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ORIGINAL ARTICLE

Elke Vinck · Pascal Coorevits · Barbara Cagnie
Martine De Muynck · Guy Vanderstraeten
Dirk Cambier

Evidence of changes in sural nerve conduction mediated by light emitting diode irradiation

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Abstract The introduction of light emitting diode (LED) devices as a novel treatment for pain relief in place of low-level laser warrants fundamental research on the effect of LED devices on one of the potential explanatory mechanisms: peripheral neurophysiology in vivo. A randomised controlled study was conducted by measuring antidromic nerve conduction on the peripheral sural nerve of healthy subjects ($n = 64$). One baseline measurement and five post-irradiation recordings (2-min interval each) were performed of the nerve conduction velocity (NCV) and negative peak latency (NPL). Interventional set-up was identical for all subjects, but the experimental group (= 32) received an irradiation (2 min at a continuous power output of 160 mW, resulting in a radiant exposure of 1.07 J/cm^2) with an infrared LED device (BIO-DIO preprototype; MDB-Laser, Belgium), while the placebo group was treated by sham irradiation. Statistical analysis (general regression nodel for repeated measures) of NCV and NPL difference scores, revealed a significant interactive effect for both NCV ($P = 0.003$) and NPL ($P = 0.006$). Further post hoc LSD analysis showed a time-related statistical significant decreased NCV and an increased NPL in the experimental group and a statistical significant difference between placebo and experimental group at various points of time. Based on these results, it can be concluded that LED irradiation, applied to intact skin at the described irradiation parameters, produces an immediate and localized effect upon conduction characteristics in underlying nerves. Therefore, the outcome of this in vivo experiment yields a potential explanation for pain relief induced by LED.

E. Vinck (✉) · P. Coorevits · B. Cagnie · G. Vanderstraeten
D. Cambier
Department of Rehabilitation Sciences and Physiotherapy,
Ghent University, 9000 Ghent, Belgium
E-mail: elke.vinck@UGent.be
Tel.: +32-9-2405265
Fax: +32-9-2403811

M. D. Muynck · G. Vanderstraeten
Department of Physical Medicine and Orthopaedic Surgery,
Ghent University, 9000 Ghent, Belgium

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Introduction

Since the introduction of photobiostimulation into medicine, the light sources used have advanced technologically and varied in characteristics over the years. Advancement and variation of the sources implicate a concomitant necessity to revise research results in the respective domains of application. Research and clinical applications, in the past particularly focused on the effectiveness of low-level lasers, have shifted now to novel treatment units, such as light emitting diode (LED) devices.

The efficacy and applicability of LED irradiation within the field of wound healing has already partially been substantiated, in vitro [1, 2] as well as in vivo [3–6]. However, LED is not only promoted for its beneficial effects on the wound-healing process, it is also suggested to be potentially effective in the treatment of pain of various aetiology, although this claim has not yet been investigated thoroughly, either experimenally or clinically. The putative analgesic effects of LED remain to be further explored.

As the basic vehicle of pain is the neuronal system [7], measuring the neurophysiological effect of LED treatment would be an appropriate experimental approach to investigate the efficacy of LED on pain inhibition. Nerve conduction studies have become a technique for investigating the neurophysiologic effects of light therapy [8, 9].

Review of the literature regarding standard nerve conduction studies revealed that previous human studies on the influence of various light sources on peripheral nerves have utilized different methods, which hampers a comprehensive comparison. In general, this research was performed on the superficial radial nerve [10–13],

described by Shin J Oh [14] as an uncommon nerve conduction technique, or on the mixed median nerve [8, 9, 13, 15–17]. Following the method of Cambier et al. [18], the authors of this study decided to investigate the effect of the light source used on the conduction characteristics of the sural nerve. By investigating this sole sensory nerve, interaction of motor nerve fibres (motor response can easily be provoked by antidromic nerve stimulation [19]) can be avoided and given the superficial nature of the nerve, it should be sufficiently amenable to the effects of percutaneous LED irradiation.

