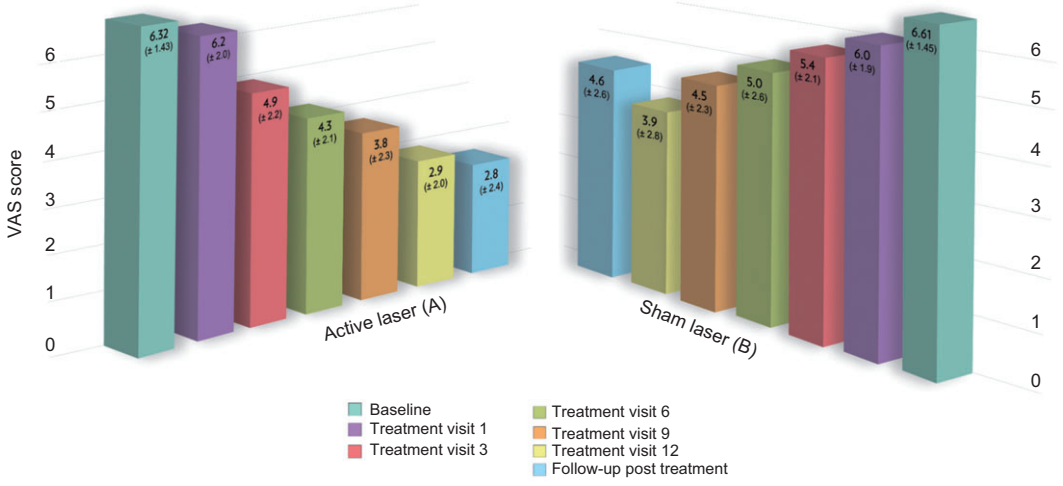

Figure 3 Comparison of mean VAS scores over time. Active laser group (group A) vs. sham laser group (group B).

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applications and limitations are still at the innovative phase.

In the present study, achieving effective therapeutic outcomes via the combined photochemical and photophysical pathways in LLLT was accomplished utilizing both a VIS red cw and a NIR super-pulsed wave. This therapeutic approach facilitates the induction of complementary photochemical and photophysical reactions at the proximal (epidermal-dermal tissue interface) and distal (up to 4 inch/ 10 cm in tissue depth) locations, thus inducing bioregulatory responses that effectively modulate local and systemic pathologic manifestations in the LLLT treated patients.

An important question for future research is which of these photochemical and/or photophysical reactions are directly responsible for certain biological and therapeutic effects? However, the clinical data clearly supports the use of both 660 nm cw VIS and 905 nm super-pulsed NIR laser light based on their role in the modulation of redox mitochondrial function, changes in properties of terminal enzymes and amplification of cellular signaling. These tissues pathways are critical steps in the bioregulatory mechanisms of LLLT [18], as well as providing a significant reduction in chronic pain due to degenerative and inflammatory conditions in our randomized controlled clinical study.

5 Conclusion

The management of chronic pain in patients with OA will always present therapeutic challenges. Anti-inflammatory agents, pharmaceutical painkillers and corticosteroids offer only temporary pain relief with hardly any mid to long-term benefits. Therefore, because of the excellent safety and efficacy profile of the therapeutic laser system under evaluation in this clinical study, it can be stated that non-invasive, super-pulsed laser therapy represents a promising therapeutic alternative for patients with chronic knee pain.

Acknowledgements: This clinical trial was funded by Theralase Inc., Ontario, Canada.

Received July 3, 2012; revised August 23, 2012; accepted August 28, 2012

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