


Photobiomodulation for modulation of neuropathic pain and improvement of scar tissue

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Abstract

Background: This case-report explores the effects of photobiomodulation therapy (PBMT) on the healing of scar tissue. The patient was a 32-year old female two years post cholecystectomy resulting in a 15 cm linear scar that was causing severe pain.

Methods: Treatment was initiated using the BIOFLEX® therapist device which consists of LED arrays and laser probes of a specific wavelength, power and frequency applied directly on the skin overlying the scar. The frequency and duration of treatment was every other day for six weeks in a clinic setting, followed by three times a week for two months at home. Then the patient continued to use the BIOFLEX® therapist home device on an as-needed basis.

Findings: The final result of this patient's treatment was significant flattening and decreased redness of her scar. Her self-reported pain decreased to a 6/10. At the one year follow up, the patient reported that she stopped taking her opioids, antidepressant and sleeping pills and that her pain decreased to a 4/10. At the last review her pain score was 1/10; and she had returned to work and took Tylenol (acetaminophen) occasionally for breakthrough pain.

Conclusions: We attribute the patient's improvement in scar appearance and pain symptoms to PBMT. Since pain is often associated with depressed mood and sleep disturbances, it cannot be determined whether PBMT was the direct or indirect cause of this patient's improved mood. For future studies, we propose the use of control subjects with similar scars treated with sham treatment compared to those who will receive the PBMT and observed for the same duration of time and compare the overall results.

Keywords

Neuropathic pain, hypertrophic scar, chronic pain, laser therapy, photobiomodulation, pain treatment

Lay Summary

Dermatological applications, especially wound healing; are accepted indications for photobiomodulation therapy (PBMT). The expansion into other clinical applications, particularly neurological ones show potential benefit. We present a case of a patient with a hypertrophic scar associated with severe neuropathic pain and concurrent depression, all of which improved directly or indirectly with PBMT. Although the original focus of treatment was dermatological the improvement in pain plus the discontinuation of therapy (opioids, antidepressants and benzodiazepines) were considered to be due to the PBMT.

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Background

The skin is the largest and most superficial organ in the human body which makes it a therapeutic target for photobiomodulation therapy (PBMT). Being a superficial organ allows light therapy to penetrate most layers of the skin. PBMT is commonly used to improve and hasten recovery in wound healing, and also improve scar appearance especially keloid and hypertrophic scars. PBMT is used for neurologic conditions and has shown good benefits in nociceptive and neuropathic pain, its use as an adjunct in treatment of mood disorders is being currently investigated. We present a patient with a hypertrophic postsurgical scar with severe Surgically Induced Neuropathic Pain (SNPP), poor quality of life and concurrent depression; all of which had a good response to PBMT.

Case presentation

The patient was a 32-year-old female who initially presented to the Meditech Rehabilitation Centre with an extremely tender hyperemic abdominal scar from an open cholecystectomy performed two years previously. A few weeks postoperatively she noted worsening pain from the surgical scar but was fully functional. A motorcycle accident exacerbated the scar pain. An abdominal ultrasound excluded a hernia and noted a small amount of thinning of the right anterior abdominal wall. The severe right upper quadrant pain was worse on movement and was attributed to an entrapment of the sensory subcutaneous nerve. At the time of presentation, she was unemployed, homebound living with and dependent on her parents, unable to exercise or travel even short distances.

Past medical history included colonic inertia treated with an ileostomy in 2011, followed by a colectomy and an ileo-rectal anastomosis, followed by an open cholecystectomy for sludge formation and cholecystitis. At her presentation the cholecystectomy incision was fully healed but scarred, with extreme pain when bending forward or backward together with intermittent hyperemia. Her family physician had noted episodes of her being woken up at night with extreme intolerable pain. She was not able to return to work despite several attempts to do so. She was seen by two surgeons for potential scar revision but was advised against it by both of them. A subsequent referral to a pain specialist who noted guarding and pain on touch over the right hypochondrium and tenderness over the right T9 to T11 ribs, but the

absence of skin discoloration or pustules. Topical application with lidocaine 5% ointment had negligible benefit and multiple epidurals and intercostal nerve blocks gave her less than two weeks benefits. At presentation her daily medication was Liothyronine 25 mcg, 6 tablets of Acetaminophen 300 mg/Codeine 15 mg daily, Escitalopram 10 mg, Dexlansoprazole 60 mg, Ondansetron 4 mg twice a day and 1 mg Lorazepam at bedtime. The family physician noted that she also had depression, anxiety, adrenal insufficiency and a complex regional pain syndrome.

