

Review

Blinding Techniques in Randomized Controlled Trials of Laser Therapy: An Overview and Possible Solution

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Low-level laser therapy has evidence accumulating about its effectiveness in a variety of medical conditions. We reviewed 51 double blind randomized controlled trials (RCTs) of laser treatment. Analysis revealed 58% of trials showed benefit of laser over placebo. However, less than 5% of the trials had addressed beam disguise or allocation concealment in the laser machines used. Many of the trials used blinding methods that rely on staff cooperation and are therefore open to interference or bias. This indicates significant deficiencies in laser trial methodology. We report the development and preliminary testing of a novel laser machine that can blind both patient and operator to treatment allocation without staff participation. The new laser machine combines sealed preset and non-bypassable randomization codes, decoy lights and sound, and a conical perspex tip to overcome laser diode glow detection.

Keywords: low-level laser therapy—allocation concealment—treatment blinding

Introduction

Low-level laser therapy in various therapeutic forms is widely used as a medical treatment modality. In general, low-level laser machines deliver laser beams in the 0.1–200 mW power range from the end of a hand held probe, and only require a small battery/charger/timer unit for normal operation: similar to the modified machine photographed in Figs 1A and B. In Australia, one in five general practitioners use acupuncture in their medical practice, including the use of laser on acupuncture points (1). Laser use has been included alongside needle acupuncture in post-graduate physician training in medical acupuncture for more than 15 years, and is reimbursed as a treatment modality by the Australian Health Insurance Commission.

Laser treatment approaches include: laser on acupuncture points (2), laser therapy for direct treatment of joint

pain (3) and the non-contact laser irradiation technique to facilitate skin and wound healing (4). Although the use of laser on acupuncture points is not yet a proven substitute for needles, it does have demonstrated effectiveness in a limited range of acupuncture responsive conditions (5). A small number of randomized controlled trials (RCTs) have demonstrated significant benefits including treatment of; neck pain, (6–9) low back pain, (10) chronic tension headache, (11) fibromyalgia, (12) enuresis, (5) and post-operative vomiting (2).

The advantages of low-level laser over needles include: ease of application, usage in anatomically dangerous areas, and use in needle-phobic patients including children. It is low cost, non-invasive and safe. (13) General advantages of laser use in RCTs include: (i) Laser light is invisible above 770 nm and can be switched off or on without visual recognition by the patient or operator. (ii) Low-level laser has been shown to have a negligible sensory stimulus, i.e. patients have difficulty discerning whether they have received real treatment.

The suitability for trial use has been tested in three double blind RCTs: a small trial by Irvine *et al.* (14) and

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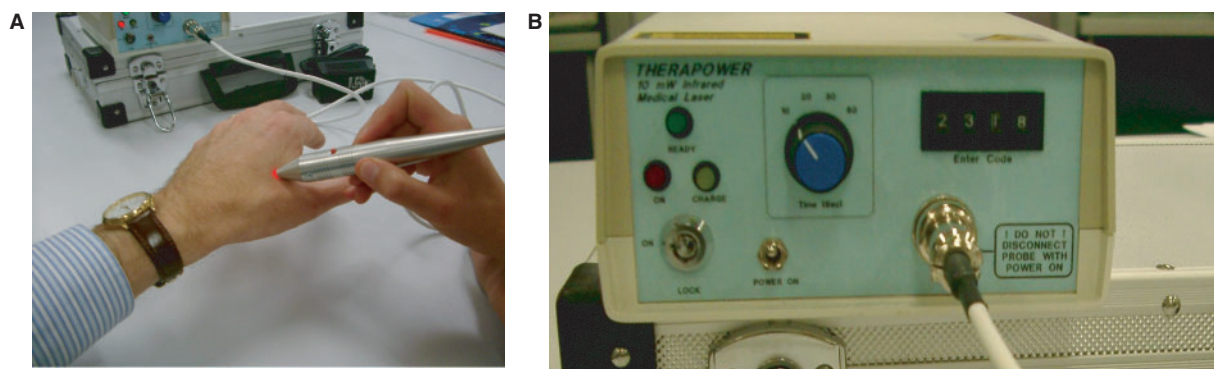


