REPORT ON A COMPUTER-RANDOMIZED DOUBLE BLIND CLINICAL TRIAL TO DETERMINE THE EFFECTIVENESS OF THE GaAlAs (830 NM) DIODE LASER FOR PAIN ATTENUATION IN SELECTED PAIN GROUPS

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The efficiency of infrared (IR) diode low reactive-level laser therapy (LLLT) has been reported in a variety of pain complaints. In order to ascertain if LLLT is particularly effective in a given pain group, 115 informed and consenting patients in two institutions (Toho University and Keio University, Tokyo, same ambient environmental parameters in treatment rooms) were assigned to groups according to the aetiology of their pain condition. Each patient's name was placed against a number, and a randomization computer program selected either real or sham (placebo) irradiation for each number, and thus each patient. The computer directly controlled the laser system appropriately, and stored the information on disc for retrieval after the trial was finished. The computer was located remotely from the treatment room. Neither the patient nor the therapist knew if they were in the real or placebo group: in placebo therapy, only laser emission was absent, the visible and audible emission indicators behaving exactly as in "real" treatment. The laser used was a gallium aluminium arsenide (GaAlAs) diode laser, 60 mW output, 830 nm, continuous wave. The laser was applied in the contact technique, with an incident power density of ≅ 3 W/cm^2, total exposure time per session of from 5-10 min (energy density ≅ 900 - 1800 J/cm^2). There were three groups: the extremity joint pain (35), cervical pain (39) and lumbar pain (41) groups. This gave a total of 115 patients (53 female, 62 male, ages from 18-82, mean age 49.2 ± 15.3). 82% of those who received real treatment in the total population reported effective pain relief, compared with 42% of those who were assigned to receive sham treatment. Following the trial, the data were analyzed statistically applying the χ^2 and Fischer's tests, giving a value of $\chi^2 = 21.328$ (df=1), with a value for $p = < 0.0001$ at a level of confidence of less than 1%, a statistically significant difference for the real versus the placebo treatment. There were no statistically significant differences in the results between the individual pain groups in the two sites. No adverse side effects were reported. It was concluded that diode laser therapy, at the parameters used in the trial, was both safe and effective for alleviation of pain in the groups treated.

Key words: low reactive-level laser therapy; LLLT; cervical pain; lumbar pain; joint pain; diode laser; double blind LLLT trial

Introduction

Particularly In the past 5 years, laser therapy, using low incident doses of laser energy, has been increasingly reported as being effective in a wide variety of acute and chronic pain entities.[1,2] Double-blind cross-over studies on the effectiveness of low reactive-level laser therapy (LLLT) for chronic postherpetic pain conducted independently in the UK, Canada, and Japan have all arrived at approximately the same level of effectiveness, around 74%, for LLLT compared with placebo sham irradiation.[3-5] No study has appeared comparing real and sham LLLT in a variety of chronic pain types with effective double blinding. The present study was designed around chronic pain entities in three main regions: pain types in the joints of the extremities, the cervical pain complex and the lumbar pain group. The trial was held in two separate sites under the supervision of a site controller for each site, and the data from the two sites were evaluated and compiled by an independent Trial Controller. In order to make sure of the complete blinding of both patient and therapist, patients were first assigned to a number, and a microprocessor-based randomizing program was designed and written which not only randomly as-

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signed these numbers to the real or sham group, but also actually controlled the laser system circuitry to give the real or placebo laser radiation, unknown to the therapist and patient. The safety of LLLT, as seen by reporting of side effects, was also documented, and both subjective patient response, and more objective physician assessment were factored into the final effective rating. The results from the two geographically-separate sites were compared, and no statistically significant difference in the findings for each pain group in either site was seen.

