Intranasal Photobiomodulation Therapy for Brain Conditions: A Review

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The effects of low-level laser irradiation on cells and tissues, known as photobiomodulation therapy (PBMT), are the basis of photomedicine. Several investigations have evaluated the therapeutic effects of PBMT for neuronal regeneration and differentiation in animal models and humans. Recently, intranasal PBMT (iN-PBMT) has shown potential as a treatment method for neurologic disorders. In this review, we have summarized the various modes of iN-PBMT delivery and their application in the treatment of brain disorders.

Key words

Photobiomodulation; Intranasal; Laser; Low-level lasers

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INTRODUCTION

Photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), is widely used to treat various medical conditions such as pain, inflammation, blood disorders, musculoskeletal conditions, as well as tissue regeneration.¹ PBMT has steadily widened the range of applications to the brain diseases: neurotrauma, neurodegenerative diseases, and neuropsychiatric disorders.^{2,3} Moreover, brain PBMT is an effective therapeutic modality for central nervous system (CNS) disorders.⁴ Through several studies, it is proven that PBMT can improve cerebral blood flow, metabolic activity, neurogenesis, and neuroprotection by antioxidant and anti-inflammatory pathway activation.^{5,6}

To deliver the laser light in brain PBMT, several approaches were proposed: transcranial,⁷ intranasal,⁸ intra-aural,⁹ and intraoral¹⁰ approaches. Among these approaches, intranasal PBMT (iN-PBMT) can overcome the limitations of the PBMT to provide effective irradiation to the brain, especially on the limbic structures and prefrontal areas.¹¹

In this review, we summarized the applicability of different intranasal irradiation approaches: from the nostril-based method to the implanted nasal methods. Evidence for the effectiveness of iN-PBMT for neurological, neurodegenerative, and neuropsychiatric disorders will also be reviewed.

INTRANASAL PHOTOBIMODULATION THERAPY

From the nostril

The nose serves as a direct pathway to the brain. Thus, nasal administration could be an effective, efficient and non-invasive option for delivering therapeutic materials to the CNS (Fig. 1A).¹² Several intranasal portable devices for iN-PBMT through the nostril approach become commercially available. These iN-PBMT devices are both with red and near-infrared (NIR) diodes (600-680 nm and 800-850 nm wavelength).

It is known that iN-PBMT through the nostril approach improves oxygenation and leads to increased adenosine triphosphate levels in various tissues, including the brain. PBMT absorbed by blood leads to partial photochemical dissociation of hemoglobin ligand complexes such as oxygen, carbon dioxide, nitric oxide (NO).¹³⁻¹⁵ As a result of light-induced photodissociation of oxyhemoglobin, decreased in arterial oxygen saturation (SpO₂) in blood capillary vessels followed by significant enrichment of local tissue oxygenation occurs.^{16,17} With 660 nm wavelength photons, the laser irradiation effect can be amplified in lymphocytes.¹⁸ In addition, releasing small amounts of the NO, vasodilation and perfusion can be increased. Thus, oxygen delivery to tissues can be improved. Thus, nostril-based iN-PBMT could be an effective and attractive modality for treatment of neurodegenerative, neuropsychiatric diseases, and ischemic brain injury.¹⁹ Nostril-based iN-PBMT could also modulate NO release from the endothelium and platelets, and can improve cerebrovascular

Fig. 1. Various approaches for intranasal photobiomodulation. (A) nostril-based approach or by (B) cribriform plate, (C) frontal sinus, (D) sphenoid sinus.

circulation.

Several studies demonstrated that direct tissue exposure to red/NIR light can reduce the influx of polymorphonuclear leukocytes into a targeted site of inflammation, thus decreasing the oxidative burst.^{20,21} The remote neuroprotective action of iN-PBMT through the nostril approach could be related to modulation of reactive oxygen species (ROS) formation.²² The role of ROS is critical for reprogramming of macrophage polarization to M2 phenotype, and M2 macrophage releases anti-inflammatory mediators which are related to tissue recovery.²³ In previous reports, 810 nm wavelength PBMT changed the macrophage polarization to an M2 phenotype and increased level of anti-inflammatory cytokines (interleukin (IL)-4, 13),²⁴ but suppressed pro-inflammatory IL-6²⁵ resulting in alternative macrophage activation.

In addition, several other possible pathways were proposed that could mediate iN-PBMT: affecting the olfactory nerve, bulb, and endothelium, the autonomic nervous system, and the lymphatic system.²⁶

From the nasal submucosal space and nasal cavity

As abovementioned, the nostril approach through portable devices only provides a negligible amount of light energy into the deep brain structures.¹¹ Thus, recently, implantable iN-PBMT devices were developed to overcome these limitations. With a simple procedure, miniature light-emitting diodes (LEDs) can be implanted into the submucosal pockets in accessible areas of the nose.