A second major difference between the trials, and therefore also hindering an appropriate comparison between the results, is the wide range of used light sources: HeNe lasers [12, 13, 16] and GaAlAs lasers [8–10, 17, 18] or a monochromatic infrared multisource treatment unit [15].

With respect to the potential importance of LED irradiation for the treatment of pain, the current investigation was designed to assess the putative neurophysiological effects of LED on the sensory nerve conduction of the human superficial peripheral sural nerve and to establish a time course of the supposed phenomenon.

The experimental hypothesis postulates that LED generates an immediate decrease in conduction velocity and increase in negative peak latency. In addition, it can be postulated that this effect is most prominent immediately after the irradiation and will weaken as time progresses.

Study design

This study was approved by the Ethical Committee of the Ghent University Hospital. After explanation of the experimental procedure, written informed consent was obtained from each subject.

Subjects

After screening, based on a brief medical history, excluding subjects with contraindications to LED irradiation (such as light hypersensitivity, fluctuating blood pressure, insufficient blood circulation, fever, inflammation of the skin) or conditions that might affect sensory nerve conduction (such as diabetes, peripheral neuropathy, radicular syndrome, peripheral nerve damage, neuromuscular disorders or peripheral edema), eligible subjects were enrolled. Sixty-four healthy volunteers, 24 males and 40 females (mean age 26 ± 6 years, range 18–42 years), participated in this study. The body mass index (BMI) of each subject varied within the normal range ($= 18.5$–24.9) [20] (mean BMI 21.6 ± 1.7, range 18.6–24.9). Subjects were randomly allocated to a placebo or an experimental group. Each group of 32 subjects was composed of 12 males and 20 females.

Experimental procedure and data acquisition

In order to be able to quantify the negative peak latency (NPL) (measured from the start of the stimulus artefact to the peak of the negative portion of the nerve action potential) and nerve conduction velocity (NCV) of the sural nerve, a rigid protocol was followed.

With respect to the known relationship between nerve conduction characteristics and temperature, the ambient temperature was kept constant (23C–26°C room temperature) during the investigation. In view of this temperature issue, the standardized protocol started with 10 min of accommodation, during which the subjects rested in prone position on a treatment table.

Immediately before this adjustment period, the skin over the dorsolateral aspect of the left calf and foot was cleaned with alcohol to remove surface lipids. This preparation of the treatment area was followed by the placement of the electrodes (TECA Accessories; Oxford Instruments Medical Systems Division, Old Woking, UK) as described by Delisa et al (1987) [21].

The two-posted (2 cm separation, anode distal) surface caption electrode was placed distal and posterior of the lateral malleolus, on the skin covering the sural nerve. The fixation of the earth electrode (Medelec; Oxford Instruments Medical Systems Division, Old Woking, UK) occurred 12 cm above the caption electrode, according to the description of Delisa et al. [21]. A standard bipolar stimulator was used at 14 cm above the caption electrode to map the ideal stimulation point. To level off intraindividual variations in the amount of sensory response, attributable to the successive placement of the bipolar stimulator in course of the investigation, a two-posted (2 cm separation, cathode distal) bar stimulating electrode was attached at the point where the maximal response was obtained.

This placement of the electrodes allows antidromic stimulation of the sural nerve. Electrophysiological stimulation and recordings were obtained with a Medelec Sapphire Premiere (Vickers Medical, Old Woking, UK), providing a monophasic pulse of 0.1 ms. A supramaximal stimulus intensity, with a nominal voltage of 72–295, was used to produce each evoked sensory response.