Materials and Methods

Trial Sites

Two geographically distant trial sites were identified in medical university hospitals in the Tokyo Metropolitan area, one handled by the Department of Neurosurgery, School of Medicine, Keio University, and the other run by the Department of Orthopaedics, School of Medicine, Toho University. The distance between the two sites is approximately 25 kilometres. Both buildings share the same method of construction, prestressed and reinforced concrete, and are of approximately the same age. The treatment areas were maintained at a similar ambient temperature of 21 - 23°C and a relative humidity of 50% - 60%. Both sites followed the same therapy protocol, but the treatment was carried out by different therapists belonging to the respective institution and scheduled during the same season of the year. The same therapist in each institution looked after all the patients in that trial site, and was responsible for filling in the detailed trial record card. The data from the record cards was then compiled by a Site Controller for each institution, and passed on to the Trial Controller for the final verification and assessment.

Laser System and Therapy Methodology

The laser used was the OhLase-3D1 (Proli, Japan, Ltd), a diode (GaAlAs) laser, consisting of a control console, to which is connected a hand-held delivery probe (Figure 1). The system gives a continuous wave output of 60 mW, at 830 nm in the near infrared, delivered to the target tissue in the contact technique. The incident power density in contact mode is fairly constant at ≅ 3 W/cm^2. Treatment times per single session ranged from 5-10 min, with a mean of 9.18 ± 1.1 min (mean ± standard deviation). Only the results from this single session were assessed for pain improvement, safety and efficacy.

Method of Double Blinding

The computer console was linked to a remotely sited computer, which had been previously programmed with a randomization program to assign patient treatment numbers randomly, but roughly equally, to either real or sham laser therapy. The computer controlled

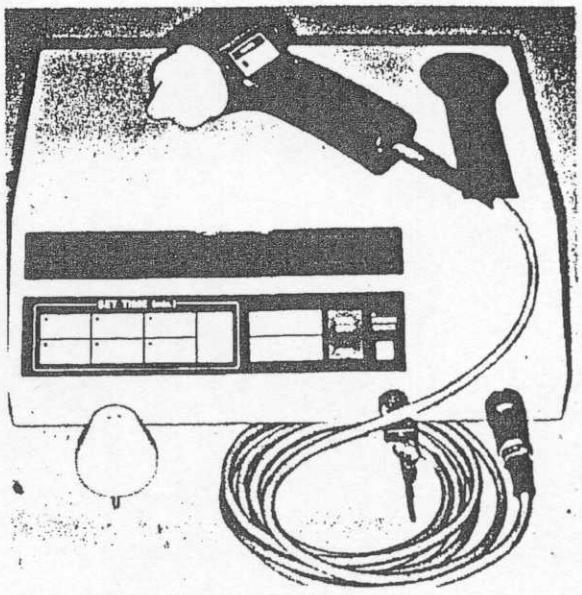

Fig 1: OhLase-3D1 GaAlAs diode laser system, showing controle console and hand-held delivery probe connected to the console by its flexible cable.

only the laser diodes themselves, when activated by the on/off switch on the probe, with the probe in contact with viable tissue. As the 830 nm beam from the GaAlAs system is invisible, its presence or absence cannot be determined by either the therapist or the patient, neither of whom knew to which group the patient had been assigned by the computer. The visible and audible emission indicators worked exactly the same for both real and sham irradiation. The computer entered "A" (actual) for real therapy and "D" (dummy) for sham therapy against the patient identification number, and stored the data to disk. These data were not accessed until after the therapy session was complete, and the data on the trial record card for each patient had been compiled by the Site Controller for each of the two sites. In this way no possible bias was allowed, either during treatment for both the therapist and the patient, or during the scoring procedure on the trial record card: the trial was thus fully double blinded.

Patient Population

The patients for the trial were all attending their respective institution on an outpatient basis, and were selected for participation in the trial based on their pain entity. There were originally 130 patients in the selected population, but 15 of them fell into a miscellaneous pain entity group, not clearly belonging to any of the three regional groupings. Accordingly the data accruing from these 15 miscellaneous group patients were removed from the final analysis, thus leaving the three main pain groups, the extremities joint, cervical and lumbar groups, (n = 35, n = 39 and n = 41, respectively). Tables 1 and 2 show the pain entity and

Table 1: Pain entities grouped by site (1 entity per patient).

