Physical Therapy Reviews 2001; **6**: 91–99

LOW LEVEL LASER THERAPY FOR TENDINOPATHY. EVIDENCE OF A DOSE–RESPONSE PATTERN

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ABSTRACT

To investigate whether low-level laser therapy (LLLT) can reduce pain from tendinopathy, we performed a review of randomized placebo-controlled trials with LLLT for tendinopathy. The literature search for trials using LLLT published after 1980 was conducted on Medline, Embase, and the Cochrane Library, together with a hand-search of physiotherapy journals in English and Scandinavian languages. Validity assessment of each trial was done according to predefined criteria for location-specific dosage and irradiation of the skin directly overlying the affected tendon. The literature search identified 78 randomized controlled trials with LLLT, of which 20 included tendinopathy. Seven trials were excluded for not meeting validity criteria on treatment procedure or trial design. Twelve of the remaining 13 trials investigated the effect of LLLT for patients with subacute and chronic tendinopathy, and provided a pooled mean effect of 21% [95% confidence interval (CI) 5.9–36.1]. If results from only the nine trials adhering to assumed optimal treatment parameters were included, the mean effect over placebo increased to 32% (95% CI: 23.0–41.0). LLLT can reduce pain in subacute and chronic tendinopathy if a valid treatment procedure and location-specific dose is used.

BACKGROUND

Low level laser therapy (LLLT) was introduced in a clinical randomized controlled trial (RCT) on musculoskeletal pain as early as 1980.[1] In the past two decades, a number of clinical RCTs have been performed with LLLT to treat a variety of musculoskeletal and neurogenic pain conditions. Clinical applications of LLLT have been performed either by direct exposure of the skin overlying the injury, exposure of trigger points or acupuncture points, or of nerves inside or outside the painful area. A broad range of doses (0.0001–38 J/cm^2)[2] has been reported to produce significant effects on musculoskeletal disorders in about one-third of the LLLT trials. Thus, the rationale behind the selection of application technique and treatment parameters, such as power density, size of exposure area, timing or treatment frequency, often remains unclear. However, the majority of LLLT trials have failed to provide successful results while employing doses within the same range as above. Recent review articles[2–4] have concluded that there is little — if any — evidence in favour of LLLT for the treatment of musculoskeletal pain. Several editorials in medical journals have supported the criticism on the clinical use of LLLT.[5–7] However, the number of RCTs with results in favour of LLLT is far too large to be explained by random-chance alone. There is a missing link between the increasing number of successful results from LLLT in the laboratory, and the mediocre results of clinical trials.[2] In an attempt to fill this gap, we decided to investigate whether there exists a dose–response pattern for a subgroup of patients from the clinical trials of tendinopathy, when the laser treatment procedure was similar to the successful laboratory trials. Three validity criteria for clinical laser treatment procedure may be vital for effectiveness. The first is that the tendinopathy is the target for irradiation. Secondly, power density and dose at the target tendon should be similar to that of the laboratory trials; and thirdly, timing and number of treatment sessions should correspond with laboratory procedures.

RATIONALE FOR TREATMENT OF TENDINOPATHY

Acute tendinitis involves an inflammatory response, often induced by repetitive strain, overload or friction of the tendon. One *in vitro* trial has confirmed that excessive repetitive motion can induce fibroblast inflammation.[5] The nature of persisting symptoms are often periodic[6] and associated with degenerative manifestations in tendon histopathology.[7] In subacute and chronic cases increased tendon thickness, degeneration of collagen tissue and presence of hyaline foci within the tendon are evident.[8] Both morphological and biomechanical deterioration of tendon properties have been observed, and some authors suggest that the ending 'itis' is misleading, as degeneration is more apparent at these stages.[7,12–15]

The 'gold standard' for tendinitis treatment of the upper extremity is considered by several reviewers to be steroid injections, or non-steroidal anti-inflammatory drugs (NSAID).[16–18] These chemical agents have primarily short-term effects, while longer-lasting effects (> 6 weeks) are less evident, and often fail to reach significance. Treatment can also be directed at the degenerative changes within the tendon matrix. An *in vitro* trial demonstrated that repetitive motion with low load increases fibroblast metabolism and collagen production.[11] In subacute and chronic cases, results from controlled trials with exercise therapy[12–14] indicate a beneficial effect, and a case-report of symptom reduction also found remission of degenerative changes by ultrasonography after exercise therapy.[13] In our opinion, the natural strategy for reducing tendinopathy pain by LLLT is two-fold, directed both at reduction of inflammation and stimulation of collagen production.

