Photobiomodulation Therapy in Recovery of Peripheral Facial Nerve Damage

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Photobiomodulation (PBM) therapy has been investigated to enhance and accelerate the recovery of injured peripheral nerves. Based on the wide range of benefits of PBM therapy and its clinical relevance, this study reviewed the efficacy of PBM in injured facial nerves. The search was performed in the PubMed database to find relevant articles published over the last 10 years. Four animal studies, two randomized controlled studies, one case series, and five case reports were reviewed. Despite the various parameters, functional analysis showed that PBM therapy using near-infrared irradiation has beneficial effects on the recovery of the acute phase of the damaged facial nerve, especially when related to faster functional improvement. There were no reported adverse effects of PBM therapy.

Key words

Facial nerve; Low-level laser therapy; Photobiomodulation; Bell's palsy

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INTRODUCTION

Facial nerve paralysis (FNP) is the most common cranial nerve disorder that causes a variety of functional and esthetic problems, as well as social and psychological issues. This condition can cause significant changes, such as impaired facial expression, changed taste, hyperacusis, and decreased salivation and tear secretion, and subsequently lead to interruption of face-to-face communications, decreased self-esteem, anxiety, depression, and social isolation.¹ Idiopathic acute peripheral FNP, also known as Bell's palsy, constitutes 60-75% of cases with an annual incidence of 23 to 25 cases per 100,000.²⁻⁴ The etiology remains unclear, various causes have been proposed including viral, inflammatory, autoimmune and vascular.³

The treatment of FNP, particularly of Bell's palsy, is controversial due to the lack of large, prospective, randomized, and controlled trials.⁵ Corticosteroids is thought to limit nerve damage by reducing swelling and inflammation of the facial nerve. A previous Cochrane analysis reported that early treatment with corticosteroids can hasten recovery and adding antiviral drugs to corticosteroids may be some beneficial.^{6,7} Physical therapies including tailored facial exercises, biofeedback, acupuncture, massage, thermotherapy, and electrical stimulation also have been used to improve facial function. However, there is no high-quality evidence to support significant benefit.⁸

Low-level laser therapy (LLLT), now commonly referred to as photobiomodulation (PBM) therapy, has been introduced as a non-invasive modality to enhance the recovery of peripheral nerve damage.^{9,10} This light-based technique involves exposure of neural tissue to a low fluence of light in the ranging from < 1 to $> 20 \text{ J/cm}^2$ and wavelengths ranging from infrared to near infrared (NIR) (600 to 1100 nm). The beneficial effects of PBM are thought to occur primarily by inducing a photochemical reaction in the cell, instead of generating a thermal effect.¹¹ The wavelength of infrared irradiation is easily absorbed by tissues and the loss of intensity is minimal, affecting metabolic modifications, DNA activity, adenosine triphosphate (ATP) formation, and the mitochondrial chain.

PBM works on the principle that, when light hits certain molecules called chromophores, the photon energy causes electrons to be excited and jump from low-energy orbits to higher-energy orbits. This sorted energy can be used by the system to perform various cellular task, such as photosynthesis and photomorphogenesis.¹¹ Cytochrome c oxidase (CCO) in the mitochondrial respiratory chain probably acts as an important chromophore

in action mechanism of PBM therapy.^{12,13} Mitochondrial CCO absorbs light energy in the red and the NIR spectral regions and PBM increases its catalytic activity. Consequently, the PBM cause photodissociation of nitric oxide (NO) from CCO, leading to an increase in electron transport, mitochondrial membrane potential and ATP production. All these results in enhancement of neuronal respiration and metabolic capacity. On the other hand, the PBM activates light-sensitive ion channels that can be activated allowing calcium to enter the cell. After then, numerous signaling pathways are activated via calcium ions (Ca^{2+}), reactive oxygen species (ROS), cyclic AMP, and NO and, leading to activation of transcription factors.^{14,15} These transcription factors can lead to increased expression of genes related to protein synthesis, cell migration and proliferation, anti-inflammatory signaling, anti-apoptotic proteins, antioxidant enzymes. Thus, photochemical and photobiological effects of PBM at the cellular level can lead to improvement of trophic conditions related to the process of peripheral nerve regeneration and promote the secretion of neural factors.

