

Dose Thresholds and Effect Mechanisms for Pain Management with LASER Phototherapy

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Summary

Arguably, the two most important aspects regarding laser phototherapy for pain management are those of effect mechanism (to determine the most appropriate application) and of dosing parameters. Herein is summarised the outcomes of more than 15 years of the author's research to date, to clarify some of these factors. Initial investigations demonstrated that the central descending inhibitory (endogenous opioid) system was involved in the effect mechanism of phototherapy and that doses below $5\text{J}/\text{cm}^2$ in the wavelengths tested, had the best effects in a chronic pain clinical model. Subsequent research using a non-invasive clinical model in lateral epicondylalgia has established that the descending inhibitory system is not the sole likely origin of the treatment response; or, if it is, it plays this role selectively for only some combinations of wavelength, dose and power output. Repeated low doses of laser (at some wavelengths) are sufficient to stimulate physiological responses and reduce pain in subjects with lateral epicondylalgia. It is clear further information is required for dosing and dose threshold factors of laser phototherapy for clinical pain management.

Introduction

Substantial research has investigated possible mechanisms underlying the therapeutic actions attributed to LLLT. The underlying mechanism of laser-mediated analgesia remains unknown (Zinman, Ngo, New, Gogov, Ng & Brill, 2004). A number of clinical trials to assess the efficacy of laser therapy for musculoskeletal pain syndromes have been undertaken (Gan, Thorsen & Lønnberg, 1993), however research in the field continues to be hampered

perhaps as a consequence of methodological shortcomings and the extensive array of combinations of dosing parameters. The increasing number of trials with a result “*in favour of LLLT is by far too large to be explained by random chance alone*” (Gur, Sarac, Cevik, Altindag & Sarac, 2004, p.230) thereby justifying further investigations. The optimisation of laser-mediated analgesia requires a sound understanding of the underlying mechanism (Baxter, 1994), and the confirmation of such mechanisms necessitates consideration of the process of pain perception and modulation.

The Gate Control Theory of pain, proposed by Melzack and Wall in 1965, shifted the emphasis of pain mechanisms from the periphery to the central nervous system. The idea that the transmission of pain from the periphery could be modulated by controls descending from the brain required the brain to be recognised as an “*active system that filters, selects and modulates inputs*” (Melzack, 1999, p.123). Current investigations of descending pain modulation originated from the work of Reynolds (1969) who reported that abdominal surgery in the rat could be performed without a general anaesthetic, and instead with electrical stimulation of the midbrain periaqueductal gray (PAG) region (Gebhart, 2004). The PAG has retained its importance for endogenous analgesic mechanisms despite other regions within the brain since being recognised as areas from which analgesia can be elicited (Wright, 1995). There appear to be two forms of analgesia that originate from distinct regions within the PAG: stimulation of the dorsal system (dPAG) elicits non-opioid analgesia with concurrent excitation of the sympathetic nervous system (sympathoexcitation); and, stimulation of the ventral system (vPAG) results in an opioid form of analgesia and is characterised by sympathoinhibition (Wright, 1995). A clinical model of lateral epicondylalgia has been developed by others, and is one that we utilise for the purpose of testing this proposed laser effect mechanism. Moreover, the model can be used to test dose efficacy and thresholds of stimulation using different combinations of laser parameters. The development of our knowledge about opioid-based and descending pathways of pain mediation is discussed below.

Human chronic pain (trigger point) model:

There is evidence to support both opioid and non-opioid based analgesia following LLLT. Walker (1983) was the first to investigate the descending pain inhibitory systems as a factor implicated in laser-mediated analgesia after finding increased levels of urinary 5-hydroxyindolacetic acid (a by-product of serotonin metabolism) and concurrent hypoalgesia in subjects with chronic pain. We were able to demonstrate support for this assertion, observing decreased pain and increased levels of adrenocorticotrophic hormone (ACTH) and β -endorphin (BEP) following laser irradiation of myofascial trigger points (Laakso, Cramond, Richardson & Galligan, 1994; Laakso, Richardson and Cramond, 1997). In a randomised, double-blind placebo-controlled study, we compared the effect of two doses (1J/cm² and 5J/cm²) of 820 nm and 670 nm laser, and near-monochromatic light (660nm, 30 nm bandwidth) in 56 participants with trigger points of pain in the neck and shoulder region. Subjects

received treatment over a 2 week period. Outcome measures included subjective pain scores and measures of plasma BEP and ACTH to assess the opioid response.