DETERMINATION OF OPTIMAL LLLT DOSE FOR TENDINOPATHY AT TARGET LOCATION

Selection of dose in clinical trials of LLLT seems to be circumstantial, and is either made at random, from the manufacturers' recommendations, or from the authors' empirical basis. In contrast, we assume that there exists an optimal LLLT dose range for the treatment of tendinitis, because laboratory trial reports almost unequivocally have stated that LLLT-effects on collagen tissue are dose-dependent.

We identified ten controlled trials investigating LLLT effect on fibroblast metabolism and in all except one trial[14] significant increases in collagen production were found. The results from five *in vitro* trials on fibroblast cell cultures,[24–28] suggested that optimal power density and dose for increasing collagen production by 34–37% were 4.5–7.5mW/cm^2 and 0.45–0.6 J/cm^2 for continuous 632.8 nm HeNe laser and 820 nm GaAlAs laser respectively. Three *in vivo* trials on sutured soft tissue injuries produced similar results on collagen production with slightly higher doses (1–3.6 J/cm^2) of continuous 632.8 nm HeNe laser, and the same power density.[29–31] In the latter trial,[29] mechanical properties of the laser-exposed tendon were significantly enhanced due to a more adequate collagen composition, i.e. with more neutral salt soluble and insoluble collagen. One *in vivo* trial suggested that pulsed 904 nm GaAs laser only needed 0.4 J/cm^2 to increase fibroblast metabolism.[17]

Interestingly, it appears that it is possible to use too high a power density or dose of LLLT, these doses were found to decrease fibroblast cell metabolism *in vitro*.[20–22] In these trials it was reported that doses lower than 0.1 J/cm^2 did not produce significant results, while doses in excess of 4.5 J/cm^2, and power density higher than 10 mW/cm^2, produced an inhibitory effect on the fibroblast metabolism and collagen production. All these trials employed a treatment frequency of 3–5 times per week for 2–4 weeks.

In *in vitro* trials, higher energy doses have been reported to suppress inflammation.[34–36] This effect was also reported to be dose-dependent, with an optimal range of 1.9–6.3 J/cm^2 and power density of 21.2 mW/cm^2. The upper range limits were not identified. The anti-inflammatory effect was highly significant after 5 days with daily laser treatment.

If these findings are combined, there is an overlap in dose and power density ranges from which the optimal treatment parameters at the target location can be derived:

- Dose: 0.1–3 J/cm^2
- Power density: 5–21 mW/cm^2
- Treatment frequency: 3–5 times per week.

BASIC TECHNICAL AND BIOPHYSICAL BACKGROUND

If we confine consideration of laser parameters to Caucasian patients, there are five physical factors that may determine whether an optimal dose reaches the target in a clinical setting. They can be summarized as:

- Distance from skin surface to target area
- Vascularity of the tissue between skin surface and target
- Volume of injured tissue
- Laser wavelength
- Mode of energy delivery (pulse versus continuous).

Only some of the above variables are known, but they provide a basis for extrapolation that can increase the precision in determining what dose reaches the target. *In vivo* trials in animals have shown that the most important absorption zone in the skin was the dermal vascular plexus barrier.[20] As blood haemoglobin is an important absorber of light,[21] highly vascularized muscle tissue is harder for laser light to penetrate than the more transparent fatty subcutaneous tissue. Improved regeneration after injury of muscle tissue *in vivo* has also been observed, but LLLT doses were about 10 times higher than doses that have been reported optimal for collagen tissue.[22] For tendon injuries that are covered by muscle, it is important that the dose is increased accordingly.

