CRITICAL CONSIDERATIONS IN PROTOCOL DESIGN FOR A DOUBLE BLIND TRIAL ON PAIN ATTENUATION BY LASER THERAPY

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An increasing number of clinical reports on the application of low reactive-level laser therapy (LLLT) in pain attenuation are appearing in the literature, but very few of these reports include a blinding procedure to offset the possible placebo effect of laser therapy, especially with smaller patient populations. The present study describes a protocol set up to remove as much as possible any skewing of the data by the placebo effect. The trial is set up in two (or more) geographically distant institutes under similar environmental conditions. Patients with a variety of pain complaints are selected for the study with similar demographic characteristics in all trial sites, and are each assigned a patient number for trial identification purposes. Treatment parameters are standardized for a single LLLT session using the same laser system at the same parameters (in the present study a GaAlAs diode laser, 830 nm, c/w, 60 mW was used). A computer is programmed to assign real or sham laser treatment randomly to each patient number, every time the number changes as sensed in the computer by the use of the laser therapy system main power switch. The same computer, located distantly from the treatment room, controls the laser system directly to produce real and sham laser therapy, and neither the patient, the therapist nor the computer operator is thus aware to which group the patient has been assigned by the computer, which stores these data to be retrieved after the trial and assessment are complete. A comprehensive record chart is used to record pre- and post therapy subjective and objective evaluations for both individual pain groups and the population as a whole, including any adverse side effects and machine safety, with a series of scores being finally compiled to give an overall efficacy rate. The last stage of the trial involves subjecting the results for the real and sham groups to direct statistical analysis using a combination of χ^2 and Fischer's tests. A value of $p < 0.01$ is significant with a level of confidence of less than 1%. These data are examined for each pain group and for the population as a whole site by site, and finally similar data for the total population in all the sites is compiled.

Key words: placebo effect; LLLT; computer-controlled double blinding; pain attenuation; diode laser

Introduction

The growing application of laser therapy for pain attenuation in a wide variety of pain types has led to an increasing number of reports appearing in the literature of both purely clinical and clinical trial natures. Unfortunately, a large number of the trial reports are not satisfactorily blinded, which may bring into question the interpretation of their data from a scientific viewpoint because of the existence of the placebo effect.^(1,2)

The present study reports on the critical design of a protocol for a computer-controlled double blind

trial to assess the safety and efficacy of laser therapy for a variety of pain types, using a GaAlAs diode laser system linked to a remote computer. The laser system is designed to operate macroscopically similarly in the real and sham groups, and the computer is programmed to allocate patients randomly to the real or sham groups, without the knowledge of either the therapist or the patient. Only after the treatment is completed and the data compiled is the information in the computer accessed to ascertain which patients were in which group.

To validate the data further, the trial is held in two or more geographically distant sites, with similar treatment environments. Each site has its own controller, and a single independent trial controller has the task of bringing the different sets of data together and subjecting them to statistical analysis.

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It is thought that this protocol offers a solid and fully blinded trial to assess the efficacy and safety of diode laser LLLT in such a way as to cancel the results of the placebo effect and give meaningful scientific data.

Materials and Methods

The following elements are required for the execution of the trial.

Laser Therapy System: In the present trial a GaAlAs diode laser (OhLase-3D1, Proli Japan: 830 nm, continuous wave, 60 mW) was used, but any LLLT system can be used, provided it is capable of having the laser circuitry controlled by an external remote computer.

Sponsor: Only required in the case of a trial aimed at a regulatory submission, for example to the appropriate branch of the health ministry of the country in which the trial is held.

Purpose of the Trial: To evaluate the safety and efficacy of the laser therapy system in the attenuation of pain of a variety of types, using computer-controlled full double blinding.

Trial Site: Two (or more) geographically remote institutions (the present study uses University Hospital centres) with similar treatment environments.

Controllers: A Site Controller is responsible for execution of the trial at each site in the trial, and for the collation of the data. An independent Trial Controller is responsible for overseeing, checking and compiling the data from each site and subjecting it to statistical evaluation to determine the efficacy and safety at each site, comparing the results from the real and sham groups, and the overall assessment for all the sites involved.