The results of the above study demonstrated that 820 nm laser at 1J/cm² and 5J/cm² resulted in significant reductions in pain ($p < 0.001$). Of interest was that only those participants who received laser phototherapy complained of side effects from the treatment. ACTH increased cumulatively to treatment with 820 nm laser at 1J/cm² ($p < 0.001$); and with 820 nm and 670 nm laser at 5J/cm² ($p < 0.05$). Plasma BEP levels were noted to increase significantly between Days One and Four ($p < 0.05$) in subjects who received 820 nm laser at 5J/cm² but this increase plateaued after this time. We concluded that laser hypoalgesia was dependent on dose, or power output. Moreover, we suggested that ongoing treatment at the higher dose (5J/cm²) had no further beneficial effects beyond a few treatments.

Although the relationship between peripherally circulating BEP and ACTH and central analgesia could not be established at the time, we hypothesised that inflammatory mediators such as lymphokines (in particular interleukin-1: IL-1) might be stimulated by the application of laser phototherapy. Furthermore, we hypothesised that IL-1 (or other cytokines) might be capable of causing central release of endogenous factors through the stress-immune system (the hypothalamic-pituitary-adrenal axis) in close relationship with the sympathetic nervous system. The alternative hypothesis that we proposed at this time, was that local inflammatory factors (e.g., corticotropin-releasing hormone - CRF) at the site of laser application may have had a direct effect on circulating opioids. This factor remained unresolved. It was not until Stein (1995) and Machelska, Cabot et al (1998) established the presence of peripheral immune-cell derived opioid and opioid receptors, and the preferential homing of immune cells to inflamed sites where they secreted opioids to reduce nociception, that a method became available to test these hypotheses. We went on to study this possible effect in an animal model.

Animal inflammatory model:

In an attempt to determine how local pain relief is mediated by laser phototherapy and how dose affects the relationship, we tested the hypothesis that peripheral opioids are involved in inflammatory pain in an animal model. The model entailed induction of inflammation in the hind-paws of male Wistar rats, and comparison of paw volume, temperature and pressure threshold in non-inflamed, and laser-treated and untreated inflamed hind-paws. Over a number of pilot trials, we tested a range of dose and wavelength combinations to learn more about this factor. The initial unpublished pilot results using 780nm laser at a dose of 5J/cm² (the chosen dose was designed to reflect the outcomes of the human chronic pain trial results above) demonstrated no significant effects on the outcome measures when assessed at 5 min after intervention. A further unpublished pilot trial using the same wavelength at 4J/cm² demonstrated no significant effects on the same outcomes measures when assessed at 1 hr and 6 hr post-intervention. In a further pilot trial using

820 nm laser at $5\text{J}/\text{cm}^2$ (reflecting the dose and wavelength used in the human chronic pain trial) we noted that repeated treatment at 1hr and 6 hr post-laser had no effect on outcome measures. We repeated the trial of 780nm laser @ $1\text{J}/\text{cm}^2$ and $2.5\text{J}/\text{cm}^2$ (Laakso and Cabot, 2005) and found that $1\text{J}/\text{cm}^2$ had no significant effect on anti-nociceptive responses (paw pressure and paw thermal thresholds) but $2.5\text{J}/\text{cm}^2$ resulted in selective significant improvement in paw pressure threshold at 30 minutes after laser phototherapy but not in paw thermal threshold. Immunohistochemistry of paw tissues demonstrated normal BEP-containing lymphocytes in the hind-paws of control animals but no BEP-containing lymphocytes after 336 h in the hind-paws of animals that received laser at $2.5\text{J}/\text{cm}^2$. We were led to conclude that the dose/wavelength combination differentiated selectively via the pressure-sensitive rather than the thermal-sensitive neural pathways. Subsequent research by Rittner and Stein (2005) suggests that efficient central analgesia signals a reduced need for recruitment of opioid-containing immune cells to the injured site perhaps suggesting that laser phototherapy may stimulate neural pathways (eg, descending pathways or the sympathetic nervous system - SNS) requiring no local opioid response.