Since 1980, the scientific interest in the therapeutic approach of rehabilitation for FNP was initiated due to the good results with the use of PBM therapy in the recovery of injured peripheral nerves. However, there are still difficulties in selecting the most suitable parameters for application to facial nerves due to the lack of standardization. The treatment parameters of PBM therapy such as wavelength, fluence, power density, number of repetitions, duration of treatment, and the mode of light delivery (continuous or pulsed) have repercussions on the biological effects.¹⁶ Due to the various treatment parameters of PBM therapy and its benefits, the aim of this research was to carry out a review of the papers published in the last 10 years verifying the relation of PBM therapy with the recovery of injured peripheral facial nerves.

MATERIALS AND METHODS

A search was performed in the PubMed database over the last 10 years and restricted to the English language. The selected keywords were ("Low-level laser" OR "photobiomodulation" OR "phototherapy") AND ("Bell's palsy" OR "facial palsy" OR "facial paralysis" OR "facial nerve injury"). The author also provided hand search of the references of the selected studies to identify other possible relevant studies. The articles included should necessarily be presented with full access to the text. We verified those articles that presented titles and summaries that approached the subject of this research, as well as method-

ology, results, and relevance for its practical application.

RESULT

Finally, 12 relevant articles were obtained from the PubMed database. Four studies used animals as a study object (Table 1).¹⁷⁻²⁰ All animal studies used male Wistar rats aged 60-80 days. One study evaluated the effect of PBM on compression of main trunk²⁰ and 3 articles evaluated its effect on neurotmeses of buccal branch.¹⁷⁻¹⁹ The wavelength of 830 nm of PBM therapy presented better morphological (especially, fiber area) and functional nerve repair in damaged terminal branches of the facial nerve that were repaired accelerated morphological and functional nerve repair by suture or fibrin sealant.¹⁷⁻¹⁹ Recent PBM study on damaged main trunk of FN also showed a better healing process than the control group, but the outcome was not statistically significant.²⁰ The main difference between recent study and previous studies was the energy density (3.2 J/cm² in recent study²⁰ vs. 6-6.2 J/cm² in previous studies.¹⁷⁻¹⁹

Of 8 human studies, 2 studies were designed as randomized controlled study (RCT)^{21,22} and 6 studies were

descriptive studies (Table 2).²³⁻²⁸ One study had two parallel RCT design, the LLLT group and control group.²¹ The other study had three parallel RCT design including high-level laser therapy, LLLT group, and control group.²² Two RCT studies applied both exercise and massage therapy in their control groups, and these exercise and massage therapy were accompanied as parts of treatment in the intervention groups. Two RCT studies used 830 nm wavelength with the energy density of 10 J/cm² for a total of 18 treatment sessions over a period of 6 weeks in LLLT groups. Researchers of these RCT studies reported significant improvement on the physical and social facial disability index (PFDI and SFDI) following LLLT at the ending of their treatment sessions (Table 3). Of 6 descriptive studies, one study was clinical intervention study on effect of LLLT in diabetics with bell's palsy²³ and 5 articles were case report.²⁴⁻²⁸ These descriptive studies applied NIR range of wavelength with various number of treatment session and period of treatment (Table 2). All researchers in the descriptive studies reported improvement of Bell's palsy on House-Brackman (H-B) grade following LLLT at the ending of their treatment sessions. The effect of LLLT on the treatment of Bell's palsy has also been reported in