Baseline measurements of NPL and NCV were immediately followed by treatment of the subjects, according the protocol detailed below. Recordings were subsequently repeated at 2-min intervals over an 8-min period, resulting in five recordings (one immediately after the completion of the treatment and one at 2, 4, 6, and 8 min after irradiation). Skin temperature was recorded concomitantly throughout the procedure: at the time of baseline measurement, immediately after LED irradiation at the time of the first recording and consequently at 2-min intervals, together with the four final electrophysiological recordings. For this, a surface digital C9001 thermometer (Comark, UK), sensitive to temperature changes of 0.1°C, was used at the same point of LED administration, namely at 7 cm above the caption electrode. The procedure was identical for both

conditions, but the subjects in the placebo group received sham LED irradiation.

Light characteristics and irradiation procedure

Irradiation was administrated with a light emitting diode device (BIO-DIO preprototype; MDB-Laser, Belgium). The probe used emitted infrared light with a wavelength of 950 nm (power range, 80–160 mW). The area of the probe was 18 cm^2 and the frequency was variable within the range of 0–1500 Hz.

Preceding baseline measurement, the treatment point was marked on the skin overlying the course of the sural nerve at 7 cm above the capture electrode, i.e. the exact mid-point between the stimulation and capture electrode. The LED probe was held in contact with the skin, perpendicular to the skin surface during the complete irradiation procedure. LED treatment consisted for all subjects of the experimental group out of 2 min lasting irradiation. The LED was set to deliver a continuous energy density of 1.07 J/cm^2, at a power output of 160 mW. These parameters were selected, as they are appropriate for the treatment of pain in a clinical setting. First of all, because the duration of the treatment is clinically feasible and secondly because the parameters are within the scope of previously described light source characteristics [1–3, 6, 9, 15].

Statistics

Although superficial skin temperature did not change significantly in the course of the investigation, the influence of the measured skin temperature on NPL and NCV was taken into account by using a correction factor of, respectively, 0.2 and 1.47 m/s°C. All corrections were calculated towards a reference skin temperature of 32°C.

Difference scores, i.e. the variation between baseline measurements and each post-irradiation recording, were used as the basis for statistical analysis. A General Regression Model for repeated measures with one within-subjects factor (time: 0 min = immediately after irradiation, 2, 4, 6 and 8 min following LED irradiation) and one between-subjects factor (group: placebo or LED irradiated) was performed, followed by appropriate pairwise comparisons (post hoc LSD or post hoc LSD), to determine whether any differences between baseline measurements and postirradiation recordings were statistically significant.

The Statistical package for social sciences (SPSS 11.0) was used for analysis and statistical significance for all tests was accepted at the 0.05 level.

Results

Figure 1 shows NCV mean difference scores of the placebo and the LED irradiated group plotted against time in minutes. The values of the irradiated subjects decrease directly after the irradiation and reach a first low point 2 min after finishing LED treatment. This decrease is followed by a marginal increase at 4 and 6 min and again an important decrease at 8 min. Statistical analysis (general regression model for repeated measures) of these data indicated a significant interactive effect ($P = 0.003$). Post hoc LSD further showed significant differences between baseline measurements and all post-treatment recordings (Table 1). Mutual comparison of the values from the post-treatment recordings did not reveal any significant difference. In addition, there was no significant difference determined in the placebo group in course of time.

A similar representation was used for the results of the NPL. Figure 2 reproduces NPL plotted against time in minutes, revealing for the irradiated group an increased latency with two important peaks, one at 4 min and one at 8 min.

Statistical analysis of the mean difference scores again indicated a significant interactive effect ($P = 0.006$). Further post hoc LSD analysis of the data, presented in Table 2, showed significant differences between baseline measurements and all post-treatment recordings of the experimental group. The mean difference score of the first post-treatment recording of this same group (LED irradiated) differed significantly with the recording 4 min ($P = 0.003$), 6 min ($P = 0.018$) and 8 min ($P < 0.001$) after LED irradiation. As well as the recording 2 min after irradiation which differed significantly ($P = 0.013$) with the 8-min post-treatment recording. As observed for the NCV, the NPL of the placebo group did not reveal any significant difference in time course.