The average distances from the skin to the various tendons have not been definitely established. For the purposes of the current paper, relevant dimensions and distances were estimated by a combination of general anatomical knowledge, diagnostic imaging studies, and a pilot study with ultrasound imaging of some tendons. Typical tendon characteristics are presented in Table 1.

Table 1. Estimation of characteristics of tendons: depth, cross-sectional diameter and area

Tendon	Depth to target tendon (mm)	Sagittal cross sectional diameter of normal tendon (mm)	Typical sagittal area of tendon defect (mm^2)
Plantar fascia	8.0–12.0	3.0–4.0	0.5–8
Achilles	1.5–3.0	4.0–6.0	5–20
Patellar	2.5–4.0	5.0–7.0	10–30
Lateral epicondyle	1.5–2.5	2.0–3.0	0.5–10
Rotator cuff	5.0–10.0	5.0–7.0	5–25

Red (HeNe/632 nm) or infrared (GaAlAs/820 nm) lasers have been used for LLLT because an optical window of penetration with these wavelengths allows about 1/5 of the laser energy to pass the skin barrier. Another type of infrared laser, the 904 nm GaAs laser, has a short, strong, pulse mode of energy delivery, but with a low average output. Through *in vitro* trials, it has been shown that infrared light penetrates slightly better (37% lost at about 2 mm) than visible red laser, which loses the same incident energy at only 0.5 mm.[23] In addition, pulse lasers seem to overcome the skin barrier at lower doses than continuous lasers in *in vivo* trials on animals, i.e. the relative penetration is better.[17,24]

Given the optimal parameters already indicated above, and the data presented in Table 1, acceptable clinical treatment parameter ranges for three laser types and five common forms of tendinopathies are summarized in Table 2.

MATERIALS AND METHODS

Literature search

A literature search was performed on Medline, Embase, Cinahl, PedRo and the Cochrane Controlled Trial Register, as advised by Dickersin *et al.*[25] for both non-clinical controlled trials and randomized controlled clinical trials. Keywords used were: low level laser therapy, low intensity laser therapy, low energy laser therapy, HeNe laser, IR laser, GaAlAs, GaAs, diode laser, tendinitis, collagen, fibroblast, tendon. Hand-searching was also performed in national physiotherapy and medical journals from Norway, Denmark, Sweden, Holland, UK, Canada and Australia. Additional information was gathered from researchers in the field.

Inclusion criteria

The randomized controlled trials were subjected to the following seven inclusion criteria:

- Diagnosis: tendinopathy
- Exposure area: skin overlying site of inflammation or post-inflammatory process in tendon

Table 2. Suggested optimal range of power density given in W/cm^2 and dose in J/cm^2 for the most common tendon injuries when treated by infrared GaAlAs (continuous) lasers with wavelength 820–830 nm, infrared GaAs (pulse) lasers with wavelength 904 nm, and red HeNe (continuous) lasers with wavelength 632 nm respectively

	IR 820–830 nm		IR 904 nm		HeNe 632 nm	
Tendon	Power density	Dose	Power density	Dose	Power density	Dose
Plantar fasciitis	0.010–0.200	1.4–14	0.004–0.200	0.6–6	0.030–0.600	4.2–42
Achilles	0.005–0.100	0.7–7	0.002–0.100	0.3–3	0.010–0.200	1.4–14
Patellar	0.005–0.100	0.7–7	0.002–0.100	0.3–3	0.010–0.200	1.4–14
Epicondylitis	0.005–0.100	0.7–7	0.002–0.100	0.3–3	0.010–0.200	1.4–14
Rotator cuff	0.030–0.600	4.2–42	0.012–0.600	0.4–4	0.120–0.600	12.6–126

- Intensity and dose: according to Table 2
- Treatment frequency and numbers: at least twice weekly and no less than six in total;
- Control group: a control group of at least ten patients that received placebo therapy should be included
- Blinding: patients and outcome assessors should be blinded
- Specific end-points within 2–6 weeks after inclusion.

