

Double-Blind, Placebo-Controlled Investigation of the Effect of Combined Phototherapy/Low Intensity Laser Therapy Upon Experimental Ischaemic Pain in Humans

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Background and Objective: This study assessed the putative analgesic effect of combined monochromatic light/laser irradiation at low intensity (660–950 nm; 31.9 J/cm²; pulsed at 16 or 73 Hz).

Study Design/Materials and Methods: The investigation was completed under double-blind conditions using a standardised form of the submaximal effort tourniquet technique. Healthy male volunteers naive to the experimental conditions (n = 45) attended on two occasions for the purposes of pain induction, the first during which baseline data were obtained and on a second occasion during which they were randomly allocated to one of two treatments or a placebo condition. For the treatment conditions, irradiation was applied to the ipsilateral Erb's point at the parameters stated; for the placebo condition, sham "irradiation" was delivered using a dummy unit. Pain was measured using computerised visual analogue scales and McGill Pain Questionnaires (MPQ) to assess "current pain intensity" and "worst pain experienced," respectively.

Results: Analysis of variance and appropriate post hoc tests demonstrated only a weak (but significant) hypoalgesic effect compared to placebo ($P < 0.05$) in the treatment group irradiated at 16Hz for the sensory component of the MPQ; other comparisons were found to be nonsignificant.

Conclusions: These results do not provide convincing evidence for the hypoalgesic potential of combined monochromatic light/laser irradiation, at least at the parameters used here, and thus indicate the necessity of additional work to investigate this modality further in order to assess the potential benefit, if any, of such treatment in the clinical setting. © 1995 Wiley-Liss, Inc.

Key words: analgesia, experimental pain, laser therapy, phototherapy

INTRODUCTION

The use of lasers at relatively low radiant exposures (<30 J/cm²) has been widely promoted since the late 1960s as a useful therapeutic modality for the treatment of a range of conditions, including open wounds, soft tissue injuries, and pain of various aetiologies [1–3]. Of these potential applications, the recommendation of such

devices as an effective analgesic modality has attracted considerable scepticism from some authors, particularly given the poor quality of some

Accepted for publication November 29, 1994.

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of the publications within this field and the lack of any obvious mechanism of action [2, 4–6]. Review of the clinically based studies carried out to date is further complicated by the range of conditions treated and the plethora of irradiation parameters employed by researchers; consequently the putative clinical efficacy of laser therapy as an analgesic modality remains debatable [7]. In contrast, results of a recent survey of current practice in this field has indicated that clinicians regard such devices as an effective therapeutic tool, whose analgesic efficacy is rated highly against other electrotherapeutic modalities [8]. Unexpectedly, this survey also established the popularity of multiwavelength/multidiode treatment arrays combining monochromatic light emitting and laser diodes. This is particularly interesting given that no published study to date has attempted to establish quantitatively the analgesic efficacy of these devices under controlled conditions.

This notwithstanding, objective data from controlled laboratory studies in both animals and humans has provided some evidence of a potential laser-mediated analgesic effect at appropriate irradiation parameters. Using tail flick and hot plate methods [9, 10], significant hypoalgesic effects have been reported in rats as a result of Helium–Neon (He–Ne) laser irradiation [11–13]. The results of these investigations would further indicate that the observed effects were not opiate-mediated but were dependent upon the pulsing frequency of irradiation, with 4 Hz producing a short duration hypoalgesia of immediate onset, 60 Hz a delayed (>48 hr), but longer lasting effect, and 200 Hz being apparently ineffective [12, 13]. These observations may go some way to explaining the insignificant results found *immediately after* laser irradiation by Lundeborg's group using an He–Ne source pulsed at 73 Hz [14].