The patient on presentation had a mood consistent with depression attributed to a general medical condition.¹ She rated her pain as 10/10 on a visual analogue scale (VAS) and 4/10 using the Douleur Neuropathique 4 (DN4) questionnaire for the previous 24 hours. On physical examination there was a moderate distension of the abdomen and on the right upper quadrant there was a linear 15 cm hypertrophic oblique scar from the open cholecystectomy. The patient had a Fitzpatrick Skin Type 2.² The scar was surrounded by hematoma and ecchymoses with severe tenderness on touch. The pain was described by the patient as severe burning, stabbing and lancinating. There was no itching in and around the scar. There was considerable scarring between the scar and the subcutaneous tissues. There was minimal to moderate tenderness in the abdominal wall but was most severe in the right upper quadrant that prevented palpation of the liver. The two other abdominal surgical scars were asymptomatic. Figure 1 shows the right upper quadrant cholecystectomy scar on initial presentation.

The patient gave consent to undergo PBMT every alternate day. This was done using the BIOFLEX® Therapist 240+ system (Meditech International Inc, Toronto ON) arrays made of 240 bicolor Light Emitting Diode (LED) array set followed by Class 3 B laser probes (Red AlGaInP Laser maximum power at 100mW and infrared GaAlAs Laser maximum power at 200mW). The BIOFLEX® Therapist 240+ system is approved by Health Canada for wound healing and soft tissue injuries; but also used off-label for treatment of neuropathic pain after informed patient consent. The LED arrays were laid directly over the cholecystectomy scar with full skin contact. The laser probes were directed along the edges of the cholecystectomy scar with only light skin contact as even light pressure triggered severe pain. Initial treatment was done on

alternate days at the Meditech Rehabilitation Centre for six weeks after which the same unit sans laser probes were provided to the patient to continue LED treatment at home. The laser probes were applied once a week in the clinic. After the clinic and home treatment the patient scored her pain at 6/10 on VAS for the previous 24 hours. The patient continued home treatment three times a week for two months after which she used the home device and laser probing in the clinic only when needed.

The following parameters were used initially:

Red LED: 660 nm. Treatment Duration: 360 s per placement \times 3 placements. Irradiance: 10 mW/cm². Fluence: 3.6 J/cm².

Infrared LED: 840 nm. Treatment time 360 s \times 3 placements. Irradiance: 20 mW/cm². Fluence: 7.2 J/cm².

Red Laser Probe: 660 nm. Treatment Duration: 7 s scattered spot treatment \times 10 min. Irradiance: 750 mW/cm² per spot treatment. Fluence: 5.25 J/cm² per spot treatment.

Infrared Laser Probe: 825 nm. Treatment Duration: 7 s scattered spot treatment \times 10 min. Irradiance: 1350 mW/cm² per spot treatment. Fluence: 9.45 J/cm² per spot treatment.

The parameters were adjusted every three treatments and included pulsing the LED arrays and gradually increasing the pulse frequency. Pulse frequencies and duty cycles were adjusted by the patient's report of pain relief; whilst other parameters remained unchanged. The pulse frequency was at a minimum of 50 Hz and a maximum of 1000 Hz. Laser diodes were maintained at continuous wave weekly applied at the clinic after the patient-initiated self-treatment at home. Figure 2 shows the right abdominal scar before starting home treatment. Figure 3 shows the scar appearance after one year. Figures 4 and 5 detail the LED array and laser probe application respectively.

Outcome and follow-up

The patient had mild itchiness over the scar just during the first six weeks of treatment. At follow-ups in the following year she noted that her scar pain and appearance had both improved. Her pain score was 4/10 on VAS for the previous 24 hours. In addition, she gradually weaned off her medication (Acetaminophen/Codeine, Escitalopram, and Lorazepam) and eventually discontinued them. She then had better function and had begun walking and exercising. Her mood symptoms had also improved with decreased depression and anxiety. She was

instructed to use PBMT only when needed for breakthrough pain.