Figure 1. (A) DBL Laser machine in operation for a placebo treatment. Demonstration of laser probe applied to left hand whilst machine is activated. The dummy red light is visible on the skin and is shining out of the end of the probe. The probe is activated by pressing the tiny button visible on the central part of the probe. In this instance, the machine is in full operation, however the invisible infrared laser is switched off as would be the situation for a placebo treatment. The machine activation light on the laser front panel can be seen at the top left of the photograph. Aspect; DBL Laser machine is in the background sitting on carry case. (B) Front panel DBL laser machine. Four-digit patient entry code switch sited in upper right of panel. Indicator lights for machine operation in upper left. Laser probe (white) cord inserted into bottom right panel. Timer switch - central. Manual key lock and power on/off toggle in lower left of panel. Aspect; DBL Laser machine sitting on steel carry case.

two larger trials by Chow ($N = 90$) (15) and Brosseau *et al.* ($N = 88$) (16) have shown that neither the patient nor operator can discern whether they are using a laser or placebo treatment. Therefore when a laser machine is used correctly it offers a useful way to ensure blinding and treatment allocation where difficulties exist with adequate placebos in needle trials (17).

Research Methods and Laser Trials

The most important determinants of well-conducted RCTs are adequacy of allocation concealment and blinding procedures. Allocation concealment refers to a process whereby an unbiased allocation sequence is implemented in a secure manner that prevents foreknowledge by either the clinician, researcher or trial participant (18). Generally, allocation concealment appears to be an important indicator of RCT quality, as an analysis of RCTs found that those trials that do not detail an adequate process for allocation concealment show a 40% increased likelihood of having positive results (19). Therefore, the design of laser machines and processes to ensure allocation concealment and double blinding may be critical to unbiased trial outcomes.

Laser machines delivering visible red light (e.g. using 630 nm laser diodes) are not suitable for double-blind trials because both the patient and operator can see when the laser is switched on. Even invisible lasers have problems in RCTs as the laser diode itself glows when in use. The diode glow can still be seen in the end of the probe whether or not the resultant beam is visible. This leaves open the possibility that participants could gain foreknowledge of treatment allocation and bias the

results. This article reviews the methods of allocation concealment and blinding used in published laser RCTs. We then report the features of a novel laser machine that can blind both patient and operator without the involvement of extra clinical staff, and the results of a small study to test this capacity.

Methods and Results of Literature Review

A literature review was performed with systematic searches of Medline, Embase, Pubmed, Amed, Cinahl, Ciscorn and Cochrane databases. Fifty-one trials of low-level laser therapy were found that were double blind clinical RCTs (Tables 1–4).

Analysis of the 51 RCTs showed 30 positive and 21 negative laser trials. However, laser beam detection or machine randomization had only been modified in less than 5% of these trials. (Table 1) The laser machine described by Toya (6) did address the problem of allocation concealment: a computer was used to turn the laser beam on/off using randomized numbers that were unknown to the operator. This is the only trial using a machine with in-built randomization. The second trial by Krashennikoff *et al.* (20) used a beam filter to preset the laser off or on. However, none of the reviewed trials use a reliable method that addresses the problems of laser diode glow, blinding and allocation concealment in a single laser machine.

The remaining 49 trials (Tables 2–4) used less rigorous methodology for adequate allocation concealment or blinding: 27 trials used identical laser probes or identical laser machines; 17 used on/off switches; eight miscellaneous trials used opaque goggles or other

Table 1. LLLT trials where laser machine modifications have positive aspects that improve blinding procedures.

Trial	Condition	Trial result	Positive aspects	Possible methodology problems
Krasheninnikoff <i>et al.</i> (20), <i>N</i> = 36	Tennis elbow	Negative	Beam filter used	IDLM
Toya <i>et al.</i> (6), <i>N</i> = 115	Musculoskeletal pain	Positive	External computer controlled	GLO

(*N* = 2) Possible methodology problems are: IDLM, Identical laser machine used; GLO, laser diode glow may be visible.

Notes: Total trials = 51; references (6, 10, 20–22, 44, 47, 49, 52) (4, 7–9, 11, 14, 23–43, 45, 46, 48, 51, 53–62).

Trials are classified by primary method of blinding.

All trials use invisible laser treatment beam unless otherwise specified.

All laser machines use decoy sound and light as per normal operation.

Three trials: Lundberg, 1987; Haker, 1990; and Haker, 1991- have been removed because of Institutional rulings on scientific practice.