Despite the generally encouraging findings in animals, the difficulties and problems of extrapolating the findings of such work to humans remain. And despite this, few studies to date have reported investigations of the analgesic effects of laser in humans using laboratory techniques. Those available studies have focused exclusively upon effects at threshold pain intensities [15–17]. Seibert and Gould [15] have reported significant increases in thermal pain threshold after only 35 s of irradiation with a 1 mW He–Ne laser, but Brockhaus and Elger [16] found that irradiation of the Hegu and Jianqian acupuncture points bilaterally for 1 min per point using a similar laser

with a peak power of 10 mW produced insignificant effects upon thermal pain threshold. Significant hypoalgesic effects upon electrical pain thresholds at the wrist have also been reported by King and colleagues in a single-blind, placebo-controlled study after laser irradiation (0.03 J/point, $\sim 0.3 \text{ J/cm}^2$) of auricular acupuncture points in the ipsilateral ear [17]. This notwithstanding, the studies completed to date would appear to be limited in their relevance to clinical practice by their sole use of pain *threshold* as a means of quantifying analgesic effect, as well as their employment of relatively low treatment dosages.

Thus it would seem that whereas there is some experimental evidence to support the hypoalgesic efficacy of low intensity laser irradiation, this is contradictory and fragmented. Furthermore, no studies to date have been completed to establish the efficacy of the type of combined phototherapy/laser therapy units, which are apparently so popular in clinical practice [8]. The aim of this preliminary investigation was therefore to quantify the analgesic efficacy of such combined phototherapy/low intensity laser therapy by means of a variation of the submaximum effort tourniquet technique (SETT). The SETT was used as it was considered a useful and reliable method of assessing the effects of putative analgesic modalities [7].

MATERIALS AND METHODS

Recruitment Procedure

Ethical approval was obtained for this study for which naive male subjects ($n=45$) were recruited from staff and students of the university. Such subjects had not previously participated in similar experiments and were unfamiliar with laser/phototherapy. Once potential subjects had expressed their willingness to act as volunteers, a mutually convenient time was agreed, which allowed each to attend the two visits necessary within the specified time period. During the first attendance, subjects received a detailed briefing on the procedure and purpose of the experiment, as well as the minimal dangers associated with the technique. All were expressly reminded of their right to terminate the proceedings at any point, invited to ask any questions that they might have, and then to sign a simple consent form. In keeping with the principles of informed consent, although overt reference to the possible use of a placebo was not made, subjects were in-

formed that combined phototherapy/low intensity laser therapy "may or may not be applied" during their second attendance.

Screening Procedure

It was determined that subjects were currently healthy and free from any symptoms or illness that would contraindicate the ischaemic procedure. Subjects were screened for peripheral neuropathy, peripheral vascular abnormality, or hypertension as well as current drug usage. Subjects' nondominant arms, which were used in this experiment for the purposes of pain induction, were examined prior to the commencement of the procedure according to routine clinical standards [18]. It was not found necessary to exclude any subjects on the basis of this screening procedure.

Preliminaries

Subjects were seated comfortably at a table in a small (~2.5 m square) light and sound attenuated cubicle. Safety goggles (IREX 500, Bolle, France) were worn by subjects on both attendances. A microcomputer (520 ST, Atari, England) was arranged on the table so that its monomonitor and a mouse control mounted on a standard friction mat were directly in front of the seated subject. Brightness and contrast on the monitor were adjusted to allow subjects to easily view the screen while wearing the goggles. Once seated, operation of the mouse control was demonstrated and subjects' nondominant arms exposed to above the bulk of biceps/triceps.

Pain Induction Procedure

An elastic bandage was applied to the exposed hand and forearm under constant tension up to a point ~8 cm above the elbow and a sphygmomanometer cuff wrapped around the limb over the bulk of biceps/triceps. Once prepared in this way, a dynamometer (Martin vigorometer) fitted with a medium-size balloon was used to assess Maximal Grip Strength (MGS) in the arm. Once assessed, a marker on the dynamometer was set to read 75% of this maximal value. Subjects were then asked to elevate the prepared arm vertically above their head for 60 s to desanguinate the limb, and a timer was started; thus this point was recorded as time zero. After this 60-s period, the cuff was rapidly inflated (<2s) to a pressure of 200 mmHg and the first of 12 computerised Visual Analogue Scales (VAS) was presented for subjects to rate their current level of pain (see below). Once this had been satisfactorily com-

pleted, the arm was returned to a position of rest on the table in front of the subject.

