Lasers Med Sci (2013) 28:1183–1188
DOI 10.1007/s10103-012-1219-8

ORIGINAL ARTICLE

Low-level laser therapy in meniscal pathology: a double-blinded placebo-controlled trial

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Received: 27 December 2011 / Accepted: 15 October 2012 / Published online: 24 October 2012

Abstract We performed a randomized, double-blinded, placebo-controlled study (ISRCTN24203769) to assess the effectiveness of low-level laser therapy (LLLT) in patients with meniscal pathology, including only symptomatic patients with tiny focus of grade 3 attenuation (seen only on 0.7 thickness sequences) or intrasubstance tears with spot of grade 3 signal intensity approaching the articular surface. None of the patients in the study group underwent arthroscopy or new magnetic resonance imaging investigation. Paired-samples *t* test was used to detect significant changes in subjective knee pain over the experimental period within groups, and ANOVA was used to detect any significant differences between the two groups. Pain was significantly improved for the LLLT group than for the placebo group (F=154, p<0.0001). Pain scores were significantly better after LLLT. Four (12.5 %) patients did not respond to LLLT. At baseline, the average Lysholm score was 77±4.6 for the LLLT group and 77.2±2.6 for the placebo group (p>0.05). Four weeks after LLLT or placebo therapy, the laser group reported an average Lysholm score of 82.5±4.6, and the placebo group scored 79.0±1.9. At 6 months, the laser group had an average Lysholm score of 82.2±5.7, and after 1 year, they scored 81.6±6.6 (F=14.82923, p=0.002). Treatment with LLLT was associated with a significant decrease of symptoms compared to the placebo group: it should be considered in patients with meniscal tears who do not wish to undergo surgery.

Keywords Menisci · Tear · Healing · Photodynamic

Introduction

Meniscal injuries are the most common traumatic injury in both athletes and nonathletes, second only to osteoarthritis as the cause of knee pain [1, 2]. Involved in load transmission, menisci are exposed to the risk of injury in combined flexion–extension and rotation movement of the knee,

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mostly when the femur rotates on the fixed tibia [3]. A normal meniscus presents with low signal intensity on T1-, PD, T2- (conventional and TSE), GRE, and STIR-weighted images, whereas an increased signal intensity identifies degeneration or tears [4]. In degenerated menisci, the pattern of magnetic resonance imaging (MRI) signal intensity may be graded on the basis of the signal morphology [2–10] (Table 1).

In the last few decades, laser therapy has become popular in the management of soft tissue injuries and other painful conditions. Laser therapy is increasingly common, but the scientific evidence to support its use is still uncertain [11]. At present, low-level laser therapy (LLLT) is used to promote wound healing, reduce pain, decrease inflammatory status, and accelerate recovery after a musculoskeletal injury [12–18]. However, the actual effectiveness is still unknown [11]. LLLT has not yet been used to manage symptomatic meniscal disorders.

We performed a randomized, double-blinded, placebo-controlled study to assess the effectiveness of the application of LLLT in patients with knee pain related to meniscal pathology. We only included symptomatic patients with tiny focus of grade 3 attenuation (seen only on 0.7 thickness sequences) or intrasubstance tears with spot of grade 3 signal intensity approaching the articular surface.

Materials and methods

From January 2009 to February 2011, participants were recruited from the Sports Medicine Clinic in Thessaloniki, Greece. All procedures were approved by the local ethics committee, and the trial was registered with number ISRCTN24203769. Prior to participating in the study, all the patients gave an informed consent according to the Declaration of Helsinki. One hundred-fifty subjects were enrolled in our double-blinded placebo-controlled trial (Table 2).

Selection criteria

We included patients with unilateral medial knee pain for more than 6 weeks and excluded patients with bilateral or lateral knee pain, history of major knee trauma or knee surgery, diagnosis of rheumatoid arthritis, hemophilia, amyloidosis, seronegative arthritis, psoriasis, or gout.