Table 1. Data of selected animal studies

Author (year)	Surgical procedures	Laser protocol	Evaluation time	Main results
Buchaim et al. (2016) ¹⁷	Neurotmeses of BB of FN, followed by end-to-end suture (right FN) or coaptation with heterologous fibrin sealant (left FN)	GaAlAs laser, 830 nm, 258.6 mW/cm ² , 6 J/cm ² , 24 s/point for 3 points on the surgical site, performed 1st day after surgery and 3 times/week for 5 weeks in the postoperative period	Morphological evaluation at 5 and 10 weeks after the surgery	LLLT showed satisfactory results on facial nerve regeneration.
Buchaim et al. (2017) ¹⁸	Neurotmeses of BB of FN, followed by end-to-end suture (right FN) or coaptation with heterologous fibrin sealant (left FN)	GaAlAs laser, 830 nm, 258.6 mW/cm ² , 6.2 J/cm ² , 24 s/point for 3 points on the surgical site, performed 1st day after surgery and 3 times/week for 5 weeks in the postoperative period	Functional analysis and morphological evaluation at 5 and 10 weeks after the surgery	LLLT stimulated axonal regeneration accelerated the process of functional recovery of whisker
Rosso et al. (2017) ¹⁸	Neurotmeses of BB of FN, followed by end-to-side suture to the ZB of the FN (right FN) or coaptation with heterologous fibrin sealant (left FN)	GaAlAs laser, 830 nm, 260 mW/cm ² , 6.2 J/cm ² , 24 s/point for 3 points on the surgical site, performed immediately after surgery and 3 times/week for 5 weeks in the postoperative period	Functional analysis and morphological evaluation at 10 weeks after the surgery	LLLT provided better morphological and functional repair in the two techniques used.
Yuca et al. (2020) ²⁰	Crush the injury to the main trunk of FN for 30 s using surgical clamp to create neuropathic damage (left FN)	Superluminescent diode, 850 nm, 100 mW/cm ² , 3.2 J/cm ² , 32 s on the surgical site for 21 consecutive days	Morphological evaluation at 3 weeks after the surgery	LLLT revealed a better healing process than the control group, but the outcome was not statistically significant

BB, buccal branch; FN, facial nerve; GaAlAs, gallium-aluminum-arsenide; s, seconds; ZB, zygomatic branch; LLLT, low-level laser therapy.

Table 2. Data of selected human studies

Author (year)	Study design (sample size)	Clinical information	Laser protocol	Main results (evaluation time)
Ordahan and Karahan (2017) ²¹	RCT (44; LLLT = 23, C = 21)	LLL = 44.7 ± 4.5 yrs, C = 45.3 ± 3.8 yrs; subacute BP (onset = not mentioned)	GaAlAs diode, 830 nm, 100 J/cm ² , 2 min/point, 8 points/session, 18 sessions for 6 weeks	Combined treatment with LLLT and exercise therapy is associated with significant improvements in FDI when compared with exercise therapy alone. (FDI, 3 and 6 weeks after treatment)
Alayat, Elsodany, and El Fiky (2014) ²²	Double-blind RCT (51; HILT = 17, LLLT = 15, C = 16)	HILT = 43.8 ± 10.4 yrs, LLLT = 43.3 ± 10.1 yrs, C = 45.1 ± 9.4 yrs; acute BP (3-5 days after onset)	HILT: Nd:YAG laser, 1,064 nm, 10 J/cm ² , 7 s/point, 8 points/session, 18 sessions for 6 weeks LLL: GaAs diode, 830 nm, 10 J/cm ² , 5 s/point, 8 points/session, 18 sessions for 6 weeks	Both HILT and LLLT improved the recovery of BP, with HILT showing a slightly greater improvement than LLLT. (FDI, HBS, 3 and 6 weeks after treatment)
Aghamohamdi et al. (2020) ²³	Clinical trial (30)	female (18) = 40.7 ± 11.7 yrs, male (12) = 42.3 ± 13.7 yrs; BP in diabetics (onset = not mentioned)	Diode laser, 980 nm, 9 points for a period of one minute, 12 sessions for one month	After LLLT, diabetic patients had a higher grade of BP, which was confirmed by EMG and NCV results. (H-B Gr, one month after treatment)
Poloni et al. (2018) ²⁴	Case report (1)	13 yrs, girl with BP (one week after onset), H-B Gr V	GaAlAs diode, 830 nm, 100 J/cm ² , 0.47 min/point, 2 points/session, 3 sessions for 3 weeks	LLL only: Total recovery of facial movement (3 weeks after treatment)
Rubis (2013) ²⁵	Case report (1)	40 yrs, male with BP (10-days after onset), H-B Gr V	GaAs, 910 nm, 100 mW, 47.6 × 10 J, 0.5–1 min/point, 6 points/session, 2 sessions	LLL + corticosteroids + chiropractic manipulation (4 times): Complete resolution
Fontana and Bagnato (2013) ²⁶	Case report (1)	3 yrs, boy with BP (onset = not mentioned, acute), H-B Gr V	GaAlAs semiconductor diode, 780 nm, 10 seconds/points, 17.5 J/cm ² (first 4 sessions), 660 nm, 10-60 J/cm ² for 6th, 7th, 8th, 0.16 min/point, up to 80 points/session, 11 sessions for 3 weeks	LLL only: H-B Gr I (in 3 weeks)
Tanganelli et al. (2020) ²⁷	Case report (1)	71 yrs, female with BP (onset = not mentioned, acute), H-B Gr V	AsGaAl 808 nm, 120 J/cm ² 10 points, 10 s/point, 10 point/sessions, 10 sessions for 6 weeks	LLL only: H-B Gr I (6 weeks after treatment)
Bernal Rodriguez et al. (2020) ²⁸	Case report (1)	25 yrs, female with BP (8 yrs after onset), H-B Gr IV	660 and 808 nm, 40.65/60.97 J/cm ² , 20/30 s/point, 59 points/sessions, 24 sessions for 8 weeks	LLL only: H-B Gr II (8 weeks after treatment) *previously treated with physical therapy and electroacupuncture, Vit B-complex