Using the previously set dynamometer, subjects were then required to perform 20 hand grip exercises within the first min, using 75% of MGS and holding each grip for ~1 s. At the end of this second min, the second of the 12 computerised VAS was presented.

DEFLATION

At the 10-min point, the tourniquet cuff was slowly deflated over a 2-min period to allow subjects' forearms to resanguinate gradually over the period. At the end of the procedure, the tourniquet cuff and elastic bandage were removed and subjects' forearms routinely examined to identify any obvious trauma or undesired side effects (e.g., residual pain). In this trial, no evidence of such trauma or side effects were noted.

Pain Measurement

A computerised VAS and conventional McGill Pain Questionnaire (MPQ) were used to assess pain. For the purposes of the current study, a short program was written so that a VAS, with ends labelled as "no pain" and "maximum pain," respectively, could be displayed on the previously specified computer monomonitor at intervals predetermined by the investigator and subjects' ratings automatically stored to disk for future analysis. The first presentation was at the 1-min point (i.e., immediately after pain induction), and at 1-min intervals thereafter, including the deflation period. Each VAS was presented for a total of 30 s, which pilot studies showed to be an adequate time for subjects to rate pain by a "marker," the position of which on the line was determined by means of a mouse control. The marker on the VAS was located halfway along the analogue scale for each new presentation of the scale, the position and orientation of which were randomised by the program. Once satisfied that the position of the marker between the two labelled extremes adequately reflected the current level of pain experienced, subjects used the integral click switch on the mouse to finalise and record the reading. Each reading was scored by the program as a percentage of the total length of the line.

In addition to the continuous rating of pain throughout the procedure, subjects were also interviewed using a conventional MPQ at the conclusion of each session in order to complement the VAS ratings with an estimation of the qualitative

and quantitative aspects of the worst pain experienced during the session [18, 19]. Five pain scores were obtained from completed MPQs: Sensory (S), Affective (A), Evaluative (E), and Miscellaneous (M) scores (collectively referred to here as SAEM scores) corresponding to the appropriate sections on the short form MPQ, as well as an aggregate Pain Rating Index (PRI) score.

Second Attendance: Experimental Conditions

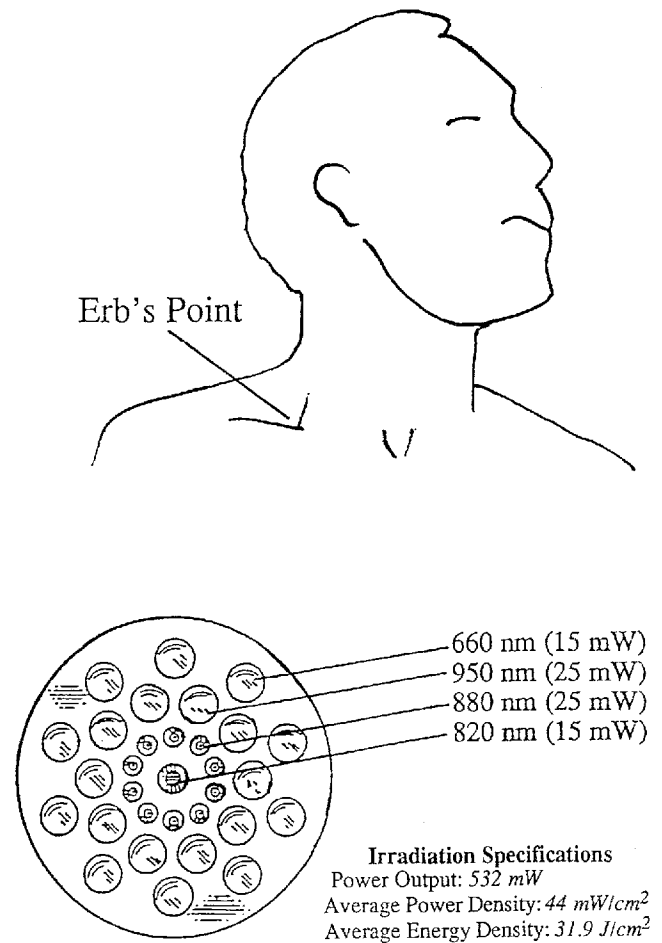
As already indicated, all subjects were required to attend on two occasions for the purposes of the trial. On the first occasion subjects completed the standard pain induction procedure to establish baseline data. Subjects were required to attend for a second session after 72 h, during which all were randomly assigned under double-blind conditions to one of three experimental conditions on the basis of a prepared master schedule. The experimental conditions were as follows.