Table 2. LLLT trials that use identical laser machines (IDLM) or identical laser probes (IDLDP)

Trial	Condition	Result	Possible methodology problems
Basford <i>et al.</i> (21) <i>N</i> = 52	Tennis elbow	Negative	GLO, IDLP, PAT
Basford <i>et al.</i> (10) <i>N</i> = 63	Back pain	Positive	GLO, IDLP, PAT, INC
Basford <i>et al.</i> (22) <i>N</i> = 32	Plantar faciitis	Negative	GLO, IDLP, PAT, INC
Brosseau <i>et al.</i> (23) <i>N</i> = 88	OA Hand	Positive	GLO, IDLP
Carati <i>et al.</i> (24) <i>N</i> = 61	Lymphoedema	Positive	GLO, IDLP
Hansen and Jhoroe (25) <i>N</i> = 40	Oro-facial pain	Negative	GLO, IDLP
Irvine <i>et al.</i> (14) <i>N</i> = 15	Carpal tunnel syndrome	Negative	GLO, IDLP
Laasko <i>et al.</i> (26) <i>N</i> = 56	ACTH/ β -Endorphin release	Positive	GLO, IDLP
Laasko <i>et al.</i> (27) <i>N</i> = 41	Pain level and side effects	Positive	GLO, IDLP
Logdberg-Andersson and Hazel (28) <i>N</i> = 176	Myofacial pain	Positive	GLO, IDLP
Papadopoulos <i>et al.</i> (29) <i>N</i> = 29	Tennis elbow	Negative	GLO, IDLP
Saunders (30) <i>N</i> = 24	Supraspinatus tendonitis	Positive	GLO, IDLP
Quah-Smith <i>et al.</i> (31) <i>N</i> = 30	Depression	Positive	GLO, IDLP
Stelian <i>et al.</i> (32) <i>N</i> = 50	OA Knee pain	Positive	GLO, IDLP
Vecchio <i>et al.</i> (33) <i>N</i> = 35	Shoulder pain	Negative	GLO, IDLP
Bulow and Danneskiold-Samsøe (34) <i>N</i> = 29	OA Knee pain	Negative	GLO, IDLM
Chow <i>et al.</i> (35) <i>N</i> = 90	Neck pain	Positive	GLO, IDLM
Ebneshahidi, <i>et al.</i> (11) <i>N</i> = 50	Headache	Positive	GLO, IDLM
Fernando <i>et al.</i> (36) <i>N</i> = 64	Tooth extraction	Negative	GLO, IDLM
Fukuuchi <i>et al.</i> (37) <i>N</i> = 82	Musculoskeletal pain	Positive	GLO, IDLM
Gallacchi <i>et al.</i> (38) <i>N</i> = 15x8	Neck pain	Negative	GLO, IDLM
Kopera <i>et al.</i> (39) <i>N</i> = 44	Chronic leg ulcers	Negative	GLO, IDLM, PAT
Seidel (8) <i>N</i> = 36	Neck pain	Positive	GLO, IDLM
Soriano (40) <i>N</i> = 85	Low back pain	Positive	GLO, IDLM
Soriano (41) <i>N</i> = 71	Neck pain	Positive	GLO, IDLM, GOG
Vasseljen <i>et al.</i> (42) <i>N</i> = 30	Tennis elbow	Positive	GLO, IDLM
Walker (43) <i>N</i> = 36	Chronic pain	Positive	GLO, IDLM, INC

Other possible methodology problems are included. (*N* = 27).

GLO, Laser diode glow may be visible; IDLP, Identical laser probes; IDLM, Identical laser machines; PAT, Patient cooperation is required; GOG, Goggles are used; INC, Incomplete explanation of method.

Notes: Total trials = 51; references (6, 10, 20–22, 44, 47, 49, 52) (4, 7–9, 11, 14, 23–43, 45, 46, 48, 51, 53–62).

Trials are classified by primary method of blinding.

All trials use invisible laser treatment beam unless otherwise specified.

All laser machines use decoy sound and light as per normal operation.

Three trials: Lundberg, 1987; Haker, 1990; and Haker, 1991- have been removed because of Institutional rulings on scientific practice.

blinding methods. The explanation of blinding was inadequate in eight trials, nine trials required patient cooperation, and the operator was not blinded in three of the trials. All trials required some degree of staff and/or patient cooperation to conceal treatment allocation and

blinding on the day that the patient was being treated, allowing the possibility of bias.

These results demonstrate a need for a laser machine that can properly blind the operator and trial participants, ensuring concealment of treatment allocation.