Intensity and dose calculations

Data on beam diameter and laser output were collected from the relevant manufacturers' manuals. All doses and power densities were calculated according to the following formulae:
Exposure area: Π (0.5 diameter ^{2}) [cm^2]
Mean output: Pulse intensity × pulse duration × pulses per second/second [mW]
Power density: Mean output/exposure area [mW/cm^2]
Dose: Power density × treatment time [J/cm^2]

Outcome measures

We chose pain as an outcome measure, preferably on a continuous scale [visual analogue scale (VAS) etc]. In trials where several aspects of pain were measured, measures of pain involving the physical function of the treated tendon (i.e. pain on isometric muscle contraction) were preferred. When possible, 95 % confidence intervals (CI) were calculated for differences in change between groups from baseline. Effect size was calculated for all trials as the difference (%) in mean change from baseline to end-point between the active treatment group and placebo treatment group.

RESULTS

Results of inclusion procedure

The literature search identified 78 clinical RCTs, of which 20 included tendinitis.

Among these, two trials had to be excluded for exposing trigger points or acupunture points and not exposing the skin directly overlying the injured tendon.[43,44] One trial[27] had to be excluded for only having three patients with tendinitis in the control group. One comparative trial was excluded for not using placebo-control.[28] Another trial[29] had to be excluded for unwittingly giving the placebo group active HeNe laser treatment well within the recommended dose range (2.25 J/cm^2). Another epicondylitis trial[30] treated with skin contact, violating the manufacturer's recommended treatment distance of 10 cm. The optical correction system then left a 'blind' spot of approximately 2.5–3 cm^2 in the middle of the treatment area that was untreated. In the case of lateral epicondylitis, the injured area of the tendon is smaller than this blind spot, and therefore it was judged as unlikely that optimal dose reached the target tendon. Subsequently, the trial was excluded from this meta-analysis. One large comparative trial was excluded because it individualized treatment and lacked a specific end-point.[31] In addition, only a small group received placebo treatment and the results for the placebo group were not presented separately. All excluded trials are presented in Table 3.

Four trials treated the correct spot, but were excluded from analysis for employing treatment parameters outside the acceptable dose and power density range. These four trials and all included trials are presented in Table 4. Three of the listed trials are split in two as they included two locations of tendinopathies and presented the results separately, which gives a total number of 16 listings in the table from 13 publications.

Results of dose and power density calculations

Complete and correct data on power density and dose were reported in only three trials.[36–38] However, in all 16 trials that exposed the skin overlying the injured tendon, sufficient information was reported to perform calculations for the missing data.

Outcome measures

All nine trials[32,38–45] using the suggested optimal treatment were calculated to a weighted mean difference 32% (95 % CI: 23–41) in favour of active LLLT (Fig. 1). Trials without optimal treatment dose/power density,[34,46–48] reported either no significant differences or, in one trial,[36] significantly poorer results from LLLT than placebo. If these four trials were included in the statistical pooling, the effect was reduced to 22.1% better than placebo (Fig. 2). The difference in results between optimal and non-optimal treatment was highly significant ($p < 0.001$). The results from all the nine trials that met our inclusion criteria for optimal parametres are shown in an effect–size plot (Fig. 2).

DISCUSSION

Previous reviews on LLLT have assumed that an optimal laser dose does not exist. Such an assumption

Table 3. List of excluded trials giving first author, year, diagnoses included, result of study and reason for exclusion