Placebo condition. "Treatment" was completed using a dummy applicator that delivered no active radiation but in other respects looked and operated as an active unit. This dummy unit was applied to Erb's point in an identical manner to that described below for the active treatment conditions.

Two treatment conditions (Treatment Groups 1 and 2). Subjects received irradiation using a multiwavelength, multidiode array (Omega Laser Systems, London, England) applied directly to Erb's point (Fig. 1). As the active unit produced visible radiation (660 nm), the irradiated area and treatment head were thoroughly shielded from the gaze of subjects and investigators alike during both placebo and treatment conditions. All treatments were performed on the basis of schedule allocation by an independent researcher who was in no other way involved in the experiment. It should be noted that irradiation as described did not produce any subjective sensation on the part of irradiated subjects.

Irradiation Parameters

Irradiation commenced at time zero and continued until deflation was complete at the 12th min (i.e., for a total of 12 min). The array used in the current study consisted of 30 light emitting diodes arranged in three concentric circles producing radiation at wavelengths of 660, 880, and 950 nm and an additional central laser diode producing coherent radiation at 820 nm (Fig. 1). Apart from the latter, all the other sources were noncollimated superluminescent diodes with an av-



NB: Only coherent source is 820 nm diode

Fig. 1. Summary of irradiation protocol: site of irradiation and irradiation parameters. Note: lower drawing represents face of multiwavelength/multidiode array, showing precise arrangement of the various diodes.

erage divergence of 6°; spectral bandwidth for these was 5 nm (100% power). The unit was pulsed at 80% duty cycle at either 16 (treatment Group) or 73 Hz (treatment Group 2); at 16 Hz the pulse duration for each diode was 50 ms, with a 12.5 ms period between pulses. The unit delivered a total of 532 mW of incident power. Across the 12 cm² area of the unit's face, this represents an average incident irradiance of some 44 mW/cm². A total of 383 J was delivered during the treatment, corresponding to an average radiant exposure of 31.9 J/cm² across the treatment head.

Analysis

Results were analysed using one-way and repeated measures analysis of variance (ANOVA)