Trial Conditions: The trial methodology, including seasonal considerations, must be discussed and standardized between the sites. The treatment method, therapy sessions and the patient population must be controlled to be as similar as possible in all sites.

Target Diseases: The target pain entities are chronic inflammation of soft tissue and musculo-skeletal origin, including neck/shoulder/arm syndromes, lumbar pain, neuralgias and so on. LLLT is used alone: no concomitant drug or physical therapy is used in the trial.

Trial Agreement: All patients involved shall sign appropriate forms of informed consent before being admitted to the trial population.

Trial Methodology

a: Assignment of patient to 'real' or 'sham' treatment.

The laser system used in the present study consists of a control console from which the irradiation time is set

Fig 1: The OhLase-3D1 diode laser therapy unit, showing the control console, the hand held delivery probe and the flexible cable connecting the probe to the console. Note the display panel on the console and the white translucent probe cap on the probe.

and on which various data are displayed, and a hand-held delivery probe, connected to the console by a flexible cable (Figure 1). The probe includes a finger operated on/off pressure switch and a set of touch sensors which allow operation of the laser in Contact Mode only when the probe is in contact with viable tissue. Both of these criteria must be met before the laser diodes can be activated. Activation of the laser diodes under normal conditions results in audible and visible emission indicators. The audible signal consists of a train of electronic 'beeps' which continue as long as the on/off switch is depressed and the touch sensors are in contact with viable tissue. Visible indicators consist of a 'sunburst' display on the console display, and a red light emitting diode (LED) mounted in the probe head, and visible through the translucent white probe cap as a red glow. The remote computer is connected directly to the laser control console and completely takes over control of the laser diode circuits only, leaving the visible and audible emission signals unaffected and operating whether the laser diodes are activated (real treatment) or not (sham treatment) (Figure 2). With the laser probe applied to the target tissue in the contact mode and the on/off switch depressed, there is thus no way that either the patient or the laser therapist can know whether the patient has been assigned to the real or the sham groups as the indicators are identical for both real and sham irradiation.

Patients in the trial are placed in no particular order on a master list and numbered in order from 1

Fig 2: Schematic showing computer control of the laser diodes, allowing normal operation of the visible and audible indicators whether the diodes are active (real treatment) or inactive (sham treatment).

upwards. The computer randomly assigns each patient number in turn to the real or sham laser therapy groups. The therapist is instructed to turn off the laser system after each treatment session is completed, and turn it on again at the start of the next session. The computer is fitted with a power on / power off detector (see Figure 2) so that the patient number is automatically advanced by the program each time the laser system is switched off and on. Patient numbers assigned to the real treatment group are identified in the computer program by an 'A' (actual), and in the sham group by a 'D' (dummy). These data are written to disk and stored there until the treatment and all assessments have been completed. Thus each patient's treatment group is not actually accessed until after therapy and all assessments are complete, giving a true double blinding factor to the trial.

b: Trial records

All data for each patient are recorded on a specially designed and comprehensive trial case card. This card gives in the first section the patient's name, age, sex, general history and history of the pain type, including details of previous therapy (which is discontinued for this trial). In the case of patients previously on any kind of drug therapy, the date of full wash-out of remaining

drugs is also given. The date of signing of informed consent is included in this section.

The second section gives details of the single treatment session, including the date, the total exposure time, the anatomical area treated (e.g. dermatomal, lymphatic, blood vessel and so on), and a note if there was any concomitant conventional therapy. For the purposes of the present trial, there will be none.

The third section consists of the usual anatomical diagram (full frontal and full dorsal) for indicating the pain area, and boxes for filling in the objective and subjective pre- and posttherapy pain scores (immediately after therapy and one day after therapy); any mechanical problems with the system; any side effects, their time of occurrence and a description; and a set of summation boxes to bring all of the above data together to calculate the final efficacy score.

c: Site Controller, Trial Controller

All of the treatments at each treatment centre (treatment site) must be carried out by the same experienced doctor, who is responsible for completing the trial case card as appropriate for each patient. The case cards are then handed over to the Site Controller, who shall compile all the data in the cards to make a composite report, breaking the pain entities up into groups, and including finally the data from the computer records

to present a double blind report on the efficacy of the laser system on the treatment of pain by comparing the results from the real therapy and sham therapy patients in the same pain group. The Site Controller shall then subject the data to statistical evaluation (χ^2 and Fischer's tests) to examine any statistically significant difference between real and sham laser therapy for each pain entity.