Author	Year	Diagnosis	Result	Reason for exclusion
Holmich[28]	1999	Adductor tendinopathy	Exercise therapy significantly better than LLLT	Comparative study, lacks placebo control
Simunovic[31]	1998	Lateral and medial epicondylopathy	Significantly better than placebo	Lacked specific end-point and individualized number of treatments. Only bilateral conditions were given placebo treament, but data for this group were not presented
Mulcahy[27]	1995	Painful musculoskeletal conditions	No significant differences	Lacks credible placebo control as only three patients had tendinitis in placebo group
Haker [30]	1991	Lateral epicondylopathy	No significant differences	Did not irradiate the tendon due to incorrect application procedure
Haker[49]	1990	Lateral epicondylopathy	No significant differences	Did not irradiate tendon, acupuncture points only
Lundeberg[26]	1987	Lateral epicondylopathy	No significant differences	Did not irradiate tendon, acupuncture points only
Siebert[29]	1987	Epicondylopathy mostly	No significant differences	Gave active laser treatment (2.25 J/cm) to placebo group, and consequently lacks placebo control

Table 4. List of included trials giving first author, publication year, and number of participants in trial. Figures given in parentheses indicate the total number of participants when the trial included several diagnoses. Diagnosis, percentual difference in effect between laser and placebo groups with asterisks indicate level of significance if found

Author	Year	No. of patients	Diagnosis	Results (%)	Laser-type (nm)	Power density W/cm^2	Dose J/cm^2
Palmieri[50]	1985	30	Epicondylitis	38 *	904 (P)	0.050	1.8
Gudmundsen[43]	1987	108 (200)	Epicondylitis	39 *	904 (M)	0.030	1.2
Haker[39]	1991	49	Epicondylitis	34 **	904 (P)	0.090	1.2
Vasseljen[32]	1992	30	Epicondylitis	17 *	904 (M)	0.006	3.5
Løgdberg-Andersson[48]	1997	38 (142)	Epicondylitis	31 **	904 (P)	0.090	0.5–1.0
Papadopuolos[36]	1996	29	Epicondylitis	−35	820 (P)	0.714	30
Krasheninnikoff[35]	1994	36	Epicondylitis	0	830 (P)	0.110	13.2
Gudmundsen[43]	1987	92 (200)	Rotator cuff	27 *	904 (M)	0.030	1.2
England[51]	1989	20 (30)	Rotator cuff./ biceps	25 **	904 (P)	0.050	1.2
Vecchio[40]	1993	36	Rotator cuff	21	830 (P)	0.428	42.8
Saunders[33]	1995	34	Rotator cuff	40 *	820 (P)	0.572	30
Løgdberg-Andersson[48]	1997	60 (142)	Rotator cuff	31 *	904 (P)	0.090	0.5–1.0
Meier[52]	1988	58 (110)	Patellar	32 *	904 (M)	0.030	1.5
Meier[52]	1988	52 (110)	Achilles	40 *	904 (M)	0.030	1.5
Darre[53]	1994	89	Achilles	10	830 (P)	0.150	20
Basford[34]	1998	28	Plantar fasciitis	3 (median)	830 (P)	0.955	31.5

Type of laser: (P) = single-point laser; (M) = multidiode laser. Power density calculated as energy delivered per second divided on the skin area exposed by the laser beam, and dose calculated as total energy delivered divided by the area on the skin exposed to the laser beam. Values in italics in the last two columns indicate that the values are outside the limits for optimal range.

*$p < 0.05$

**$p < 0.01$

implies that whichever tissue is injured, or whatever the pathophysiology, the same dose can be employed for treatment. Even well-known variations in the effect, based upon such factors as penetration depths and absorption abilities; distance and type of tissue lying between the laser-exposed skin and the injured