Table 3. LLLT trials that use on/off switches (SWI)

Trial	Condition	Result	Possible methodology problems
Åzdemir <i>et al.</i> (44) <i>N</i> = 60	Neck pain	Positive	GLO, SWI
Basford <i>et al.</i> (45) <i>N</i> = 81	Thumb OA pain	Negative/Positive	GLO, SWI, PAT
Bjordal <i>et al.</i> (46) <i>N</i> = 27	Achilles + PGE-2	Positive	GLO, SWI
Ceccherelli <i>et al.</i> (7) <i>N</i> = 27	Neck pain	Positive	GLO, SWI
Cetiner <i>et al.</i> (47) <i>N</i> = 39	TMJ pain	Positive	GLO, SWI
Conti <i>et al.</i> (48) <i>N</i> = 20	TMJ pain	Negative	GLO, SWI, INC
de Bie <i>et al.</i> (49) <i>N</i> = 217	Ankle sprain	Negative	GLO, SWI
Dundar (50) <i>N</i> = 64	Neck pain	Negative	GLO, SWI, OPE
Gur <i>et al.</i> (51) <i>N</i> = 60	Neck pain	Positive	GLO, SWI, OPE
Gur <i>et al.</i> (52) <i>N</i> = 90	Knee pain	Positive	GLO, SWI
Klein and Eek (53) <i>N</i> = 24	Low back pain	Negative	GLO, SWI
Kreisler <i>et al.</i> (54) <i>N</i> = 52	Dental pain	Positive	GLO, SWI, PAT
Rogvi-Hansen <i>et al.</i> (55) <i>N</i> = 40	Knee pain	Negative	GLO, SWI, INC
Roynestal <i>et al.</i> (56) <i>N</i> = 25	Post-operative pain	Negative	GLO, SWI, INC
Snyder-Mackler (57) <i>N</i> = 24	Skin res/pain	Positive	GLO, SWI, PAT, GOG
Thornsen <i>et al.</i> (58) <i>N</i> = 47	Neck pain	Negative	GLO, SWI
Waylonis <i>et al.</i> (59) <i>N</i> = 62	Myofacial pain	Negative	GLO, SWI, PAT

(Other possible methodology problems are included. (*N* = 17).
 GLO, Laser diode glow may be visible; SWI, Switch on/off; PAT, Patient cooperation is required; OPE, Operator not blinded; GOG, Goggles are used; INC, Incomplete explanation of method.
 Notes: Total trials = 51: references (6, 10, 20–22, 44, 47, 49, 52) (4, 7-9, 11, 14, 23–43, 45, 46, 48, 51, 53–62).
 Trials are classified by primary method of blinding.
 All trials use invisible laser treatment beam unless otherwise specified.
 All laser machines use decoy sound and light as per normal operation.
 Three trials: Lundberg, 1987; Haker, 1990; and Haker, 1991- have been removed because of Institutional rulings on scientific practice.

Table 4. Miscellaneous LLLT trials (*N* = 5) Other possible methodology problems are included

Trial	Condition	Result	Possible methodology problems
Hopkins <i>et al.</i> (4) <i>N</i> = 22	Wound healing	Positive	GLO, OPE, GOG
Schindl and Neumann (60) <i>N</i> = 50	Recurrent herpes	Positive	GLO, GOG
Snyder-Mackler (57) <i>N</i> = 40	Nerve latency	Positive	GLO, PAT, OPE
Toida <i>et al.</i> (61) <i>N</i> = 20	Stomatitis	Positive	GLO, INC
Lim <i>et al.</i> (62) <i>N</i> = 39	Dental pain	Negative	GLO, INC

GLO, Laser diode glow may be visible; PAT, Patient cooperation is required; OPE, Operator not blinded; INC, Incomplete explanation of method; GOG, Goggles are used.
 Notes: Total trials = 51: references (6, 10, 20–22, 44, 47, 49, 52) (4, 7-9, 11, 14, 23–43, 45, 46, 48, 51, 53–62).
 Trials are classified by primary method of blinding.
 All trials use invisible laser treatment beam unless otherwise specified.
 All laser machines use decoy sound and light as per normal operation.
 Three trials: Lundberg, 1987; Haker, 1990; and Haker, 1991- have been removed because of Institutional rulings on scientific practice.

We now describe the features of a recently developed laser machine that combines these aims and report a small study to test these properties.