The Trial Controller is an independent observer whose function is to take the data from the separate Site Controllers and, after verifying them, combine the data from the sites to provide figures for each pain group across all sites and for the total trial population as a whole. These figures are then subjected to statistical evaluation (χ^2 and Fischer's tests) to ascertain the statistically significant difference between real and sham laser therapy.

d: Treatment

The patient shall be treated with LLLT using dermatomal pain point and neural pathway considerations, taking blood vessel and lymphatic system pathways into consideration.^(3,4)

e: Probe management

The probe shall be applied in the pressure contact method on the pain point,⁽⁵⁾ so that the patient can feel pain at the beginning of treatment. In the normal course of treatment events, this pain is rapidly removed during treatment. The irradiation time per point shall not exceed 3 minutes maximum, and the total treatment time per session shall range from 5 to 15 minutes, depending on the severity of the pain, its location, and so on.

Objective Assessment of Treatment Effect

Table 1: Objective evaluation: scoring table.

	Before Treatment	Soon After Treatment	One Day After Treatment
SYMPTOM	Date:		Date:
	A	B	C
pain	4 3 2 1	4 3 2 1	4 3 2 1
numbness	4 3 2 1	4 3 2 1	4 3 2 1
dullness	4 3 2 1	4 3 2 1	4 3 2 1
pressure pain	4 3 2 1	4 3 2 1	4 3 2 1
movement pain	4 3 2 1	4 3 2 1	4 3 2 1
referred pain	4 3 2 1	4 3 2 1	4 3 2 1
pain-related ROM limitation	4 3 2 1	4 3 2 1	4 3 2 1
Lasègue's sign	°	°	°
TOTAL POINTS:			

Eight individual symptoms or components are combined by the therapist to arrive at the degree of total pretherapy and posttherapy severity as shown in Table 1 (taken from the trial case card):

Each component is assessed and scored under one of four degrees: severe (4 points); intermediate (3 points); light (2 points); and none (1 pt). The scoring is indicated by circling the appropriate point value. Assessment is carried out before treatment (column A), soon after treatment (column B) and on the day following treatment (column C). The columns are totalled, and the following summations are then made

$$S_a = S(A-B)$$

$$S_b = S(A-C)$$

Objective Assessment of Total Clinical Improvement

the value for S_b is taken as the assessment of the overall clinical improvement, as the total points soon after treatment tend to be better than on the day after treatment and the value for S_a usually tends to be better than S_b , thus giving a more realistic assessment for clinical efficacy. This value is then used in the following table (Table 2) to calculate the assessment points score for clinical improvement.

The value in the right-hand column is then entered in the appropriate box on the trial record card.

Subjective Estimation of Effectiveness

Using the same table and components as already described above, the patients are asked to give a subjective assessment of any improvement in their pain condition on the day following laser therapy, and the same method to assign assessment points is used as for clinical improvement, so that subjective assessment is scored at 3, 2, 1, 0, and -2 points for excellent, good, fair, little or no change and exacerbation, respectively. This value is then entered in the appropriate box on the trial record card.

Overall Assessment of Efficacy

The overall efficacy of the laser therapy for pain attenuation is examined under three headings: improvement in pain; the safety of the treatment (from the point of

Table 2: Assignment of assessment points for clinical improvement.

Assessment Grade	Value for S_b	Assessment Points
Excellent	> 7	3
Good	5-6	2
Fair	2-4	1
Little or No Change	0-1	0
Exacerbation	minus value	-2

any adverse side effects); the overall efficacy of the laser therapy.

a: Improvement in pain

The improvement in the patient's pain is worked out using the following formula

$$\text{Score A} = \left[\frac{\text{Score B} + \text{Score C}}{2} \right]$$

This value is assigned to a 5-level assessment from 3 to -2 points just as in Table 2. Fractions are rounded down to the nearest whole number, and any minus value is assigned to -2 points. This value for the pain improvement is entered in the appropriate box on the trial record card.

b: Safety of treatment

The assessment of the safety of the therapy is carried out on a 4 level scale as seen in Table 3, and is recorded in the appropriate box on the trial record card.

