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REVIEW ARTICLE

Transcranial Near-infrared Laser Therapy in Improving Cognitive Recovery of Function Following Traumatic Brain Injury

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Abstract: Traumatic brain injury (TBI) has turned into a major health and socioeconomic problem affecting young people and military personnel. Numerous TBI patients experienced the sequela of brain injury called cognitive impairment, which reduced functions in attention, working memory, motivation, and execution. In recent years, transcranial near-infrared laser therapy (tNiRLT) as a possible therapy has been gradually applied in treating cognitive impairment post-TBI. In the present review, the biological mechanisms of transcranial tNiRLT for TBI are synthesized mainly based on the photonic impact of chronic mild TBI. Various exciting molecular events possibly occur during the procedure, such as stimulation of ATP production, regional cerebral blood flow, acupoint, neurogenesis and synaptogenesis, as well as a reduction in anti-inflammatory effect. Some animal experiments and clinical studies of tNiRLT for TBI are outlined. Several labs have displayed that tNiRLT is effective not only in improving neurological functions but also in increasing memory and learning capacity in rodent animals' model of TBI. In a 2 patients case report and a 11-case series, cognitive functions were ameliorated. Efficacy on cognitive and emotional effects was also observed in a double-blind, controlled clinical study. Several Randomized, parallel, double blind, sham-controlled trials are underway, aiming to evaluate the efficacy of tLED on cognitive functions and neuropsychiatric status in participants post-TBI. Therefore, tNiRLT is a promising method applied to cognitive impairment following TBI.

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1. INTRODUCTION

Traumatic brain injury (TBI) is becoming the main health and socioeconomic issue affecting public awareness worldwide [1, 2]. About 1.7 million people suffer from TBI in the United States each year [3]. TBI is defined as a sudden and powerful force to the brain which contributes to neurological and psychogenic lesions [4]. Based on the initial evaluation *via* Glasgow coma scale (GCS), TBI is regularly categorized as mild (GCS 14-15), moderate (GCS 9-13), or severe (GCS 3-8) [5]. Young children and young adults are at great risk of TBI, followed by old people older than 65 years [6]. Falls comprise more than 30% of total TBI and traffic accidents are also major causes of TBI [7].

Large number of patients who suffer from TBI undergo cognitive deficits, such as declined functions in attention, working memory, motivation, and executive deficits [6, 8]. The extrinsic force impels the brain to experience acceleration and deceleration rapidly in the skull, leading to damage of the grey matter, white matter regions and vasculature structure [9]. These damages are common to take place in the frontal lobe and temporal lobe due to adjoining upon the cristae and tuberosities of the interior skull [10]. Once the frontal lobe is damaged, the balance of the neurotransmitter and dopamine accommodating cognitive and behavioral function is destroyed simultaneously. There are corresponding regions in the frontal lobe in charge of active memory with purpose, including short-time memory, long-time memory, and the specific memory for words, substance and space. Some researchers reported that spoken language and spatial memory are correlated with frontal lobes close to the left periventricular, whereas spatial memory is associated with frontal lobes close to the right periventricular [11, 12]. Focal attention, processing information across time and concentrate on thinking, generating the accumulation of knowledge, which also has an association with the frontal lobe.

Diffuse axonal injury is regularly detected in the anterior corona radiata and frontotemporal regions [13]. The prefron-

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tal cortex and the anterior cingulate gyrus are two areas greatly impressionable to injury within the frontal lobes. Cognitive managing matters are rooted in the destroyed tissue and incapable cellular function in these cerebra regions. The prefrontal cortex is related to keeping, monitoring, and manoeuvring information in the working memory and especially in continuous attention [14, 15].

2. TNIRLT FOR COGNITIVE IMPAIRMENT POST-TBI

2.1. The History of TNIRLT

A Hungarian researcher detected that HeNe had the capacity to stimulate wound healing in animals not soon after the finding of the first ruby laser and first HeNe laser in 1960 and 1961, respectively [16]. After further researches, low-power lasers were applied to various disease and injuries because of a stable decline of inflammation, pain relief, tissue regeneration and other diverse positive roles [17]. NiR light is mainly applied as low-power laser or light-emitting diode (LED). For searching the radical treatment for cognitive disorder after TBI, NiR light has been researched for its capacities to regulate the molecular events. It has presented prospective results in numerous administrations as well. NiRLT was regarded as the ability to push this stalled field forward since little has been discovered to change over the cognitive sequela following TBI.