Study design

All patients underwent clinical examination and MRI investigation (Magnetom Essenza 1.5 T Siemens, Erlangen, Germany). A knee MRI protocol was used, consisting of a proton density 3D Spair sequence 0.7 mm thick (distance factor 10) and coronal T1-weighted and sagittal T2 MED sequences 4 mm thick with a distance factor of 20. A single fully trained radiologist with a special interest in musculoskeletal imaging reviewed the MRI scans of each patient. MRI inclusion and exclusion criteria are summarized in Table 3. On the basis of the MRI findings, we included only symptomatic patients with tiny focus of grade 3 attenuation (seen only on 0.7 thickness sequences) or intrasubstance

Table 1 MRI meniscal abnormality grades

MRI meniscal grades	Description
Grade 1	Focal or globular intrasubstance increased signal intensity.
	Foci of early mucinous degeneration and chondrocyte-deficient or hypocellular regions at histology [3, 4]
	Usually observed in response to mechanical loading and degeneration
	May be asymptomatic and not clinically relevant
Grade 2	Horizontal linear intrasubstance increased signal intensity
	Not involving an articular meniscal surface
	Microscopic clefting and collagen fragmentation may be noted in hypocellular regions of the fibrocartilaginous matrix
	Usually asymptomatic [2]
	Usually occur in the posterior horn of the medial meniscus [2, 5]
	Grade 2 signal intensity and discoid menisci may represent cystic areas or cavities of mucinous degeneration, which can be symptomatic and may require partial meniscectomy [2]
	Not an indication for surgery, even when symptomatic
Grade 3	There is an area of fluid signal intensity involving at least one articular surface
	<5 % of cases confined as intrasubstance cleavage or closed tears [6]
	Intrasubstance tears may be painful [7, 8].
	Require arthroscopic management

Table 2 Demographics of all participants

	Demographic information for all study participants
Number of participants	64
Gender, *n* female/male	44/20
Age, years	42±11 (35–62)

Values are mean±SD or mean (range)

tears with spot of grade 3 signal intensity approaching the articular surface (64 patients; 20 males and 44 females, mean age 42±11 years, range 35 to 62 years)

After enrollment, patients were randomly assigned to receive LLLT (n=32) twice per week for the first 3 weeks and once per week for the next 3 weeks (giving a total of nine sessions) or identical placebo therapy (n=32). Randomization was performed using a computer-generated list, and each patient was given a badge number.

LLLT was administered using a GaAs laser with an infrared wavelength of 904 nm (Irradia Medical Laser, M/D Laser Professional, Stockholm, Sweden) with four infrared diodes by the same blinded experienced physiotherapist. On the laser probe, an A/B switch determined whether active (A) or sham irradiation (B) was given. During the procedure, the laser appeared identical for both active and sham irradiation, since there was no visible aiming beam. Treatment was standard, and continuous irradiation was applied over the anatomic area of the medial meniscus (stationary mode procedure, from point to point). According to our protocol, the medial meniscus was divided into two rows of ten segments of equal size [spots] each, and each spot was irradiated once per session. The output of the laser averaged 240 mW (4×60, Irradia Medical Laser, M/D Laser Professional, Stockholm, Sweden). The laser has a built-in sensor for auto-calibration of the optical output before each application); the frequency of the pulse was 2,400 Hz (anti-inflammatory frequency) and 700 Hz (healing frequency), and the duty cycle of the pulsed modes was 100 %. The spot area was almost 1 cm^2 over the meniscal area, with a power density of 0.24 W/cm^2. Each patient was treated for 420 s per knee and per session (210 s using 2,400 Hz and 210 s using 700 Hz, 10.5 s per point). The dose of active treatment was 2.52 J per point, 100.8 J per knee. The knee to treat with the laser probe in switch position A or B was decided by opening an opaque envelope containing the patient's badge number and the letter A or B. The A/B switch on the laser was switched by a technician, and the medial side was treated every time. Thus, the allocation of patients to groups was concealed from patients, physiotherapist, and observer. The code of the A/B switch positions on the laser probe was known to the technician who was responsible for opening the envelopes and to the physiotherapist who administered the treatment.

Table 3 MRI inclusion and exclusion criteria

MRI inclusion criteria	MRI exclusion criteria
Tiny tears seen only on 0.7 thickness sequences	Meniscal tears seen on classic protocols
	Knee ligament injuries
	Chondromalacia
Intrasubstance tears (with spot of grade 3 SI approaching the articular surface)	Osteochondral lesions
	SONK lesions/insufficiency fractures
	Stress fractures

The subjective knee pain of the 64 symptomatic patients was assessed at baseline and after either therapy using a subjective-based 100-mm visual analog scale (VAS) ranging from 0 (no pain) to 100 (maximal pain) [19]. Participants were also asked to complete the Lysholm Knee Scoring System [20], a knee-specific questionnaire evaluating pain, function, and swelling of the knee (Fig. 1).