Table 3: Scale and points for assessment of therapy safety.

Scale	Description	Points
1	No side effects	3
2	Some side effects, but the therapy can be continued	2
3	Side effects apparent: lower dosage required to continue with the therapy	1
4	Severe side effects: therapy must be discontinued	-2

c: Overall efficacy

The overall efficacy is arrived at by using the device seen in Figure 3 which relates the scores obtained in the improvement and safety sections above. For example, if the improvement score is 4 and the safety score is 4, then the point at which the lines meet (reading down from improvement and across from safety) gives an overall efficacy score of 5. If improvement is 1 and safety is 3, then the overall efficacy score is 3, and so on. This value is entered in the appropriate box on the record card.

After gathering the data for improvement, treatment safety and overall efficacy from all the trial record cards, the Site Controller for each site submits the data to statistical analysis, after retrieving the data from the computer on which patients received real therapy, and which received sham therapy. Only at this stage is the 'A' or 'D' factor entered in the record cards, so that there can be no possible bias in any of the assessments already discussed. The statistically significant difference between real (A group) and sham (D group) laser therapy can then be examined for each of the sites in the main pain groups and for the population as a whole. Finally, these data from each of the sites are passed on to the independent Trial Controller for

		IMPROVEMENT				
		1	2	3	4	5
SAFETY	1	1	2	3	4	5
	2	2	3	4	5	5
	3	3	4	5	5	5
	4	4	5	5	5	5

Fig 3: Method for relating the scores for pain improvement and treatment safety to give a score for overall efficacy. By reading downwards from the improvement score and across from the safety score, the point at which these lines cross will give the value for overall efficacy.

verification, and the Trial Controller then works out the figures for each pain group across all of the sites, which gives a more meaningful patient number, and then for the whole patient population in all of the sites. Data are evaluated using the χ^2 and Fischer's tests.

Discussion

One of the main claims by critics against the efficacy of laser therapy in pain attenuation is the lack of controlled studies, and it is a valid complaint, as far as scientific evaluation of the efficacy of laser therapy is concerned. True double blinding of a trial is often very difficult because of the equipment design or laser type. For example a HeNe laser used in noncontact mode has a visible red beam: absence of the beam is very obvious in sham irradiation, unless the patient is blindfolded, or treatment is on an area not visible to the patient, such as the upper back. The problem then arises with the laser therapist, however, who must surely be aware if the laser is on or off. In this case double blinding becomes very difficult, and single blinding has to be accepted. The other element which can be added to an extended clinical trial is the crossover, where patients in group A receive sham therapy for the first half of the trial, and real therapy for the second half, and patients in group B receive real therapy for the first half and sham in the second half. However in the present protocol there is only one treatment session, so crossover in this protocol is not possible. Also, since there is only a single therapy session, it can make any good results very clear. The true double blinding in this study also completely eliminates any bias on the part of the therapist and the patient, as only the computer knows who is to receive real therapy and who will get sham treatment. These data are then kept in the computer until after all the

evaluations and assessments have been done, and are added to the trial record card as the last item, so once again there is no possible bias from knowing which treatment is real and which is sham.

The use of two or more sites which are geographically separate but with as closely as possible the same treatment conditions and parameters acts as a control in itself, as widely variant results between sites would point to some possible flaw in the therapy. On the other hand, similar results will indicate real efficacy. The use of multiple sites also increases the total patient population beyond the capabilities of a single site, which enhances the value of the statistical analyses.

The use of Site Controllers at each site for the data analysis, and especially the independent Trial Controller who is responsible for the final statistical analyses across all the trial sites and the total population brings an element of total detachment to the trial, and surely adds to its value as a solid scientifically-constructed protocol.

The authors therefore propose this protocol as a solid, true double blind trial to determine the statistical significance between real and sham laser therapy in the treatment of chronic pain conditions.

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