At the time of the final recording, the NCV and NPL mean difference scores of the irradiated group did not return to their respective baseline values.

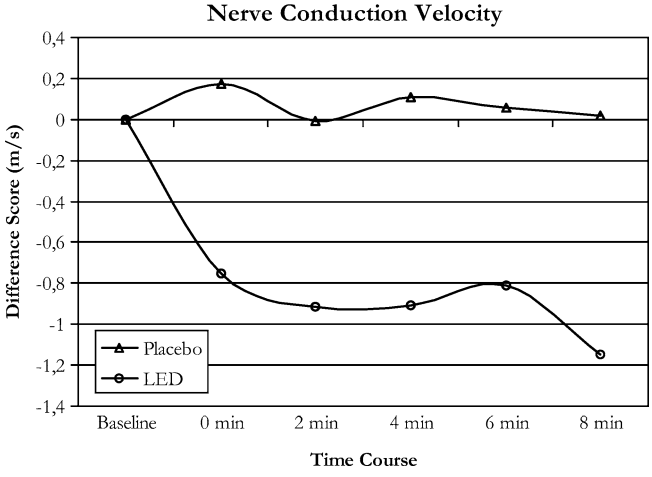

Fig. 1 Mean difference scores (m/s; variation between baseline measurements and post-treatment recordings) of the nerve conduction velocity plotted against time (minutes) (means ± SD; $n = 32$)

Table 1 Summary of the influence of LED irradiation on nerve conduction velocity

Minutes	Placebo[a]	Time-related significance[b]	LED[a]	Time-related significance[b]	Group significance[c]
0	0.171 ± 0.353	0.329	−0.752 ± 1.348	0.002*	< 0.001*
2	−0.008 ± 0.357	0.969	−0.915 ± 1.520	0.004*	0.002*
4	0.111 ± 0.377	0.647	−0.908 ± 1.898	0.021*	0.004*
6	0.055 ± .397	0.770	−0.809 ± 1.301	0.002*	< 0.001*
8	0.021 ± 0.386	0.932	−1.146 ± 1.881	0.003*	0.001*

[a]Mean difference scores and standard deviations of the recorded nerve conduction velocity of the placebo and the LED irradiated group

[b]*P* values of the pairwise comparison (post hoc LSD) between baseline measurements and all post-treatment recordings (baseline = preceding irradiation, 0 min = immediately after irradiation, 2, 4, 6 and 8 min following LED irradiation) of the placebo and the LED irradiated group

[c]*P* values of the pairwise comparison (post hoc LSD) between placebo and irradiated subjects, for all post-treatment recordings (0 min = immediately after irradiation, 2, 4, 6 and 8 min following LED irradiation)

*Significant *P*-values ($P < 0.05$)

Furthermore, post hoc LSD analysis, also presented in Tables 1 and 2 (group significance), revealed statistical differences between the experimental and the placebo group for NCV as well as for NPL. NCV and NPL were statistical significant between both groups at all points of time, except from the NPL recording immediately after finishing irradiation.

Discussion

Notwithstanding the above-mentioned difficulties in comparing results between different trials, on nerve conduction, we attempt to discuss the current findings in view of the results of the previous studies.

This investigation revealed that percutaneous LED irradiation at feasible and current clinical parameters, generates measurable and significant changes in human sural nerve antidromic conduction latency and velocity. These results thus support previous findings of light-mediated nerve conduction latency shifts in vivo [8, 10, 12, 18], although there are several important issues to be discussed.