Follow-up

At the end of the trial, the placebo group patients were referred either for active LLLT or to an orthopedic surgeon, according to their own choice. Follow-up of the patients in the laser group was undertaken at 6 months and 1 year through direct face-to-face contact with the senior sports and exercise physician. A full clinical examination was performed. All the participants were asked to complete also the Lysholm Knee Scoring System. None of the patients in the study group underwent arthroscopy or new MRI investigation.

Statistical analysis

The study statistician reviewed unblinded data for safety and efficacy. The paired-samples t test was used to detect significant changes in subjective knee pain over the experimental period within groups, and ANOVA test was used to detect any significant differences regarding knee pain between the two groups. p values less than 0.05 were considered statistically significant. Statistical analysis was performed with SPSS software, version 16.0 for Windows (SPSS, Chicago, IL, USA).

Results

The demographics of the two groups are reported in Table 2. The two groups did not differ significantly (p=0.000) in age. MRI findings of the study participants are outlined in Table 4.

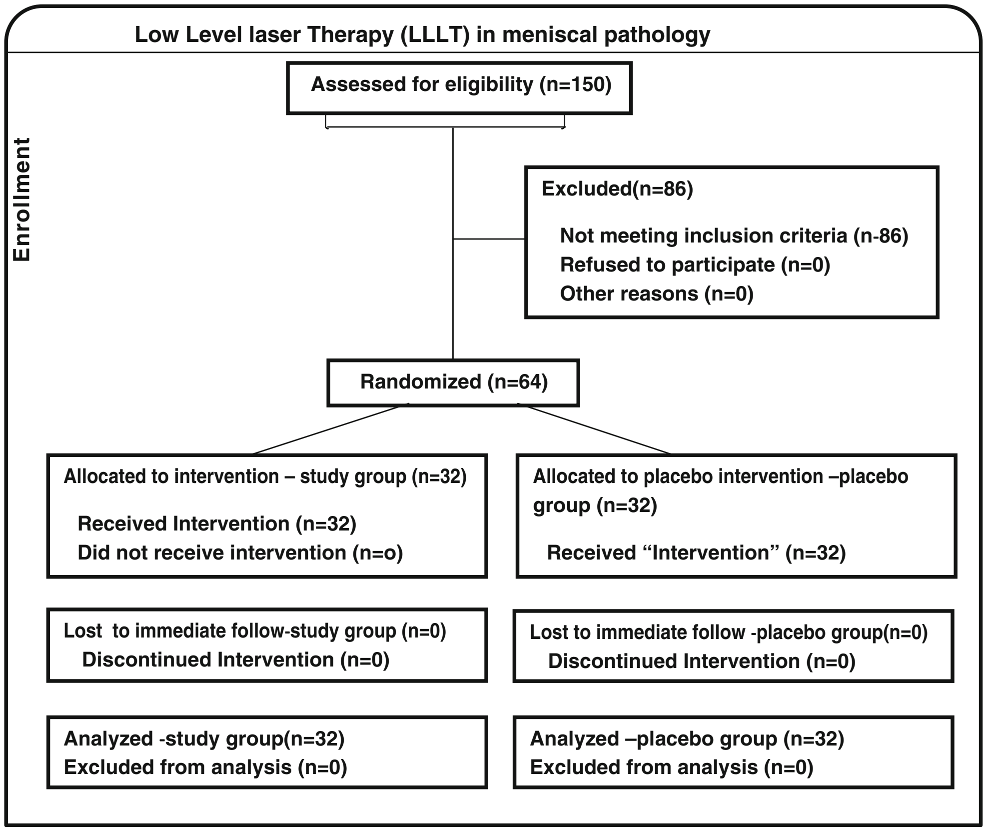

Fig. 1 CONSORT flow plot

On the visual analog scale, pain estimation was significantly improved for the LLLT group compared to the placebo ($F=154$, $p<<0.0001$). Additionally, pain scores were significantly better after LLLT (paired t test, $p<0.0001$) (Table 5). The pain decreased approximately by 65 % 4 weeks after LLLT and by 22 % in the placebo group. Four (12.5 %) patients did not respond to LLLT.

At baseline, the average Lysholm score was 77±4.6 (range, 70–89) for the study group and 77.2±2.6 (range, 72–87) for the placebo group ($p>0.05$). Four weeks after LLLT or placebo therapy, the laser group reported an average Lysholm score of 82.5±4.6 (range, 77–94), and the placebo group scored 79.0±1.9 (range, 77–84). This difference was statistically significant ($F=14.82923$, $p=0.0002$) (Table 5). All the patients tolerated well the application of LLLT, and none of them experienced side effects or adverse reactions (e.g., localized pain or skin irritation).