LLL, low-level laser therapy; yrs, years; C, control; BP, Bell's palsy; GaAs, gallium-arsenide diode; GaAlAs, gallium-aluminum-arsenide; FDI, facial disability scale; HBS, House-Brackman scale; H-B, House-Brackman grading system; S-B, Sunnybrook facial nerve grading system; EMG, electromyography; NCV, nerve conduction velocity.

Table 3. FDI scores of studies by Ordahan and Karahan (2017) and Alayat, Elsodany, and El Fiky (2014)

Study	Groups	PFDI			SFDI		
		Before	3 weeks	6 weeks	Before	3 weeks	6 weeks
Ordahan and Karahan (2017) ²¹	LLLTG	27.05 ± 14.13	37.42 ± 8.13*	39.21 ± 9.08*	22.80 ± 18.76	35.41 ± 10.12*	37.53 ± 9.65*
	CG	26.52 ± 11.07	25.41 ± 13.12	29.06 ± 11.09*	23.40 ± 15.23	23.25 ± 15.27	28.76 ± 12.14*
	<i>p</i> -values	ns	< 0.05**	< 0.05**	ns	< 0.05**	< 0.05**
Alayat, Elsodany, and El Fiky (2014) ²²	HILTG	20.06	37.41*	39.74*	21.91	39.21*	38.47*
	LLLTG	27.06	25.53*	21.8*	28.77	22.33*	25.73*
	CG	26.84	9.81*	10.84*	23.25	10.91*	8.5*
	<i>p</i> -values	ns	< 0.01**	< 0.01**	ns	< 0.01**	< 0.01**

PFDI, physical facial disability index; SFDI, social facial disability index; LLLTG, low-level laser therapy group; CG, control group; HILTG, high intensity laser therapy group; ns, not significant.

**p* < 0.001 = significant differences in intra-group evaluation according to baseline (before treatment) using Friedman analysis and post-hoc analysis with Bonferroni correction.

***p* < 0.05 = significant differences among the treatment groups using Mann-Whitney U test or Kruskal Wallis test.

diabetic patients,²³ children,^{26,29} and chronic Bell's palsy.²⁸ When reviewed the human studies, there were no reported adverse effects during treatment and/or follow-up sessions.

DISCUSSION

This study aimed to review the papers published in the last 10 years in order to verify the effects of PBM therapy on the recovery of peripheral facial nerve damage. Totally, 4 relevant animal studies and 8 human studies were reviewed. The functional analysis in both animal and human studies evidenced the recovery of FN associated with LLLT with wavelengths ranging from NIR (600 to 1100 nm). Previous animal studies have demonstrated that PBM in the nerve injury was related to reduced inflammatory cytokine and elevated expression of neural growth factor (NGF) and brain-derived neurotrophic factor (BDNF).³⁰⁻³³ However, there was no studies on the mechanism of PBM therapy on the regeneration of damaged facial nerve. All human studies were designed to evaluate effects of LLLT on Bell's palsy recovery. Except one case report, all studies started LLLT in acute or sub-acute stage of nerve damages. Therefore, it was difficult to conclude the effect of LLLT in chronic stage of nerve damages.

In summary, relevant evidences cautiously suggested that LLLT with wavelengths ranging from NIR can effectively improve the recovery of acute facial nerve damage. However, the relevant human studies were mostly case report or case series that rank lowly in level of evidences. Since there were only two RCTs included in this review, it is difficult to generalize clinical results. Thus, further

RCTs with enlarged sample sizes and other objective outcome measures are needed. In addition, animal studies on the effect of PBM on the regeneration of damaged facial nerves are needed to support the clinical results.

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