Beside PBMT the patient was also under the care of her family physician and an endocrinologist for her hypothyroidism. There were no changes in her hormonal treatment during the PBMT period. Her latest pain scores were 1/10 on VAS and 0/10 using the DN4 questionnaire. There was an overall improvement in the patient's quality of life. As mentioned previously, she had discontinued her opioid and benzodiazepine medication taking the occasional acetaminophen and/or maintenance PBMT at a low fluence for breakthrough pain and Levothyroxine 75mcg daily. The patient is now in full-time employment and lives independently.

Discussion

One of the most frequent uses and indications of PBMT is in dermatology, especially in complex wound healing. NASA have previously reported on accelerated wound healing in singular atmospheric conditions and submarine conditions using PBMT.³ The reason for the tissue response to PBMT is the energy absorption by certain photo-accepting molecules. Various molecules have been considered to play this role, including melanin, water, as well as chromophores in microorganisms present on the skin. However, the biological molecule most responsive to the wavelength we used for our patient at 660 nm and 825–840 nm is cytochrome-C oxidase; which is present in mitochondria and is one of the molecules responsible for the electron transport chain and production of adenosine triphosphate. This reaction involves the production of reactive oxygen species (ROS) that activates nuclear factor kappa B (NF- κ B), a cytoplasmic molecule that signals a cascade which includes wound contraction, inflammation, fibroblast differentiation and collagen deposition.⁴ This may lead to the extracellular activation of transforming growth factor β (TGF- β) which has an effect on a large range of cells in the wound milieu, including hemostasis (platelet-derived TGF- β), inflammatory cells (macrophage-derived TGF- β) and its prominent role on the extracellular matrix (latent TGF- β -binding protein-associated TGF- β 1 sequestered in the matrix). PBMT also influences pain and inflammatory mediators such as histamine, serotonin, bradykinin, and prostaglandins; it also promotes epithelial migration and proliferation, endothelial migration and organization for angiogenesis, inflammatory infiltration, macrophage phagocytoses, immune

surveillance, fibroblast matrix synthesis, and wound contraction.⁵

Keloids and hypertrophic scars are caused by a dysregulated wound-healing process. These scar types are difficult to eradicate, and conventional treatments are not always successful. Keloids or hypertrophic scars could potentially benefit from PBMT by modulating the key cellular features of skin fibrosis. This includes increasing ROS generation, inhibiting fibroblast proliferation without increasing apoptosis, collagen production, and fibroblast migration speed. Several authors have documented the effect of PBMT in restructuring keloids, similar to the processes most also likely controlled by TGF- β .^{6,7}

Surgically Induced Neuropathic Pain (SNPP) as defined by Borsook et al.,⁸ is 'persistent pain estimated to occur in 10–50% of individuals after common operations' (p. 2). It frequently has a delayed onset of months to years after the actual surgery. They described three types of pain typical of SNPP: nociceptive pain, which results from activation of high threshold peripheral sensory neurons such as caused by an incision; inflammatory pain due to inflammatory mediators lowering the threshold of nociceptors that innervate the damaged and inflamed tissue, and finally; neuropathic pain due to nerve injury that is characterized by sensory loss with paradoxical hypersensitivity.⁸ Both nociceptive and inflammatory pain can improve once the offending stimulus settles after wound healing; but neuropathic pain syndromes tend to be chronic and are due to direct nerve damage.

Pain perception is subjective and requires cortical input. While anesthetized during surgery, nociceptive signals are still present, activating well-described afferent pathways to multiple brain areas including sensory, emotional, autonomic, and modulatory pathways. Inadequate anesthesia leads to the perception of pain. The transformation of nociception into pain, and acute pain into chronic pain is complex and hard to define; but once a nerve is injured an ongoing process unfolds that may be modulated but not easily reversed by current treatments. Even with improved post-operative pain management, intermittent (breakthrough) pain can still lead to a chronic syndrome. Treatment options for chronic pain secondary to SNPP include temporary regional and epidural blocks, continuous analgesic blockade, and a range of medication from simple analgesics to anticonvulsants, antidepressants, and opioids. Unfortunately, treatments for neuropathic pain are not highly effective. Placebo-controlled trials in neuropathic pain