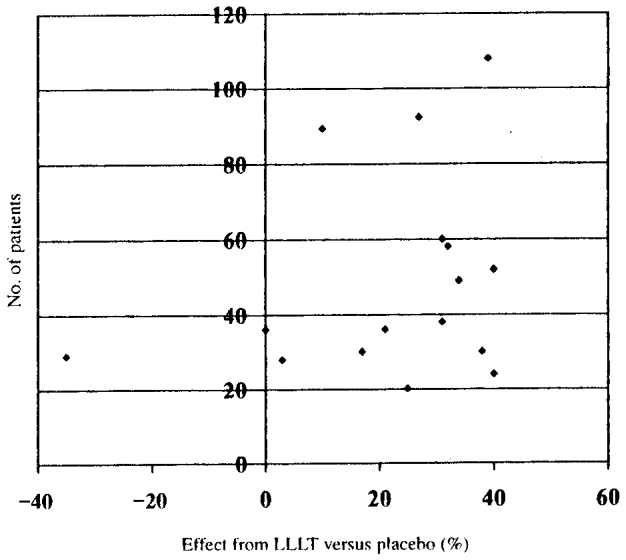

Fig. 1. Effect versus size plot. All trials are plotted by their size (number of patients included) (y-axis) and the difference in percentual effect when compared to placebo (x-axis). The trials without optimal treatment dose are found as the four points farthest to the left-hand side of the figure

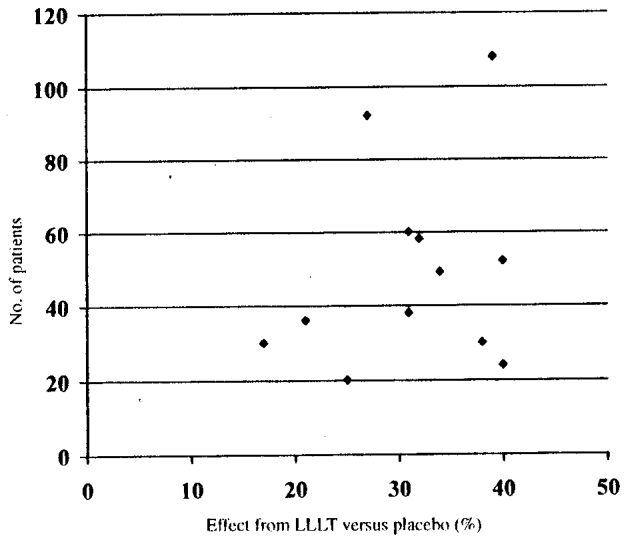

Fig. 2. Trials with optimal treatment are plotted by their size (number of patients included) (y-axis) and the difference in percentual effect when compared to placebo (x-axis)

tissue; and laser type, have been overlooked in many studies. The assumption that there exists a common, 'universal', LLLT dose in the treatment of musculoskeletal disorders is unreasonable, not only in terms of face validity, but also because of the distinct dose–response patterns that laboratory trials on collagen tissue have revealed.

Another common assumption about LLLT has been that only one therapeutic window of optimal dose exists when living tissue is exposed by laser energy.[37] Recent research findings on dose–response relationships may shed new light on the apparent chaos regarding dose and response in the LLLT literature. This assumption has been recently contradicted by a research group that found seven response peaks in a broad dose range for four different cell cultures.[38] These results also imply that there might be ineffective dose intervals within the broad dose range that has been used in clinical trials.

Contrary to previous reviews, we found a dose–response pattern broadly resembling that from the laser laboratory trials. Treatment success was invariably associated with the use of treatment parameters inside our suggested optimal range. In one trial[36] the placebo group improved more than the active LLLT group; the calculated dose and power density at the target tendon was very high in this trial. In fact, these parameters were within a range where inhibitory effects on fibroblast metabolism have been reported.[20,21] The clinical outcome may be explained by inhibition of the natural improvement over time for the intervention group. Thus, this trial adds further support for the identified dose–response pattern. However, even if we seem to have identified an optimal dose range, there are several unanswered questions. One question is which effect is most important: a reduction of inflammatory mediator activity, or an increase in collagen metabolism? Or maybe further improvement can be achieved through variation of laser dose during the rehabilitation process? Another point is that laser therapy has no known effect on the remodelling phase of the injured tendon. How and when should the physical loading of the tendon be performed in order to restructure and strengthen the tendon after laser therapy? These questions can only be answered through controlled dose–response studies, either *in vivo* or in a clinical setting.