Group 1: Articular Pain of the Extremities (n=35)	
Shoulder periarthritis	11
Avulsion fracture	2
Chronic shoulder joint pain	1
Chronic shoulder spondylosis	1
Elbow spondylosis	1
Chronic elbow pain	2
Thumb spondylosis	1
Chronic thumb sprain	1
Chronic articular fracture	1
Knee spondylosis	5
Knee periarthritis	3
Chronic knee pain	1
Chronic ankle pain	1
Chronic rheumatoid polyarthritis	4
Group 2: Cervical Pain (n = 39)	
Greater occipital neuralgia	3
Occipital pain	1
Muscle spasm headache	3
Occipital/shoulder/upper arm pain	1
Neck/shoulder/arm syndrome	13
Neck pain	2
Cervical spinal nerve injury	1
Postcervical musculofascial syndrome	5
Cervical/vertebral syndrome	10
Group 3: Lumbar pain (n = 41)	
Lumbago	23
Ischiatic neuralgia	9
Lumbar musculofascial pain	2
Herniated disc	3
Lumbar spondylosis	4

demographic breakdown of the 115 patients. There was no significant difference between the male - female ratio or the average ages in the two sites.

None of the patients during the trial received any other form of physical or medical therapy, other than diode LLLT. Any patients previously on any medication were given a period of time off the medication to allow for wash-out of the drug or drugs.

Clinical Trial Record and Data Management

Data for each patient were recorded by the therapist on a specially-designed trial record card. in addition to recording the usual history of the patient and the pain

Table 2: Demographic breakdown for the two institutions and the population as a whole.

Site	M	F	Age		
			M (mean ± SD)	F (mean ± SD)	Average (mean ± SD)
Keio Uni.	36	27	20-82 (53.4 ± 15.5)	28-79 (49.46 ± 12.7)	20-82 (51.7± 14.4)
Toho Uni.	26	26	18-75 (41.3 ± 19.6)	27-78. (53 ± 13.6)	18-78 (46.6 ± 17.7)
Both Sites	62	53	18-82 (47.3 ± 15.3)	27-79 (51.2 ± 17.1)	18-82. (49.2 ± 15.3)

entity, the record card contained a series of boxes for both subjective and objective pain improvement assessment (before, soon after and one day after the single LLLT session), from which a differential score was assessed to give the overall improvement. The safety of the system as far as side effects and their management was examined and scored. The scores given to overall improvement and safety were then cross-linked to give the final efficacy score. These calculations were carried out by the therapist without any indication as to whether the patient had received real or sham laser therapy. The mechanics of this protocol have been described fully elsewhere.[6]

The data for each were then processed by the Site Controller, who added for the first time the data from the computer identifying the real and sham therapy patients. The trial controller then submitted the data for the real and sham therapy patients (both in the individual pain groups and for the population as a whole) to statistical evaluation using χ^2 and Fischer's tests. Values for p of less than 0.01 were considered statistically significant at a level of confidence of less than 1%.

Results

Table 3 shows the breakdown of data on pain removal from the Toho University site for each of the three pain groups for real (A) and sham (D) irradiation, showing the ratio of total efficacy to ineffective therapy: there were no adverse side effects reported. Although a better result was reported overall for real therapy, there was no significant difference between real and sham therapy in the extremities joints group ($p = < 0.04$), but the value for p in the other two groups was less than 0.01. Table 4 shows the same data from the Keio University site with no adverse side effects reported. Real therapy was more effective overall, but there was no significant difference between real and sham therapy in the extremities joints or lumbar groups, however the value for p in the cervical group was less than 0.01.

Table 3: Efficacy of real and sham therapy compared for each pain group, Toho University.

Pain Group	Total No	A Group		D Group		Efficacy A/D (%)
		Effective	Ineffective	Effective	Ineffective	
Extremities	19	7	0	7	5	100/58^{ns}
Cervical	17	7	2	1	7	77.7/12.5*
Lumbar	16	6	0	4	6	100/40*

ns = no statistical significance
$p < 0.01$

Table 4: Efficacy of real and sham therapy compared for each pain group, Keio University.