The olfactory epithelium is an epithelial tissue layer in the nasal cavity. It is defined by the cribriform plate, which separates the nasal cavity from the brain. As it is close to the cribriform plate, it is proposed as possible and effective implant location for iN-PBMT device. If the implantable light device is located at the cribriform plate, the ventromedial cortex (PFC) and the olfactory bulb could be effectively irradiated (Fig. 1B). Intranasal delivery of red/NIR light can illuminate anteromedial and posteromedial portions of the orbitofrontal cortex (OFC). In addition, when the light source is positioned proximal to the cribriform plate, deposition of the energy on the ventromedial PFC is 658- and 46-fold greater than when the light source is implanted in the nostril or the middle of the nose, respectively.¹¹ In addition, comparing with the dorsolateral PFC, the light source positioned in the cribriform plate led a higher light influence on the ventromedial PFC and OFC. In addition, limbic structures (amygdala and hippocampus) receive only negligible energy from a light source from the nostril, both the cribriform plate and

the mid-nose locations can allow a higher deposition of light.¹¹

PFC and OFC can be also effectively irradiated when the implantable light device is inserted at the frontal sinus (Fig. 1C).

From the sphenoid sinus

In the sphenoid sinus, an implantable optical fiber can be positioned (Fig. 1D). For instance, the tip of the optical fiber connected to a LED source can be placed as an indwelling device through endoscopic visualization in the sphenoid sinus.²⁷ However, this requires a surgical procedure to place the device in a fragile bone structure. The sphenoidal sinus lies adjacent to important limbic system structures such as the pituitary gland, amygdala, hypothalamus, and hippocampus. The amygdala is located anterior to the hippocampus and medially in the temporal lobes. The amygdala resides lateral to and somewhat posterior to the sphenoid sinus. In general, the amygdala processes emotional responses (perception of facial expression, anxiety, fear, memory, aggression, decision making).²⁸ Adjacent to the pituitary gland on either side of the third ventricle and above/posterior to the sphenoid sinus, the hippocampus is located. It is involved in the regulation of endocrine, body temperature, food water intake, reproduction and sexual behavior, circadian rhythms, fatigue, emotional responses, and memory function. The hippocampus is a convex structure composed of gray matter tissue inside the para-hippocampal gyrus. It mediates several higher cognitive functions (e.g., learning, long-term memory, spatial navigation, regulation of hypothalamic functions, and emotions).²⁹

The sphenoid sinus could be used as a proper location of an implanted light source. It could provide therapeutic amounts of light to the limbic structures (Fig. 1D). A study made an effort to experimentally examine the light delivery and photon distribution from a transsphenoidal approach, in order to achieve sufficient irradiation of the pars compacta of substantia nigra (SN) in a human cadaver.¹⁰ In this study, authors coupled an optical fiber-based light diffuser to a laser diode emitting different wavelengths of 671 or 808 nm, and then the probe was placed in the sphenoidal sinus towards the pars compacta of SN under endoscopic guidance. In compacta of SN, about 0.36% of 808 nm wavelength and 0.03% of 671 nm wavelength light emitted by the optical fiber could be reached. When sufficient power was used, these delivered light could provide a sufficient poststimulatory fluence to the SN. In motor planning, movement and reward-seeking, the SN plays an important role.

With transsphenoidal illumination, a reasonable fraction of the light energy could be deposited in the amygdala, hypothalamus, hippocampus, and pituitary gland, before reaching the SN.

INTRANASAL PHOTOBIO-MODULATION THERAPY FOR BRAIN CONDITIONS

Neurodegenerative disorders

In one recent study, rapid reversal of cognitive decline and olfactory dysfunction in a mild cognitive impairment (MCI) patient after PBMT via transcranial and intranasal approach was reported.² Cognitive enhancement was observed by improvements in executive function/visuospatial ability, mathematical ability, and orientation. Working memory and attention also showed significant improvements in the patient.