2.2. tNiRLT in Pre-clinical Studies

The efficiency of tNiRLT for neurological disease, such as stroke, compelled the researchers to examine the treatment in post-TBI animal models [18, 19]. For example, Oron [20, 21] had examined that tNiRLT could bring convenient neurological functions to post-trauma mice. Furthermore, other researchers discovered that tNiRLT potentially played a vital role in contributing to cognitive augmentation [22]. As evaluated through Morris Water Maze (MWM), Khuman and colleagues found significant improvement on spatial learning and memory after 800 nm and 60 J/cm^2 low-level laser therapy (LLLT) of 60-80 min in post controlled cortical impact (CCI) mice [23]. When using other doses, and a 4 h time point or 7 days administration, little or no impact on cognitive condition after CCI was observed. Xuan and co-workers performed an 810-nm laser with energy of 18 J/cm^2 LLLT for 12 min for one or three times a day at 4 h post-TBI mice [24]. As a result, LLLT TBI mice did not show a huge significant reduction in latency to the visible platform compared to non-LLLT TBI mice. Furthermore, there was a significant improvement in LLLT TBI, compared to non-TTTL TBI mice for the latency in the probe test. The outcomes of these tests in MWM showed that LLLT TBI mice could improve learning and memory levels. Therefore, the preclinical studies indicated that TTTL may have functions for treating cognitive disorder in post-TBI mice.

2.3. tNiRLT in Clinical Trials

Other than in experimental TBI, tNiRLT on improving cognitive function in TBI patients has been reported as well. For instance, Naeser reported cognitive function improvements after transcranial light-emitting diodes (tLEDs) therapy in two chronic, mild TBI cases [25]. Red/NIR LED cluster heads (870 nm and 633 nm, totally 500 mW) were placed in midline sagittal regions and bilateral forehead regions. Case 1, who was a 66 years old woman, started TLT therapy at 7 years after the car accident which led to closed-head TBI. After tLED treatments for several years, she improved attention, self-awareness, and inhibition. Case 2, who was a 52 years old woman, suffered from multiple closed-brain traumas and was diagnosed with fronto-parietal atrophy by MRI for 5 months. After about 9 months of tLEDs treatments, statistically meaningful improvement, such as +1 SD in immediate and delayed recall, +2 SD in executive function and inhibition, was indicated by neuropsychological tests.

Another study reported a case series of 11 chronic, mTBI patients (26-62 years old, 6 men) who were subjected to sustained cognitive impairment and treated with NiRLT [26]. LEDs irradiated light of 633 nm and 870 nm wavelength, and altogether 500 mW energy. Three LED cluster heads were placed on each of the 11 scalp areas for 10 min. The NiR light was applied on the midline and bilaterally on temporal, parietal, and frontal regions for these 10 months to 8 years post-mTBI patients. The NiRLT was administered 3 times weekly for a total of 6 weeks. Consequently, strong effects on inhibition, inhibition switching, learning, memory, and long-delay free recall were observed for the duration of the neuropsychological test. In the meantime, patients were also managed better in social occupational and social incidents.

Barrett and Gonzalez firstly proved convenient impacts on cognitive functions in humans after stimulating with transcranial laser *via* a double-blind, controlled study [27]. The main parameters generated from the laser diode CG-5000 during LLLT were the following: wavelength, 1064 nm; irradiance, 250 mW/cm^2; fluence, 60 J/cm^2. Participants in the treated group (n=20) obtained 4 1-min periods LLLT to right forehead (alternant 2 sites between medial and lateral of the frontal pole point), in order to directly target the right frontal pole of the cerebral cortex. While in control group (n=20), the 1-min cycle was comprised of a first 5 s therapy and a following 55 s no therapy. Except for the specific treatment time, the remaining procedure of the two groups remained the same. Better attention was observed in the psychomotor vigilance task after 2 weeks' treatment comparing treated group to control group. Participants also received better memory measured by Delayed Match-to Sample examination.