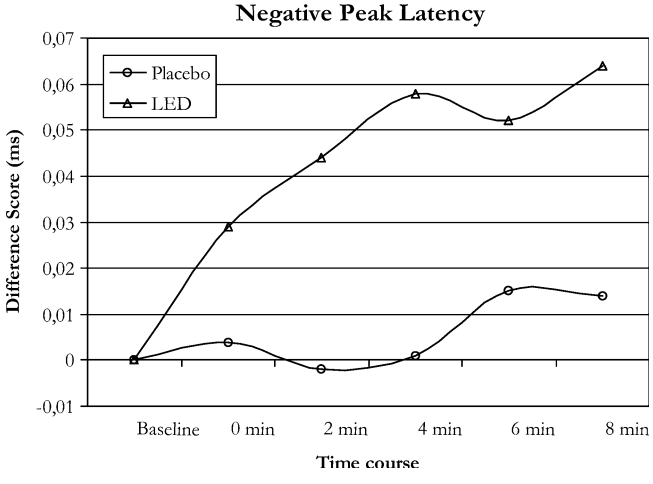

Fig. 2 Mean difference scores (variation between baseline measurements and post-treatment recordings) of the negative peak latency plotted against time (minutes) (means ± SD; $n = 32$)

A first comment deals with the progress of the NCV and NPL in function of time. As postulated, the NCV decreases significantly immediately after irradiation, corresponding with a significant increased NPL. However, this effect does not weaken as time progresses, both variables remain significant throughout the 8 min during the observation period.

Cambier et al. [18] noted a similar significant effect of GaAlAs laser irradiation on the conduction characteristics until 15 min post-treatment, as did Walsh et al. [10], although this slight increase in NPL was not significant at any moment. Two other studies [8, 22] with a GaAlAs laser even registered comparable effects over a period of 55 [8] and 60 min [22] post-irradiation, respectively. Given the results of these previous studies, post-treatment conduction measurements should be extended in time. At present, for all studies, it remains unclear at what point of time the effect extinguishes, although the interval of time during which LED treatment remains effective is clinically important when treating pain.

Noble et al. [15] also noticed relatively long-lasting neurophysiological effects (at least 45 min) mediated by a monochromatic multisource infrared diode device, although it needs to be mentioned that this study, performed with a comparable light source as the current investigation, revealed a significant decrease of the NPL. These inverse results between the study of Noble et al. [15] and the current investigation could be attributed to the concomitant increase of the skin temperature [15]. As it has been well recognised that a variation in tissue temperature causes a corresponding alteration in nerve conduction velocities and peak latencies [9, 15, 23–27], the temperature changes may indeed provide an explanation for the observed findings. In an attempt to analyse the influence of a direct photobiological effect on sural nerve conduction characteristics, rather than working out the effects based upon thermal mechanisms, the present study corrected the skin temperature towards a reference temperature of 32°C. This correction was performed notwithstanding the fact that the superficial skin temperature did not change significantly before and

Table 2 Summary of the influence of LED irradiation on negative peak latency

Minutes	Placebo[a]	Time-related significance[b]	LED[a]	Time-related significance[b]	Group significance[c]
0	0.004 ± 0.053	0.755	0.029 ± 0.080	0.019*	0.145
2	−0.002 ± 0.046	0.856	0.044 ± 0.100	0.002*	0.021*
4	0.001 ± 0.056	0.925	0.058 ± 0.090	< 0.001*	0.004*
6	0.015 ± 0.054	0.216	0.052 ± 0.079	< 0.001*	0.034*
8	0.014 ± 0.052	0.264	0.064 ± 0.088	< 0.001*	0.007*

[a]Mean difference scores and standard deviations of the recorded negative peak latency of the placebo and the LED irradiated group

[b]*P* values of the pairwise comparison (post hoc LSD) between baseline measurements and all post-treatment recordings (baseline = preceding irradiation, 0 min = immediately after irradiation, 2, 4, 6 and 8 min following LED irradiation) of the placebo and the LED irradiated group

[c]*P* values of the pairwise comparison (post hoc LSD) between placebo and irradiated subjects, for all post-treatment recordings (0 min = immediately after irradiation, 2, 4, 6 and 8 min following LED irradiation)

*Significant *P*-values ($P < 0.05$)

after LED irradiation, as well as despite the fact that influencing nerve temperature takes place long after affecting skin temperature [23], and thus being (almost) impossible after 2 min of irradiation, followed by 8 min of registration. Introduction of the correction factor implies likewise that eventual influence on nerve conduction by cooling of the limb due to inactivity, as described by Greathouse et al. [11], can be excluded.