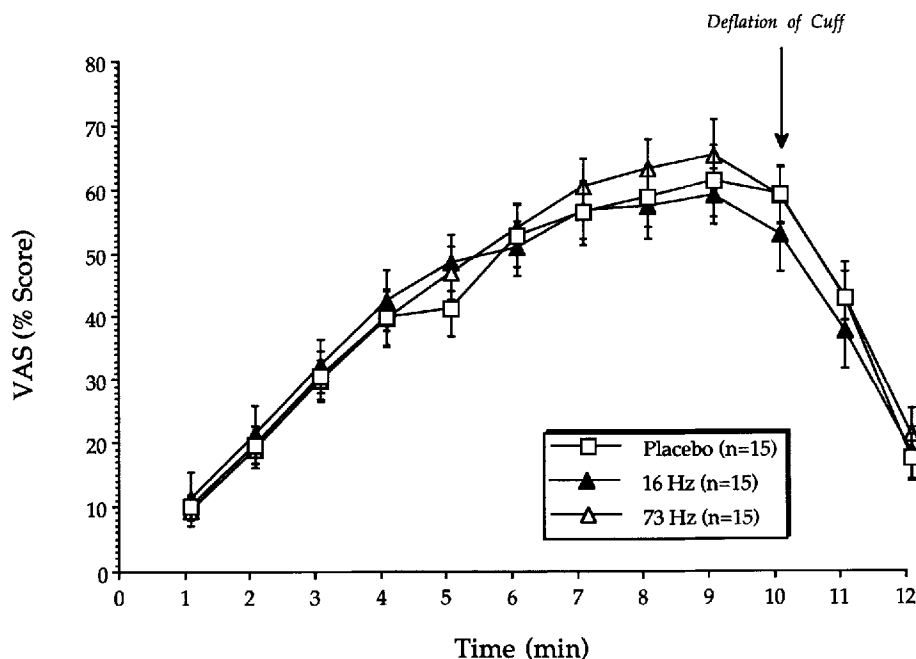


Fig. 2. Summary of Visual Analogue Scale (VAS) scores for initial attendance (points show means \pm s.e.m.).

and posthoc Fischer tests as appropriate. Results were considered significant at $P \leq 0.05$, with appropriate corrections for the posthoc tests.

RESULTS

Visual Analogue Scale Scores

Figure 2 plots VAS scores (%) against time (min) for subjects' first attendance, points show means \pm s.e.m. for subjects in each group. It should be stressed that the three groups as labelled are based upon subsequent (second attendance) group allocation; no treatment, active or sham, was completed during the first attendance. This graph clearly shows the progressive increase in pain intensity experienced by subjects during the first 10 min of the ischaemic pain induction procedure, followed by the rapid decrease in reported intensity during deflation of the cuff (Fig. 2). Analysis of these results using repeated measures ANOVA showed no significant differences in first attendance VAS scores between groups, indicating groups to be well matched for the procedure. In order to assess the effect of treatments compared to placebo, VAS scores were standardised for each subject by subtracting scores obtained during their initial attendance from those obtained during second (final) attendance; Figure 3 plots such VAS differences, between first and

second attendance, against time; hypoalgesia is represented by negative and hyperalgesia by positive scores. These resultant "difference" scores were compared between the experimental conditions using repeated measures ANOVA. Whereas Figure 3 shows a clearly superior effect at the 4- and 5-min points for Treatment Group 1 (16 Hz), compared to Placebo and Treatment Group 2 (73 Hz), no significant differences were found between VAS scores for the different conditions ($P = 0.44$).

MPQ Scores

Initial and final MPQ scores were analysed using ANOVA and corrected Fisher tests based upon difference scores as already described for VAS; these are summarised in Figure 4. MPQ scores, representing "worst pain experienced" during the procedure, showed significant differences between experimental conditions for the S component of the SAEM ($P \leq 0.05$), but not for the PRI scores. Corrected Fisher tests completed on the S score data indicated significant differences between Placebo and Treatment Group 1 (16 Hz); no other significant differences were found between groups. However, Figure 4 clearly shows a similar hypoalgesic tendency (compared to placebo) in the 73 Hz group in terms of PRI and S scores.