In addition, some researchers have reported the potential neurotherapeutic role of iN-PBMT for Alzheimer's disease (AD) and Parkinson's disease (PD). In a recent case series, 3-months of transcranial plus intranasal PBMT significantly enhanced cognitive performance in patients with mild to moderately severe dementia.⁸ With a wearable transcranial device, an intranasal LED applicator (810 nm wavelength) was applied providing a 13.8 J/cm² to the nasal cavity. Besides the improvement in cognitive abilities as assessed by the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale (ADAS-cog), increased sleep quality and decreased levels of anxiety, anger outbursts, and wandering were also observed. In a recent study, Vielight Neuro Gamma device (Vielight Inc., Canada) was used in four patients diagnosed with dementia or AD.³⁰ With a transcranial headset device, the intranasal LED applicator (810 nm wavelength, 40-Hz pulse wave, 15 J/cm²) was applied to the nasal cavity for 3 days/week for 12 weeks at home. Cognitive and behavioral functions were improved according to the neuropsychiatric inventory scores and the ADA-cog score. With multimodality PBMT, cerebral perfusion and connectivity between the lateral parietal nodes in the default-mode network (DMN) and the posterior cingulate cortex.

Some researchers have tested the therapeutic role of iN-PBMT for PD patients.^{31,32}

Traumatic/ischemic brain injury

In a randomized, double-blind, sham-controlled pilot trial study in eight veterans with mild-TBI, combined application of the transcranial LED helmet and intranasal LED applicator for 2 days/week for 8 weeks, resulted in significant improvements in attention and executive func-

tion as well as sleep quality at 1-week post-treatment.³³

In one study, intranasal intranasal laser irradiation (10 days, 30 minutes, 650 nm, 8.38 mW/cm²) showed improvement of aggregation of red blood cells, plasma viscosity of blood, and lipid profiles.³⁴

Neuropsychiatric disorders and insomnia

Recently, long-term PBMT showed the overall therapeutic effect in a patient with major depression and anxiety.³⁵ For the first 22 months, single-modality iN-PBMT (810 nm LED) was applied to both nostrils providing a 10.65 J/cm² per nostril. With the progressive increase of the frequency of iN-PBMT sessions, the anxiety symptoms showed regression with about a 3-fold reduction in Anxiety Symptoms Questionnaire Scores. However, iN-PBMT alone did not improve the depressive symptoms until an additional transcranial laser irradiation to the forehead. According to their speculation, the systemic effects of iN-PBMT via the blood cells possibly contributed to the observed anxiolytic effect.

There is also proof of the therapeutic application of PBMT in sleep disorders. Red-light irradiation (658 nm, 30 J/cm²) for two weeks using a whole body treatment machine has been shown to improve sleep quality and serum melatonin levels.³⁶ In studies of the application of t-PBMT in TBI patients, improvement in sleep was reported by many of the patients.^{37,38} A combined transcranial and intranasal PBMT also resulted in better sleep in patients diagnosed with AD and TBI.^{8,33} According to a previous report, sleepiness is a common side-effect following the use of 10-Hz intranasal portable devices, inducing brain alpha wave (8-12 Hz), while also producing neuronal stimulation.² Although mechanisms of action involved in PBMT for sleep improvement are still unknown, modulation of circadian rhythms via an increase in serum melatonin levels^{36,39} and stimulation of systemic homeostatic response via the blood circulatory system⁴⁰ were proposed as possible mechanisms.

CONCLUSIONS

Table 1 summarizes the results of some clinical studies on the effects of iN-PBMT on various brain conditions. While iN-PBMT through nostrils for wellness is available, its efficacy and effectiveness is still unproven. Submucosal and frontal iN-PBMT has potential as a novel therapeutic modality, however, there are no available device in the market. Other approaches through the deeper nose (cribriform plate or sphenoid sinus), iN-PBMT is not yet available with current technology. However, iN-PBMT,

Table 1. Intranasal photobiomodulation therapy (PBMT) for brain conditions

Application		Study design	Intranasal PBMT condition	References
Neurodegenerative disorders	Mild cognitive impairment Dementia	Case report	810 nm wavelength 10-Hz pulsed wave	Salehpour et al. ²
		Case series	810 nm wavelength 10-Hz pulsed wave	Saltmarche et al. ⁸
		Case series	810 nm wavelength 10-Hz pulsed wave	Chao ³⁰
	Parkinson's disease	Prospective proof-of-concept study	810nm wavelength 50-Hz pulsed wave	Liebert et al. ³²
Traumatic/ischemic brain injury	Mild traumatic brain injury	Randomized, double-blind, sham-controlled pilot trial study	810 nm wavelength 10-Hz pulsed wave	Bogdanova et al. ³³
	Cerebral infarction	Randomized, double-blind, placebo-controlled study	650 nm wavelength	Liu et al. ³⁴
Neuropsychiatric disorders	Major depression, anxiety	Case report	810 nm wavelength 10-Hz pulsed wave	Caldieraro et al. ³⁵

using LED applicators, has potential as a novel approach for neurorehabilitation. Thus, more future studies comparing sham, and transcranial PBMT are also warranted.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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