At 6 months, 2 of 32 patients (6.25 %) had reported a recurrence of the pain. After 1 year, 5 of 32 patients (15.6 %) had reported a recurrence of the pain.

At 6 months, the laser group had an average Lysholm score of 82.2±5.7 (range, 67–95), and after 1 year, they scored 81.6±6.6 (range, 67–95). These values were statistically significant when compared to baseline scores (paired t

Table 4 MRI outcome of study participants

MRI findings at symptomatic side	Number of participants
Tiny tears seen only on 0.7 thickness sequences	38/64
Intrasubstance tears (with spot of grade 3 SI approaching the articular surface)	26/64
Posterior horn/anterior horn	53/11 (out of 64)

Table 5 VAS and Lysholm score at the beginning, after therapy, and during follow-up

Study group	VAS scale, mean±SD	Lysholm score, mean±SD
Before	74.4±4.8	77±4.69
After	26.31±13.53*	82.46±4.58**
6 months	25.5±8.4*	82.21±5.75**
1 year	27±6.3*	81.56±6.6**
Placebo	VAS scale, mean±SD	Lysholm score, mean±SD
Before	74.4±3.99	77.2±2.65
After	58.12±4.51**	79.03±1.92
6 months	75±3.76	72.34±3.02
1 year	76.2±4.21	75±2.76

* $p<<0.0001$; ** $p<0.05$

test, $p=0.00127$ and $p=0.00607$, respectively), and they did not differ significantly when compared to Lysholm scores after LLLT (paired t test, $p=0.3$ and $p=0.07$, respectively). VAS scale scores and Lysholm scores are outlined on Table 5 and graphs 1 and 2 for both groups.

Discussion

Our study aimed to assess the effectiveness of LLLT in patients with knee pain related to meniscal tears. We undertook a double-blinded placebo-control trial, according to WALT scientific recommendations for clinical trials [21]. To our knowledge, this is the only study in humans using GaAs LLLT of 904 nm for the management of meniscal grade 3 changes. According to our selection criteria, we excluded patients with grade 3 signal change at MRI. We only included symptomatic patients with tiny focus of grade 3 attenuation (seen only on 0.7 thickness sequences) or intrasubstance tears with spot of grade 3 signal intensity approaching either articular surface. Our principal finding was a significant decrease of symptoms in the patients after LLLT when compared to the placebo group.

LLLT is widely used to provide analgesia [22, 23]. In addition, LLLT may accelerate the healing of injured tissues [24–29] by promoting wound healing and tissue repair [23, 29–31]. LLLT exerts a positive effect on fibroblast proliferation [32] and collagen synthesis [26].

In the present trial, the analgesic effect of LLLT was probably twofold. Firstly, it could be the result of a healing response stimulated by laser-activated photodynamic processes. LLLT could stimulate cell proliferation and increase proliferation of fibroblasts and fibrochondrocytes in the avascular zone of the meniscus. Normal menisci are composed of spindle-shaped fibroblastic cells on the meniscal surface and rounder fibrochondrocytes in the interior [33–35]. In addition, LLLT could induce micro-neovascularization in the peripheral zone of the meniscus; neovascularization is a sign of healing [35]. LLLT boosts microvascularization [22, 36, 37]. Secondly, LLLT could block the intrameniscal pain receptors. Nerve fibers and sensory receptors have been found mainly in the peripheral, vascular zone of the menisci, mostly in the wider portion of the anterior and posterior horns. Larger nerve fibers are disposed circumferentially in the peripheral zone, whereas smaller branches of nerve fibers maintain a radial disposition into the meniscus. In patients with meniscal tears, part of the pain could arise from the meniscus itself, especially if the tear is peripheral [9]. However, nerve tissue may have a photosensitive component, which could be blocked after exposure to the laser. Therefore, LLLT probably reduces the excitability of these nerve cells [38]. Since the mechanism of action is still unclear, further research is needed. Follow-up MRI could possibly demonstrate changes in menisci after LLLT.

The present trial has some limitations. Firstly, we are unable to state whether the improvement in pain after application of LLLT was accompanied by more favorable MR findings, since the patients did not receive an MRI at follow-up. Secondly, the stimulatory effects of LLLT on meniscal healing could be better investigated if histological analysis had been feasible.

In conclusion, these preliminary results show the potential usefulness of LLLT in the management of patients with painful meniscal lesions, especially in patients with focus of grade 3 attenuation seen only on thin sequences or intrasubstance tears.

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