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Photobiomodulation with Super-Pulsed Laser Shows Efficacy for Stroke and Aphasia: Case Studies

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Abstract

Background: Brain disorders have become more and more common today, due to both the aging population and the ever-expanding sports community. However, a new therapeutic technology called photobiomodulation (PBM) is giving hope to thousands of individuals in need. Traumatic brain injury (TBI), dementia, post traumatic stress (PTSD) and attention deficit (ADD) disorders are in many cases quickly and safely improved by PBM. PBM employs red or near-infrared (NIR) light (600 - 1100 nm) to stimulate healing, protect tissue from dying, increase mitochondrial function, improve blood flow, and tissue oxygenation. PBM can also act to reduce edema, increase antioxidants, decrease inflammation, protect against apoptosis, and modulate the microglial activation state. All these effects can occur when light is delivered to the head, and can be beneficial in both acute and chronic brain conditions. **Methods:** In this case series, we used a high power, FDA-approved superpulsed laser system applied to the head to treat four chronic stroke patients. Patients received as few as three 6 - 9 minute treatments over a one-week period. The follow up time varied, but in one case was two years. **Results:** Patients showed significant improvement in their speech and verbal skills. Improvements were also noticed in walking ability, limb movement, less numbness, and better vision. **Conclusion:** The use of PBM in stroke rehabilitation deserves to be tested in controlled clinical trials, because this common condition has no approved pharmaceutical treatment at present.

Keywords

Low-Level Laser Therapy, Photobiomodulation, Stroke Rehabilitation, Traumatic Brain Injury, Alzheimer's Disease, Aphasia

1. Introduction

According to the Center for Disease Control, stroke is the most common cause of aphasia, and it has been estimated that about 20% - 40% of stroke patients develop debilitating problems with speech. Some patients may recover from aphasia within a matter of hours or days after onset of the stroke, however many others do not recover at all [1].

A stroke, sometimes referred to as a brain attack, occurs when a blood clot blocks the blood supply to the brain leading to an ischemic stroke. Alternatively the occurrence of a tear in a blood vessel can lead to a hemorrhagic stroke. In an ischemic stroke, a blood vessel becomes blocked, usually by a blood clot, and a portion of the brain becomes deprived of oxygen leading to the death of cortical neurons. Ischemic strokes are the most common type, representing about 87% of all strokes. In one second, 32,000-brain cells die, and in I minute an ischemic stroke may have killed 1.9 million brain cells [2].

A hemorrhagic stroke can occur when an aneurysm, a blood-filled pouch that balloons out from a weakened artery, ruptures and floods the surrounding tissue with blood. The fatality rate is high and the prognosis is poorer for those who experience a hemorrhagic stroke [3].

In 2020, 1 out of 6 deaths from cardiovascular disease was due to stroke. Every 40 seconds, someone in the United States has a stroke and every 3.5 minutes, someone dies of stroke [4].

Photobiomodulation (PBM) previously known as "low level laser therapy, LLLT" involves the delivery of red or near infrared (NIR) light to various parts of the body to treat many diseases involving pain, inflammation or tissue death [5]. Formerly in PBM research, animal models were used due to concerns for the safety and side effect of laser treatment. However after years of research and practical application safety is no longer a concern. Patients are easily treated with PBM delivered to the head (NB: if a brain tumor is present, this is considered the one contra-indication for PBM). PBM for brain disorders has demonstrated positive effects on cognitive function, learning and memory, as well as reduced inflammation and preventing cell death in the brain [6]. There is evidence that PBM can help the brain repair itself by stimulating neurogenesis, upregulating BDNF synthesis, and encouraging synaptogenesis [7]. In healthy human volunteers (including students and healthy elderly women), PBM has been shown to increase regional cerebral blood flow, tissue oxygenation, and improve memory, mood, and cognitive function. Clinical studies have been conducted in patients suffering from the chronic effects of TBI [8] [9]. There have been reports showing improvement in executive function, working memory, and sleep. Functional magnetic resonance imaging has shown modulation of activation in intrinsic brain networks likely to be damaged in TBI (default mode network and salience network) [10].