These facts suggest that temperature changes did not contribute to the demonstrated effects of LED on nerve conduction. Nevertheless, the underlying mechanism of the observed effects remains indistinct.

A following remark regarding the fluctuation of NCV and NPL in function of time considers the fact that both the NCV and the NPL do not change in a constant way up to eight minutes after LED irradiation (Fig. 1, 2). The decrease in NCV and the increase in NPL display a small though not significant inversion of the effect at 4 and (NCV) or 6 (NPL) min. This is probably attributable to the fact that some degree of fluctuation is to be expected when measuring NCV and NPL, besides there is a similar variation in the placebo groups.

Although investigating dose dependency was not intended, an additional remark considers the fact that the use of optimal irradiation parameters is essential to obtain the observed neurophysiological effect. Nevertheless, it is impossible to determine ideal light source characteristics for effective treatment, as the range of used wavelengths (632–950 nm), radiant exposures (1.07–9.6 J/cm^2) and even frequency (pulsed or continuous) are not sufficiently similar between the different studies. It can only be concluded that a pulsing light source [9, 10, 28] does not provide the postulated results. Radiant exposure, exposure time, power range and wavelength are not yet established, but based on this study and previously described assays, it can be speculated that the ranges of these parameters are quite large.

In comparison with other studies where the number of subjects is 10 or less [8–11, 15, 16, 22, 29] (with the exception of the studies from Cambier et al. [18] and Snyder-Mackler et al. [12], who respectively tested 15 and 24 subjects), a relatively large number of subjects ($n = 32$) was investigated in each group. In spite of the large investigated population, it should be noted that the magnitude of the described changes in NCV and NPL can simply be replicated by lowering the temperature of the extremity, as the observed changes are within the expected physiological ranges, making the clinical significance of the change questionable. (This fact does not implement that the decrease and the significant changes were temperature mediated.)

A key question, and meanwhile the initial impetus for future investigation, is whether the measured effects can be extrapolated to the actual nociceptive afferents, namely the myelinated Aδ-fibers(12–30 m/s [14]) and unmyelinated C-fibers (0.5–2 m/s [14]), respectively, conducting acute and chronic pain. The functional testing of these nociceptive pathways has recently been extensively evaluated. The currently accepted neurophysiological method of assessing nociceptive pathways relies on laser-evoked potentials (LEPs) [30], as they selectively activate Aδ-fibres and C-fibres [31].

As up till now, LEP is not available in the own or any surrounding research centre, the investigators of this study had to perform a standard nerve conduction study (assessing the large myelinated Aβ afferents). Therefore, the current and previous beneficial results of low level light therapy on conduction characteristics of nerves in vivo should initiate measurements of clinical effectiveness, first of all in laboratory settings and afterward at a clinical level.

Conclusion

Despite these remarks and the limited knowledge regarding the underlying mechanism, the present findings enable the following conclusions to be drawn: LED irradiation at clinical applied densities produces an immediate and localized effect upon conduction characteristics in underlying nerves. More specifically, it is proven that LED treatment lowers the NCV and augments the NPL, resulting in a reduced number of impulses per unit of time. Therefore, the outcome of this in vivo experiment assumes that LED possibly induces pain relief.

In order to encourage widespread acceptance for the use of this non-invasive pain-reducing modality in clin-

ical settings, prospective research should establish the precise relationship between LED and pain relief, as well as determine the ideal irradiation parameters and verify which painful conditions can be treated with this treatment unit.

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