suggest approximately 30% efficacy; so, the possibility of SNPP should be considered and treatment initiated pre-operatively. The central nervous system (CNS) manifestations that occur are termed "centralization of pain" and affect sensory, emotional, cognitive systems, etc. as well as contributing to some of the manifestations (depression and anxiety) of chronic pain syndrome.⁸ PBMT can relieve nociceptive pain by partially inhibiting nerve conduction and reducing afferent stimulation, similar to the effect of local anesthetic injections as frequently used by dentists. Although current evidence shows that cutaneous application of light acts primarily via peripheral mechanisms and thus only has peripheral analgesic effects, in contrast to visual applications of light treatment which may induce central analgesic effects.⁹ PBMT applied on the skin may not only induce reduced stimulation of peripheral nerve endings, but it may also result in reduced synaptic activity with second-order dorsal horn neurons, which in turn modulates the afferent input to higher centers, a term now frequently called neuroplasticity. PBMT also leads to reduced inflammation and the release of endorphins that further provide pain relief.¹⁰

For the treatment of pain, red and near infrared wavelengths are administered only topically with a short duration of exposure ranging from seconds to minutes. In our case report, pain nerve entrapment was deemed not to be resolvable by surgery, but her pain was most likely to be modulated by PBMT.

The treatment of neuropathic pain is more complex and treatment may aggravate the pain, often resulting in patients discontinuing with treatment. Pulsed light seems to be effective in modulating this type of pain as shown by our patient. Moore et al.¹¹ previously applied an 830nm, 60mW continuous wave laser for six to eight minutes immediately following wound closure leading to decreased postoperative analgesic drug use in a group of open cholecystectomies patients. However, we demonstrate here the effectiveness of pulsed modes in modulating chronic pain, with the same result.¹² In our opinion, our patients' maintenance use of PBMT is for the continued modulation of pain signals. There are reports of recurrence of symptoms with discontinuation of treatment¹³ although a placebo effect cannot be totally ruled out.

PBMT has also been considered as a potential tool for treatment of mood disorders, specifically major depression and posttraumatic stress disorder. Whilst proper clinical trials using PBMT specifically for mood disorders are still lacking,



Figure 1. Appearance of two-year-old post-surgical hypertrophic scar on presentation prior to initiation of PBMT. Appearance of ecchymoses is noted surrounding the scar after resolution of hematoma.



Figure 2. Appearance of post-surgical scar after two weeks of every other day treatment with PBMT.

there is support for its use in neurological disorders, such as following concussion. Affective symptoms like depression are typical following concussion and several studies have shown that

PBMT improves mood, as well as other symptoms of concussion like anxiety, sleep difficulties, memory and cognition^{14,15}. Perhaps the factors that lead to affective symptoms in concussion



Figure 3. Appearance of scar after one year of PBMT home treatment with flatter overall appearance and no pigmentation. The treatment was continued up to the current time mostly to modulate the pain symptoms, but the effect of PBMT on improving the superficial appearance of a two-year-old hypertrophic scar is noticeable.



Figure 4. Mode of application of LED arrays across the skin.

are also responsible for mood disorders in general. Most studies investigating PBMT for these conditions usually use the transcranial route.¹⁶ The improvement in our patient by previous treatments directed at the scar in the abdominal wall cannot be ruled out.¹⁵ The skin

may serve as a neuroendocrine organ and promotes signal exchange with the brain.¹⁶ It is possible that specific molecules like nitric oxide (NO) from the body's largest organ (the skin) can be mobilized with potential beneficial effects.¹⁷ The systemic effects of PBMT on



Figure 5. Mode of application of laser probes.

mood have been previously reported. Although we cannot directly attribute her improved mood symptoms directly to PBMT, as it may just be the improved pain symptoms. However other studies have described the role of remote PBMT in improving certain central nervous system conditions such as Parkinson's disease.¹⁸ Improving scar tissue appearance, decreasing pain and increasing mobility - leading to better function and decreasing depression symptoms - all lead to a better functional quality of life, but a placebo effect cannot totally be ruled out. However, the patient's symptoms were present for years before initial presentation despite being on an opioid, anti-depressant and benzodiazepine. There are limitations to this paper, one of which is it is a single case-report and future controlled studies on subjects with significant surgically induced neuropathic scar pain (SNPP) are needed.

In conclusion, PBMT was used in this case mainly for the purpose of improving overall scar appearance. Providing neuropathic pain relief and improving mood may indicate a potential for PBMT as treatment for postsurgical pain syndromes and decrease the reliance on opioids and psychotropic medication.

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