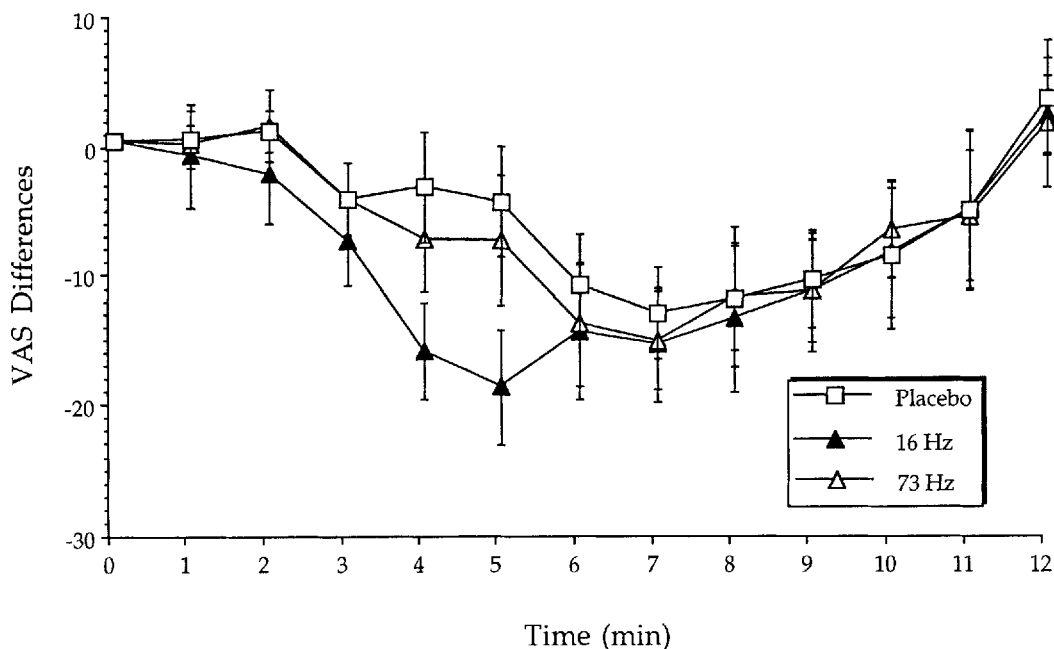


Fig. 3. Summary of differences in initial and final Visual Analogue Scale (VAS) scores (points show means \pm s.e.m.).

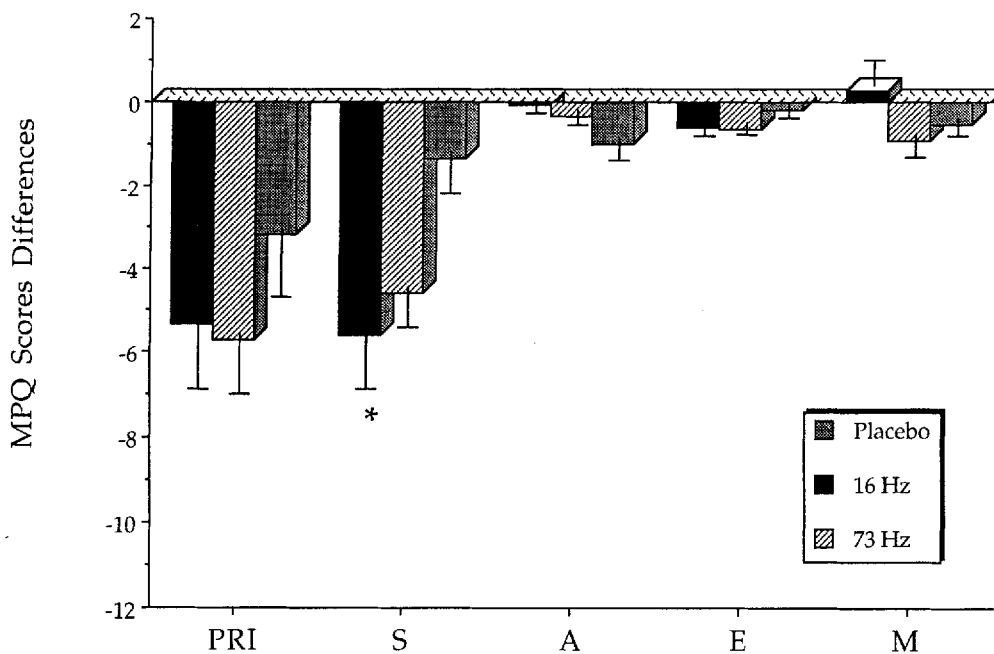


Fig. 4. Summary of differences in initial and final Pain Rating Index (PRI), and Sensory (S), Affective (A), Evaluative (E), and Miscellaneous (M) scores from McGill Pain Questionnaires (MPQ) (columns show means \pm s.e.m.; * $P < 0.05$).

DISCUSSION

The current study found a weak but significant treatment-mediated hypoalgesic effect upon MPQ (S) scores at one of the sets of irradiation parameters specified (i.e., Treatment Group 1; 16

Hz), but no other significant effects were demonstrated for any of the other components of the MPQ nor for the VAS scores. Although widely used and recommended as one of the best models of clinical pain for the laboratory assessment of

putative pharmacological analgesics [20–25], use of the ischaemic technique for such assessment of physical modalities has typically met with mixed success [26–28]. In failing to demonstrate a convincing treatment-mediated hypoalgesic effect with the combined phototherapy/laser therapy unit used here, it might be argued that these results merely provide further evidence of the unsuitability of the SETT as a laboratory method for assessment of the analgesic effects of physical modalities. However, this is unlikely, as the variant of the SETT technique described here also has been successfully used at this centre to demonstrate the analgesic potential of other physical modalities including transcutaneous electrical nerve stimulation [29].