It is interesting to note that subsequent to the above studies, in a study that investigated the effect of 830nm laser @ $200.7\text{J}/\text{cm}^2$ on peripheral endogenous opioid analgesia in rats, Hagiwara et al (2007) have established that proopiomelanocortin (POMC – a precursor molecule to ACTH and BEP) and CRF demonstrated significantly increased levels at 24 h after laser (compared to controls). In the same study, paw thermal threshold increased at 24 h after laser phototherapy, with the effect being transiently reversed under the influence of naloxone. Paw pressure threshold was not measured. The authors also found that there was a larger accumulation of BEP positive cells in harvested paw tissue at 48 h after laser phototherapy compared to controls.

We have gone on to examine further the effect of laser phototherapy in this model (Kingston, Cabot and Laakso, 2008), and found that anti-nociceptive responses in rats are not evident at 10 minutes after laser phototherapy, confirming the time-dependent nature or threshold for stimulation effects. Furthermore, we have also examined the effect of laser phototherapy on BEP content in regional lymph nodes in response to 780nm laser at $2.5\text{J}/\text{cm}^2$. The conclusion to be drawn from these results is that there is indeed an opioid-based analgesic effect selectively based on dose and/or wavelength; and on timing of laser application with a probable peak physiologic threshold for effect. The challenge is to identify the specific dose and wavelength combinations which provoke the effects; when it is most efficacious to apply the laser phototherapy; and to confirm these effects in humans. We have gone on to test an innovative, non-invasive method for doing so in a clinical model of pain, in the construct that the mechanism of effect is regulated through the SNS. A summary of the outcomes of our clinical research to date follow.

Human chronic pain model to test sympathetic nervous system outflow:

Sympathoinhibition following laser therapy was demonstrated in a study

investigating the effect of laser phototherapy on sympathetic activity in individuals with myofascial trigger points (Snyder-Mackler, Barry, Perkins & Soucek, 1989). The finding provides support for an opioid-based (sympathoinhibitory) effect of laser-mediated analgesia. Conversely, early animal studies demonstrated that analgesia elicited by irradiation to the tails of experimental rats was only partially reversed by naloxone, a potent opioid antagonist, suggesting the analgesia was not opioid-dependent (Jacob & Ramabadran, 1978). As noted above, there is some evidence to the contrary (Hagiwara et al, 2007), and the effect may be transient or dose/wavelength-dependent, or time-dependent.

To further investigate the role of the SNS to laser stimulation, a pilot study using pain-free subjects was undertaken to test the feasibility of the model (described in Graham and Laakso, 2008). It is possible to measure physiological responses such as heart rate (HR), blood pressure (BP), skin temperature (ST) and skin conductance (SC) which are reflective of SNS outflow. The direction of change in sympathetic activity (either sympathoexcitation or sympathoinhibition) occurring following the intervention, concurrent with analgesia, may provide support for an analgesic effect mediated by the dPAG (causing a non-opioid response) or the vPAG resulting in an opioid-response. A change in pain levels without observing changes in SNS measures supports an alternative mechanism not involving the SNS. In the pilot study, no significant changes in SNS measures were found in pain-free subjects. Following the work of Karu (1989) in which she concluded that the intensity of effect is determined by a cell's physiologic state prior to irradiation, this result was not unexpected. The pilot trial resulted in establishing the procedure as a non-invasive method by which to investigate the effect of laser phototherapy on SNS activity using symptomatic subjects.

Subsequent to the above studies, we have gone on to test the effect of laser phototherapy in a clinical model of pain, i.e., lateral epicondylalgia (LE – tennis elbow). The model is convenient as the incidence of LE is between 1-3% of the general population (Shiri et al, 2006); the elbow is easily accessed in affected individuals; the procedure is non-invasive; and the methodology (as a reflection of central hypoalgesia) has been established in research investigating other interventions (Paungmali et al, 2003; Simon, Vicenzino & Wright, 1997; Chiu & Wright, 1996; Vicenzino, Collins & Wright, 1996).