Pain Group	Total No	A Group		D Group		Efficacy A/D (%)
		Effective	Ineffective	Effective	Ineffective	
Extremities	16	7	2	3	4	77.8/42.3^{ns}
Cervical	22	6	2	3	11	75/21.4*
Lumbar	25	9	1	8	7	90/53^{ns}

ns = no statistical significance
$p < 0.01$

Table 5: Pain removal graded over whole population, real *vs* sham therapy: Toho University. Grading: +++ = excellent, ++ = good, + = fair, ± = little or no change, − = exacerbation.

Group	Total No	+++	+		±	−	Efficacy (%)
A	24	6	8	9	1	0	95.8*
D	28	0	4	6	18	0	37.9*

** significant: $\chi^2 = 11.385$ (df=1), $p = < 0.0007$*

Table 6: Pain removal graded over whole population, real *vs* sham therapy: Keio University. Grading: as for Table 5 above.

Group	Total No	+++	+		±	−	Efficacy (%)
A	25	3	8	9	5	0	80
D	28	0	3	3	22	0	21.4

significant: $\chi^2 = 9.669$ (df=1), $p = < 0.0016$

In both tables 'effective' treatment represents the sum of the 'excellent', 'good' and 'fair' grades, and 'ineffective' represents the sum of 'little or no change' and 'exacerbation' (see Tables 5 and 6).

Tables 5 and 6 show the data for the populations as a whole for Toho and Keio sites, respectively, showing an overall statistically significant difference between real and sham laser therapy for both sites. The tables show the 5 assessment grades and the total efficacy of both the A and D groups.

Table 7 shows the data for effectiveness over both sites, broken down by pain group, for both Toho and Keio. There is an overall difference between real and sham therapy which was significant for the cervical and lumbar pain groups ($p = < 0.0003$ and $p = < 0.0026$, respectively). Table 8 shows the data for the whole patient population. Pain improvement following real therapy was significantly better than sham therapy ($p = < 0.0001$). The data for Tables 7 and 8 are shown graphically in Figures 2 and 3.

Discussion

Despite the very strict double blinding protocol of this trial, the results from each institute singly and overall from both trial sites show a statistically significant difference in favour of real laser therapy versus sham or placebo therapy in the treatment of the majority of chronic pain entities in this study. Although there was a noticeable difference between the real therapy and sham therapy groups both overall and when broken

Table 7: Efficacy of real and sham therapy compared for each pain group: both sites.

Pain Group	Total No	A Group		D Group		Efficacy A/D (%)
		Effective	Ineffective	Effective	Ineffective	
Extremities	35	14	2	10	9	87.5/55.3^{ns}
Cervical	39	13	4	4	18	76.5/18.2*
Lumbar	41	15	1	12	13	93.8/48**

ns=no significant difference
** significant: χ^2 = 13.251 (df=1),p = <0.0003*
*** significant: χ^2 = 9.081 (df=1), p = <0.0026*

Table 8: Pain removal graded over whole population, real *vs* sham therapy: both sites together. Grading: +++ = excellent, ++ = good, + = fair, ± = little or no change, −= exacerbation.

Group	Total No	+++	++	+	±	−	Efficacy A/D (%)
A	49	8	14	20	7		85.7
D	66	0	3	13	40		31.4

significant: χ^2 = 21.328 (df=1), p = < 0.0001

down and compared by pain group, the difference was not statistically significant in the extremity joint group in either institute. Pain of the joints is probably one of the most difficult pain entities to treat successfully, simply because joints are designed to move, and movement exacerbates any pain present as well as possibly reinforcing the root cause of the pain. However there was still a difference in the real therapy compared with the sham therapy even although it was not statistically significant. The reader must remember that these data were gathered from a single LLLT session. Future studies involving multiple treatment sessions will in all probability show a higher degree of statistically significant difference especially with results already reported.