Future well-designed clinical trials are warranted due to rare human data at present. Randomized, parallel, double-blind, sham-controlled trials are in progress at VA Boston Healthcare System, outpatient-Neurotrauma center at the University of Sao Paulo and Boston Children's Hospital, with semblable purposes to assess the efficacy of tLED on cognitive functions and neuropsychiatric status in participants, who suffered from mild, moderate or severe TBI (Table **1**).

2.4. Mechanism

There are several potential mechanisms in improving cognitive deficits *via* the application of tNiRLT in TBI [25] and summarized as follows, also shown in Fig. (**1**).

Table 1. Summaries of ongoing clinical trials of LED light therapy used for TBI. (http://www.clinicaltrials.gov/).

Official Title	Study Design	Groups	Purpose	Phase	Place
Noninvasive LED Treatment to Improve Cognition and Promote Recovery in Blast TBI	Randomized, parallel, double blind	LED/sham LED	To investigate the efficacy of a novel neuromodulation treatment, light emitting diodes (LED), on cognition, neuropsychiatric status and quality of life in individuals with traumatic brain injury (TBI).	2	Boston, Massachusetts: at the VA Boston Healthcare System.
The Effects of Transcranial LED Therapy (TCLT) in Patients With Traumatic Brain Injury (TBI): a Prospective, Randomized Controlled Trial	Prospective, randomized, parallel, double blind	LED/sham LED	To evaluate the early and late effects of Transcranial LED Therapy (TCLT) in memory and executive functions in patients with moderate and severe TBI history in the initial phase (3-6 months).	2	Outpatient center-Neurotrauma Unit at University of Sao Paulo
Transcranial LED Therapy for the Treatment of Chronic Mild Traumatic Brain Injury	Randomized, parallel, double blind	LED/LED placebo	To asess the early of Transcranial LED Therapy in executive functions and other cognitive functions in patients with Chronic Mild Traumatic Brain Injury within 6 weeks.	2	Children's Hospital Boston
LED Light Therapy to Improve Cognitive/Psychosocial Function in TBI-PTSD Veterans	Double blind	LED/sham LED	To learn if an experimental treatment can help thinking ability, and memory in Veterans with mild or moderate traumatic brain injury (mTBI), and post-traumatic stress disorder (PTSD).	2	VA Boston Healthcare System Jamaica Plain Campus

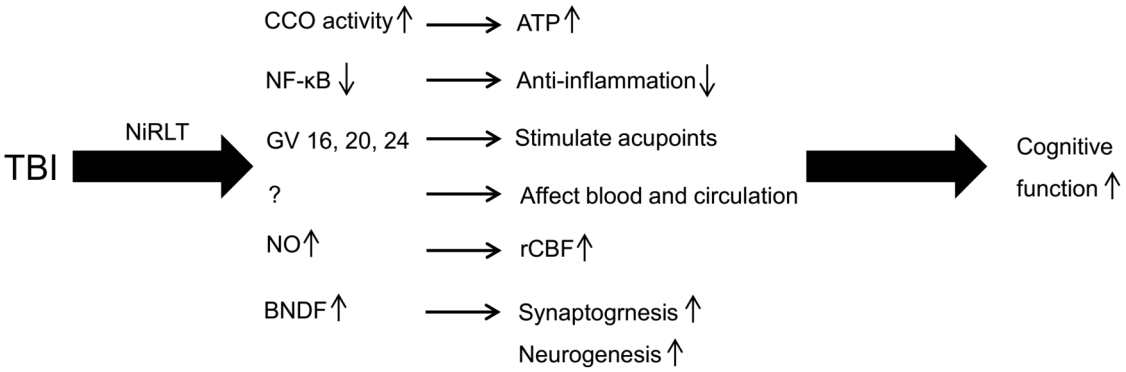

Fig. (1). Possible mechanisms of tNiRLT in improving cognitive recovery following TBI. Abbreviations: TBI, traumatic brain injury. tNiRLT, transcranial near-infrared laser therapy. CCO, cytochrome c oxidase. ATP, adenosine triphosphate. NF-κB, nuclear factor kappa B. GV, Governing Vessel. NO, nitric oxide. rCBF, regional cerebral blood flow. BNDF, brain derived neurotrophic factor.