In the first (thus far unpublished) study (McKirdy and Laakso, 2005), we conducted a repeated measures, randomised, placebo-controlled, double-blind trial in 21 subjects with chronic LE. Participants received 3 interventions on 3 separate days in random order: (1) control - no intervention (2) placebo (deactivated) laser, and (3) laser at 780nm (Compu-Lase SM 2000, Spectra-Medics Pty. Ltd.) at 2.5 J/cm² to the 3 most tender points at the lateral epicondyle. Participants acted as their own controls. Subjective pain scores, pain-free grip strength, pain pressure threshold, HR, BP, mean arterial pressure (MAP), blood flux (BF), SC and ST were measured during baseline, intervention and post-intervention periods on each experimental day. The results demonstrated a statistically significant treatment effect on cutaneous BF (p=0.036) and MAP (p=0.032). The change in BF (increase of 2.69%) and

MAP (decrease of 1.75 mmHg) indicated a sympathoinhibitory (opioid) response to LLLT. No statistically significant treatment effects were noted for other sympathetic outcome measures or for the pain-related measures.

In a separate follow-up single case study, we applied laser (780nm) at 3 J/cm² to each of 11 tender points at the lateral epicondyle and insertion of the common extensor tendon. The single case study (of a 49 year old female) demonstrated a statistically significant treatment effect on BF, glabrous ST, pileous ST, and ulnar SC ($p=0.01$). In contrast to the group comparison study described above, the change in BF (decrease of 62.41%), glabrous ST (decrease of 1.20%), pileous ST (increase of 1.88%), and ulnar SC (decrease of 8.34%) indicated a sympathoexcitatory (non-opioid) response to laser phototherapy.

To clarify the disparate nature of the above results, we conducted another single case study (of a 39 year old male) using 780nm laser at 2.5 J/cm² to each of 13 tender points at the lateral epicondyle and insertion of the common extensor tendon (Laakso, Meppem et al, 2006). On this occasion, grip strength and pain pressure threshold improved after laser phototherapy; BF decreased by 30% and glabrous ST also decreased after treatment. The results reflected a mixed sympathetic nervous system response with likely bias towards sympathoinhibition indicating opioid-based analgesia.

In a further attempt to clarify the nature of the effect as well as identify whether a dose threshold is apparent, we have recently replicated some of the methodologies described above. In a repeated measures, randomised, placebo-controlled, double-blind study of 19 participants with chronic LE, we investigated the effect of 830nm laser (OmniLase, Laserdyne Technologies, N. Stenning & Co., Pty Ltd) at 3 J/cm² applied repeatedly to the 3 most tender points for a total of 13 exposures (Barnes and Laakso, 2008). Participants acted as their own controls. The same outcome measures were included as used in the above study by McKirdy and Laakso (2005). The findings demonstrated no measurable effects on immediate post-treatment pain scores or on sympathetically-mediated outcome measures. However, all participants reported improved pain scores at 24 h after the laser intervention.

The above study (Barnes and Laakso, 2008) was designed to identify the minimum laser dose threshold required to gain an immediate treatment effect. Despite the improved pain scores at 24 h, the decision to use a different wavelength in this study (compared to the wavelength used in the previous study by McKirdy and Laakso, 2005) confirmed the wavelength-dependent nature and the time-dependent nature of laser hypoalgesia, and partly confirms the WALT guidelines which recommend only wavelengths between 780-820nm or 904nm for LE.

Conclusions

The studies described above, outline the continuum of work which we have pursued over a number of years, in order to understand the nature of dosing, timing of treatment responses, and the effects of wavelength on possible descending pathways of pain. Much work is still required to elucidate

the effect mechanisms / pathways for laser hypoalgesia, and the effective laser and dose parameters required. At this point in time, it is reasonable to conclude that some wavelength/dose combinations have an effect through opioid-dependent pathways, and other such combinations do not. Beyond a better understanding of the specific conditions in which laser is likely to be most efficacious, knowledge of effect mechanisms is unlikely to have a significant bearing on those who are 'laser converts'. However, this knowledge is important in convincing those who remain yet to be convinced of the efficacy of laser. Most importantly, knowledge of the minimum effective dose threshold is important to understand, if we wish to optimise the way in which we utilise laser phototherapy.

Acknowledgements

Some results presented herein have been from studies with research students Julia McKirdy, Erin Kingston and Allison Barnes (at Griffith University); Dr David Graham (at The University of Queensland and the Gold Coast Hospital); or in collaboration with Dr Peter Cabot (at The University of Queensland).

[Human and animal research ethics approval was gained for all studies described above].

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