The weak hypoalgesic effect found in the current study was based upon employment of irradiation dosages at the upper end of the therapeutic range [7] and the lower pulsing repetition rate (16 Hz), which previous work on animals had suggested might be more appropriate for the production of a short duration hypoalgesia of rapid onset [13]. Whereas in demonstrating such a treatment-mediated effect, these results might appear to refute the findings of Brockhaus and Elger [16], the disparate methodologies and irradiation parameters employed precludes direct comparison of the two sets of results. Brockhaus and Elger [16] assessed the effects of low intensity He-Ne laser irradiation upon thermal pain threshold, whereas the current study was designed to investigate the effects of phototherapy/low intensity laser at therapeutic dosages upon experimental ischaemic pain at relatively high levels of intensity. Scrutiny of mean PRI scores obtained in this investigation (>20 for all groups on first attendance) showed that the intensity of pain experienced by subjects in the current study was comparable to that experienced by patients suffering from a number of common painful clinical conditions [20].

The hypoalgesic effect in the current study was apparently most noticeable at the 4- and 5-min points. This is consistent with the action of a relatively weak analgesic, which is effective only at the lower levels of pain, but a further possibility is that the observed phenomenon is due to the existence of a therapeutic dosage “window” for this modality. If the latter were true, this would imply that the most effective dosages range between ~ 10 and 13.5 J/cm^2 . However, further work will be required to discriminate between these two alternatives.

Results of the current investigation thus serve to underline the necessity of additional laboratory-based work to definitively establish and further characterise the analgesic potential of this relatively new modality. Furthermore, such an approach would also allow investigation of the possible relevance of such parameters as irradiance, energy density (radiant exposure), wavelength, coherence, and other pulse repetition rates under carefully controlled conditions as a necessary precursor to any possible future clinical trials. To this extent the current results can in no way be seen as a definitive base upon to which to initiate clinical studies.

Despite the positive finding upon one component of the MPQ reported here, two essential caveats need to be stressed with regard to the continued clinical application of such devices as an analgesic modality. In the first instance, the current study was conducted under experimental conditions using a single dose of monochromatic light/laser irradiation. Prudence therefore needs to be exercised in using such results to support the clinical application of this treatment. To this end, and as has already been intimated elsewhere, carefully controlled and well-reported clinical studies represent the ideal method of definitively establishing the clinical efficacy of laser therapy and as was used here, combined phototherapy/laser therapy [2–3, 8]. Furthermore, although not essential to the determination of the clinical efficacy of this modality, the putative mechanism of analgesic action of low intensity monochromatic light/laser irradiation remains unclear and thus contributes to the scepticism surrounding this area. Systematic investigations of the neurophysiological effects of monochromatic light and laser should therefore form an essential component of any future research initiative within this field. To this end, recent research at this centre has demonstrated the potential neurophysiological effects of low intensity laser irradiation where appropriate irradiation parameters are used. Findings include significant laser-mediated increases in antidromic conduction latencies in the human median in vivo [30], conduction latencies in the frog sciatic nerve in vitro [31], and in intraneural microstimulation evoked pain thresholds [32]. Thus, whereas the current results would in no way refute Devor’s recent comments [5], it would appear that further controlled studies are indicated definitively to establish, or otherwise, what such devices might be able to offer for the treatment of the patient in pain.

ACKNOWLEDGMENTS

The authors thank the Physiotherapy Research Foundation of the U.K. and the D.H.S.S. (N.I.) for financial support, Dr. Tony Dusoir for statistical advice, Mr. Alistair Gilmore for writing the VAS program, and Mr. Robin Ritchie for technical assistance.

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