One criticism that may arise is that the results of two included trials were reported as not significant by the trial authors.[39,40] In the first trial, the authors chose to base their conclusion on the data from a five-category scale for detection of change. We consider that our choice of using data on a continuous scale for pain-free grip strength is appropriate and more sensitive to clinically relevant differences. From the other trial, disagreement was caused by an incomplete statistical calculation that did not include significance testing of change, which also has been commented upon in a previous review.[41] Testing and calibration of laser output was only performed by the authors in one of the clinical trials.[32] Some authors have pointed out existing discrepancies in laser dosimetry and measured deviations in laser output to be on average up to 40% lower than manufacturers' claims.[52,53] We assume that this problem affects dose and power density similarly in all the trials. With the wide optimal range that we have suggested, this knowledge may only affect one or

two borderline trials, and does not alter our conclusion.

Two findings should be of particular interest for clinicians. The first is that the 904 nm GaAs pulse laser seems to overcome the skin barrier more easily, i.e. without needing the same meticulous variation in dose according to tendon location as is needed with the 820 nm GaAlAs lasers. The second finding is that the small beams and high outputs of the 820 nm lasers might give too high a power density and dose, which possibly inhibits treatment success in cases of superficially situated tendinopathies.

Our findings contradict those of several previous reviews on LLLT. In a recent review on the 904 nm GaAs lasers, de Bie and colleagues[3] found little evidence of effect from this laser. There are several possible reasons for this. The research group in Maastricht around Prof. de Bie is probably the group that has contributed most to an understanding of possible dose–response patterns for LLLT and musculoskeletal pain. Their review, however, did not confine the focus to a single diagnosis, but included a variety of conditions. They did not use dose or power density as inclusion criteria, and did not investigate doses for the different sub-groups of diagnoses. Our literature search is also more recent and extensive, and includes another three large scale trials.[40–42] These trials were also not included for evaluation of effect in the meta-analysis of Gam *et al.*[44]

Poor methodological quality in trials may compromise the conclusions of reviews. Although there is room for much improvement, the general picture of methodological quality in LLLT trials is similar to that of medical interventions on the same diagnoses.[45] Four of the nine included trials with optimal treatment have been assessed previously by others and evaluated as being of good or acceptable methodological quality.[3,41,46]

We decided to present our results in an effect versus size plot, which is visually informative.[47] From the plot, including all trials regardless of dose, one can deduce a slight tendency towards publication bias in favour of small trials publishing negative results. Our effect–size plot resembles that of a 'funnel plot', which is often thought to strengthen the evidence of effect.[47] In fact, all the three largest trials seem to converge towards the calculated mean effect of 32% better than placebo. As this value complies well with the results of the laboratory trials on collagen tissue, this further strengthens our conclusion.

The patient sample mainly consisted of subacute and long-lasting cases of tendinopathy, with a 3–4 month average duration of symptoms and, thus, the review conclusion is limited to this stage in the natural history of tendinitis. Two trial reports suggested that the duration of symptoms was inversely related to treatment success, when symptom duration was dichotomized to either more or less than 3 months.[43,48] Whether LLLT can reduce pain in acute tendinitis/bursitis remains to be evaluated.

CONCLUSION

LLLT has a credible biological action on tendon tissue when used with power density and dose within a suggested optimal range. There is a highly significant correlation between the suggested optimal range and a successful treatment result for subacute tendinitis. An optimal treatment procedure includes laser exposure at the skin directly overlying the injured tendon daily, or every second day, for at least 2–4 weeks. Treatment dose and power density must be differentiated for various tendon locations according to laser type, distance from skin surface and the volume of injured tissue.

Nine randomized controlled clinical LLLT-trials, the majority being of acceptable methodological quality, have shown a significant effect of LLLT of about 32% (95% CI: 23–41,) on pain intensity according to our statistical pooling. LLLT appears to be an effective and safe alternative in the treatment of subacute tendinopathy if a location-specific dose and valid treatment procedure are used. However, a number of questions about LLLT remain unanswered. LLLT's role when used in combination with other interventions, and especially exercises, in the remodelling phase of the tendon repair, may be the most important for future investigations.

ACKNOWLEDGEMENT

This work was supported by grants from the Norwegian Fund for Post-Graduate Education in Physiotherapy.

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