The trial sites were geographically separate, therapy was carried out by a different therapist in each site, and the Toho site was based in the Department of Orthopaedics while the Keio site was administered by the Department of Neurosurgery: despite these factors the results from both sites were not significantly different. This gives added strength to the fact that LLLT is effective for the treatment of chronic pain entities. There was overall greater effectiveness seen in the Toho data, but this could perhaps be accounted for by the

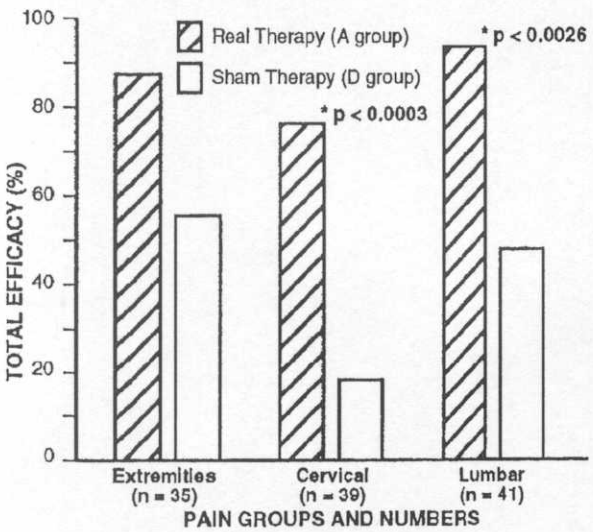

Fig 2: Real (A group) and sham (D group) LLLT compared for the three separate pain groups. The asterisk (*) denotes a statistically significant difference between the real and sham effective rating.

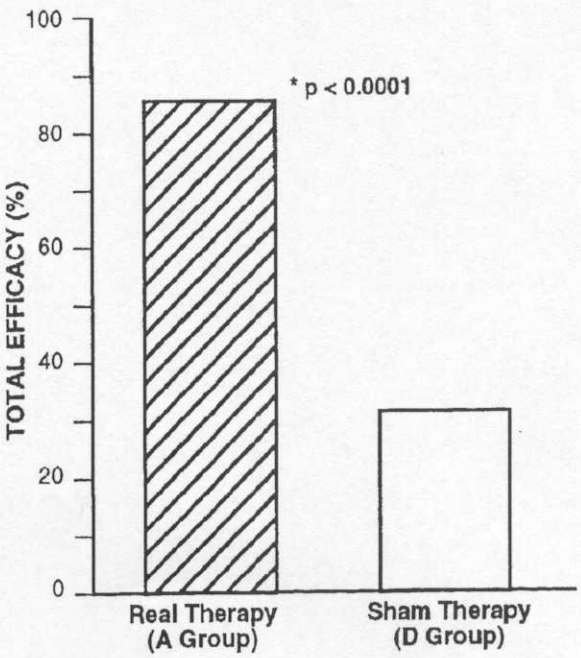

Fig 3: Real (A group) and sham (D group) LLLT compared over the whole patient population from both trial sites (n = 115). The asterisk (*) denotes a statistically significant difference between the real and sham effective rating.

fact that department of orthopaedics staff are much more used to dealing with such chronic pain types, particularly musculo-skeletal pain entities, compared to staff in a department of neurosurgery.

There were no adverse side effect reported from either site, and the laser systems functioned normally. The safety aspect of LLLT was thus confirmed, at least for the numbers and parameters relevant to the present study.

In conclusion, the authors find that LLLT using the GaAlAs diode laser at the parameters shown is a safe and effective treatment method for the chronic pain types listed in the present study. The double blind trial showed that this efficacy is statistically significant compared to sham treatment, but the percentage of placebo effectiveness still ranged from 12.5% to 58%. However this study was designed around a single therapy session, and with chronic pain patients, further treatments may well show more success for the real treatment compared with the sham: there is still however an obvious powerful psychological influence from the use of 'laser' in treatment of pain. Provided the placebo effect is recognized, and is used but not abused, the authors would argue that it is helpful in actual clinical therapeutic practice.

Some studies at tissue, cellular and subcellular levels have started to point to possible photomechanisms to explain scientifically why LLLT is effective in the therapy of chronic pain, but more studies are required. However, it is clear from the practical clinical viewpoint that LLLT provides a safe, side-effect free, effective and easily tolerated modality for the attenuation of chronic pain.

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