Novel Laser Machine for RCTs (Figs 1A and B, 2)

A laser machine suitable for use in RCTs should have the following attributes:

- An invisible laser beam.
- Disguised laser diode glow.

- Ability to preset randomized number sets and seal them into the machine.
- Security of internal structures to prevent tampering.

We have developed a new laser machine that is similar in appearance and function to a normal low-level laser machine i.e. it has a typically sized hand held laser probe connected to a power source. It also has a timer, sound emitter (beep) and key lock as is normally required by law for laser devices. Added to this are disguises to overcome the ability of operators

<p>DBL laser specifications:</p> <p>830nm Gallium Aluminium Arsenide infrared laser machine.</p> <p>Probe 10 mW probe exit strength.</p> <p>Standard usage per point = 0.2 J.</p> <p>Four digit switch for preset sealed randomisation codes/treatment allocation.</p> <p>Hand held probe with aluminium casing and conical perspex tip.</p> <p>Decoy red light in probe tip offset from laser path.</p> <p>Decoy beeping sound preset—always on—when probe activated.</p>

Figure 2. DBL Laser machine specifications.

or patients to see the laser diode glow. These are as follows:

1. **A red decoy light:** A biologically inactive (63), red, non-coherent non-laser light at <0.1 mW, is installed beneath the Perspex cone, next to the diode inside the end of the probe. (Fig. 1A) This red light acts as a decoy light and overshadows the small incandescent glow from the diode. This level of red light is below threshold for measurable clinical effects (45,59).
2. **Conical perspex cone tip:** A conical perspex cone tip has been added to cause partial internal reflection of both the dummy red light and the laser diode glow; thereby 'blending' the two light sources and making direct visual detection of the diode glow impossible. After fitting the conical perspex tip to the laser probe, the laser diode strength has been reset to an exit power of 10 mW as per the machine's original specification.
3. **Allocation concealment is ensured using a randomization keypad:** The randomization schedule is generated and held by an independent researcher. This schedule is then built and sealed into each machine at manufacture. This preset schedule number is a code that allocates patients into treatment or placebo groups. Therefore, each participant will be allocated without the knowledge of the participant or treating doctor/operator. Each participant is allocated by entering their particular patient code number into the keypad on the front of the laser machine. (Fig. 1B) As mistakes can occur with the keypad number entry, the patients are asked to check their keypad number with the operator before each treatment.
4. **Decoys:** When the machine is activated for treatment, it makes an audible beep and the console lights turn on; indicating to the patient that the machine is switched on. These decoys are in operation whether or not the real laser beam is activated. (Fig. 1B)
5. **Non-bypass system:** the four-digit patient code switch cannot be bypassed. It is impossible for the treatment group allocation to be altered after being preset and sealed in manufacture.
6. **Equipment testing:** the preset randomization schedule can be checked by an independent researcher prior to the commencement of the trial.

Method of Laser Machine Testing

To test our novel machine in its capacity to ensure allocation concealment and blinding, a sample of 20 doctors was asked to participate in a double blind test. The group was an opportunistic sample of doctors who practiced medical acupuncture and presented for a discussion group on medical acupuncture treatment in chronic pain. All of them were familiar with the usage and risks of low-power lasers and consented to participate. There were no refusals. They knew there were deliberate disguises in place i.e. the decoy red light and perspex cone. Participants were asked to examine the laser machine and activate the laser whilst switched between two-unknown preset positions that switched the real laser beam off and on. The participants were asked to determine whether they could see the laser diode operating through the perspex cone. The possible responses: either 'on', 'off' or 'cannot tell', were recorded.

Results and Discussion of Laser Machine Testing

In this preliminary study, none of the 20 laser familiar participants could see the operation of the laser diode. This is supportive evidence that the laser diode disguise is effective and overcomes this important problem in double blinding laser trials. The preset concealed randomization-coding system also worked effectively.

Conclusions

Analysis of 51 double blind RCTs of laser treatment revealed 58% showed benefit of laser over placebo. However, less than 5% of the trials had addressed beam disguise or allocation concealment in the laser machines used. This indicates significant deficiencies in laser trial methodology. A new laser machine has been developed that can blind both patient and operator to treatment allocation without staff participation. Preliminary testing has verified that the laser machine diode operation could not be detected, and the preset sealed randomization-coding system was effective. We consider this machine could be a useful tool in conducting double blind RCTs, however a larger clinical study should be undertaken before it can be fully validated as a trial instrument.

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