1. Many studies indicated diverse mitochondrial dysfunction after TBI. Instead of generating heat, LLLT induced a photochemical effect in the cell. Luminous energy was transferred into bioenergy when chromophores absorbed the photon energy from LLLT. Mitochondria merely are the most crucial organelle in cells regulating LLLT reaction. A large transmembrane protein complex on the mitochondrial inner membrane, called cytochrome c oxidase (CCO) [28], is a vital chromophore in the cell responding to LLLT [29]. Absorption of NiR photons by CCO stimulates the CCO activity, which as a result, produces more adenosine triphosphate (ATP). The increased production of ATP in injured cells is feasible to invoke cells in metabolism disorganized and injured areas [30]. Hence, increased ATP after LED therapy in chronic TBI would bring about convenient impacts, incorporating an increase of the cellular respiration and oxygenation.

2. It has been proved that reactive oxygen species (ROS) and cell redox activity were increased through LLLT [31]. NF-κB is one of regulated transcription factors because of changes of cellular redox state. There is one proposal that mitochondria of illuminated cells generated low levels of ROS *via* LLLT. These ROS then activated NF-κB which upregulated the mitochondrial superoxide dismutase (MnSOD), through the redox-sensitive sensor enzyme protein kinase D1 [32]. Increased NF-κB was detected *via* a single exposure of LLLT-LED *in vitro* with fibroblasts [33], whereas decreased NF-κB and pro-inflammatory cytokines were observed when stimulating dendritic cells in the longer term [34]. Hence, repeated LED treatments after TBI for a long-term are hypothesized to decline inflammation and upregulate cytoprotective gene products, such as heat shock protein, superoxide dismutase and glutathione [32, 35, 36].

3. Acupuncture points on the skull, such as acupuncture meridian of Governing Vessel (GV), located in part or along the midsagittal suture line, were treated with red/NIR LEDs [25]. GV located inferior to occipital pro-

tuberance, on the vertex and near center-front hairline were called GV 16, GV 20 and GV 24 respectively. Historically, these acupuncture points have been employed to treat patients with stroke [37], and in coma [25]. In an animal model, increased oxygenation in the frontal cortex was observed after stimulating the GV 26 point, located on the philtrum area near the upper lip, on the midline [25].

4. A red-beam laser for blood irradiation *in vitro* directly has been discovered to improve the deformability and rheology of erythrocyte [38]. When illuminating a coronary artery directly with the low-level, red-beam laser (10 mW, 650 nm) during a stenting operation, a benefit was observed from such *in vivo* direct laser blood irradiation [38]. The restenosis rate was substantially decreased and no disadvantaged side effects took place. Therefore, there is a surmise that transcranial red/NiR LED may irradiate the blood through valveless and emissary veins, yet linking with veins in the superior sagittal sinus. It is probable that photons enter small vessels lying between the pia mater and the arachnoid, which contains the arterial blood provided to superficial areas of the cortex, if red/NiR photons permeate deeply enough to reach the cortex. Thus, local intracerebral blood may affect when irradiating blood at regional scalp; Nevertheless, it is unclear the impact that would be produced and further studies are warranted.

5. Nitric oxide (NO) [39], as a vasodilator through influence on cyclic guanine monophosphate production, may have photodissociation from CCO during LLLT [40]. Therefore, LLLT potentially increased the blood flow at the tissue level after release of the NO [41]. An increased blood flow may have existed in the regional brain tissue, especially in the frontal lobes. One patient indicated meaningful improvement in executive and memory in neuropsychological test after LED therapy [25]. These outcomes showed functional improvements in anterior cingulate gyrus and prefrontal cortex regions.

6. Secondary injuries may result in inflammation, apoptosis, and diffuse axonal injury [42, 43]. These pathological alterations gave rise to changes in synaptogenesis and neurogenesis in the hippocampal. As a healing response, after the primary and secondary injuries, neurons begin to reorganize and repair axonal connections *via* enabling synaptic growth [44]. Some researchers regarded increased possible neurogenesis and synaptogenesis as the most significant impacts applied to NIR light in the acute phase post-TBI animals [24, 45]. Increased neuroprogenitor were found in both dentate gyrus and subventricular zone by Xuan *et al*. [24]. BDNF (brain derived neurotrophic factor), as a neurotrophin, plays a critical part in regulating neurogenesis synaptogenesis in the brain [46-48]. A large increase of BDNF was observed in the perilesional cortex *via* immunofluorescence on day 7 post-TBI in TTTL groups [24, 45]. Meng and coworkers demonstrated that LLLT increased BDNF expression through ERK/CREB signaling pathway and reduced dendritic atrophy and neuronal loss with Alzheimer's disease in an animal model [49].

2.5. Biological Dose-response and Attenuation

tNiRLT has postulated that inherent bimodal dose-response curve existed [50]. To be specific, some amount of laser is beneficial, while irradiating more light is likely to miss the helpful influence of laser. Furthermore, too much light even does harm the tissue indeed. Biphasic dose-response to light irradiation in fibroblasts *in vitro* has been testified by Chen *et al*. [33]. Their laboratory finding showed that transcription factors were activated when the energy density ranging from 0.03 J/cm^2 to 0.3 J/cm^2, with 3-30 J/cm^2 of those factors were inhibited. Although such dose-dependent impact in photobiomodulation after NIR light has also been proved by many other studies [51-53], the hypothetic theory is not a pervasive truth. For example, no threatening effects were observed when the power density turned into 30 J/cm^2 in a microglial cell experiment [54].

Only to reach the targeted tissue can the photons be transmitted from the emitter trigger molecular events [55]. So, another key matter is that the amount of photonic energy reaching the deep targeted tissue depends on damping of the energy due to penetrating the overlying tissue. NIR light at 808 nm wavelength and 0.9 J/cm^2 power densities, was projected on human scalp for a total of 40 min during the NEST-1 and NEST-2 trials [56, 57]. However, a clinical contradiction was exposed in both trials with the parameters of NiRLT set up in these studies probably delivering deficient power to the brain tissues to work. Taking a notice that animal models of stroke or TBI showed NiR power densities ranging from 0.9J/cm^2 to 36 J/cm^2 contributed to meaningful biochemical and behavioral alterations [18, 20, 21, 24, 30, 55, 58]. The alarm induced from the NEST trials [59] is that clinical trials currently examining the validity to treat TBI *via* NiR light may yield useless or imprecise efficacy data, not on account of the incompetence of NiR to give rise to a change, but for the sake of a dose error.

Almost entire photon is absorbed within the initial 1mm of human abdominal skin when irradiated by 850 nm wavelength NIRL [55]. Before ultimately reaching the brain, photons must pass through the skin and skull ordinally. Lapchak *et al*. systematically compared different penetrability employing 800nm wavelength, 700 mW/cm^2 energy densities in four species (mouse, rat, rabbit, and human) [60]. 59.90% (mouse), 78.76% (rat), and 88.64% (rabbit) of administrated NIL passed through the dehydrated skulls, and their skull thickness was 0.44 mm, 0.83 mm, and 2.11 mm accordingly, as calculated from bregma. 4.18% at bregma and 4.24% in the parietal skull energy were residual in the human skull where the mean thickness was in a range of 7.19 mm to 5.91 mm. Also, penetration was detected potentially correlated with mean thickness measured of the skull, yet not correlated with skull density. As a result, novel applications used in animals should consider human skull characteristics optimized. The recent review concentrating on low-power NiR penetration indicated that no more than 0.05% of energy at the surface could reach 1 cm depth [61]. Besides, retrospective data showed an energy of 10-15 W at a wavelength 810 nm or 910 nm being able to supply biological benefit at a depth of 3 cm.

CONCLUSION

tNiRLT is a non-invasive, inexpensive, domiciliary treatment, with unknown side effect. Bain ATP production and regional cerebral blood flow increase, acupoint stimulation, anti-inflammatory, particularly neurogenesis and synaptogenesis stimulation, potentially play key roles in the mechanism of tNiRLT for cognitive impairment after mTBI. Increased attention has been focused on NIR light therapy for TBI, especially on following cognitive deficit. Also, rapid increasing evidence has indicated that NiR light is a promising application in improving cognitive function post-TBI. Although tNiRLT is not in mature phase temporarily, in view of the amount of TBI experiences continuing to grow, NiR light may become a real contributor to patient health. For preclinical or clinical trials, it is crucial to guarantee sufficient light power to the injured brain tissue. If the effectiveness works stably, tNiRLT may expand to certain neurodegenerative diseases and mental disorders.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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