The mechanism of action of PBM on the brain is multifactorial in nature, and different biochemical and cellular processes have been proposed to be responsible for the beneficial effects [11]. Several theorized mechanisms of action have been proposed as follows. 1) Stimulation of mitochondria by photons and the consequent increase in cytochrome c oxidase activity and intracellular adenosine triphosphate (ATP) [12]. 2) Improvement in regional blood flow and oxygen delivery to the brain parenchyma by triggering nitric oxide (NO) production [13]. 3) Anti-inflammatory effects caused by changing the phenotype of the brain microglia from pro-inflammatory M1 to anti-inflammatory M2 [14]. This switch results from changing the mitochondrial metabolism from glycolysis towards oxidative phosphorylation by light absorption. It should be noted that M2 microglia can carry out phagocytosis, and could therefore dispose of beta-amyloid plaque in the brains of Alzheimer's patients. 4) Anti-apoptotic affects caused by PBM, which could prevent the death of cortical neurons [15]. 5) Stimulation of neurogenesis (production of new neurons from progenitor cells existing in the brain), and synaptogenesis (production of new connections between existing neurons) [14]. 6) Balancing of connections between intrinsic brain networks in the brain (especially the default mode network) [16].

2. Methods

The laser (Theralase TLC-900 MULTIPLE PROBE, Theralase Technologies Inc, Toronto, Canada) has received FDA approval for the safe and effective treatment of chronic knee joint pain. The laser contains five super-pulsed 905 nm diodes (200 nsec pulse duration) each with the ability to put out 200 mW average power, plus four 660 nm diodes each with the ability to put out 100 mW power. Patients were treated on the part of the head corresponding to the brain area identified as damaged in the stroke. Protocol for stroke patients consisted of illuminating the pre-frontal cortex for two minutes 15 seconds per site (four areas). The power settings were 65 mW for the five 905 nm diodes and 65 mW for the four 660 nm laser diodes. The energy delivered per site was 79 J, and the total energy delivered over four sites was 315 J. The patient was placed in a supine position and wore protective eyewear.

The patients received various numbers of sessions and had varying lengths of follow up time as detailed for each specific patient in the text. In this preliminary case series the improvements were documented by self reports of symptoms from the patients and by individual clinical assessments by the practitioner. No objective diagnostic methods were employed, but these should be performed in any future controlled trials.

3. Case Studies

Case 1. A 58-year-old male business owner. Patient reported suffering a stroke five years previously. He complained of intermittent moderate to severe headaches with accompanying aphasia. A series of three treatments were administered and the patient reported a significant improvement in speech and verbal skills. Patient also reported better focus and greatly improved organizational skills, along with the positive drive and energy needed to run his business.

Case 2. A 61-year-old male active hockey player. The patient suffered a stroke 2 years ago and then received weekly treatment with acupuncture over the course of one year, but still had problems with numbness and the use of his left hand and arm. After the second PBM treatment, he suddenly realized where his left arm was positioned in bed (outside the covers). A series of four treatments utilizing the stroke protocol restored significant improvement in his ability to use his left arm and hand in a normal manner, and sensitivity had returned to his hand.

Case 3. A 38-year-old female, under the care of a primary care physician for 3 months with a history of stroke and possible TBI caused by spousal abuse. She had moderate to severe migraines three to four times per week over a 5-year period. Her previous primary care physician had prescribed a very high dosage of OxyContin. Her new primary care physician asked me if I could help wean her off the OxyContin. Her mother was needed to bring her to her appointments. After the first treatment her headache pain was eliminated, however cutting back on her medication led to her migraines recurring. A course of eight treatments (sometimes on an emergency basis) was then administered over a 14-day period and she reported significant relief after every session. When she came in for her seventh visit, she was walking without her cane and her leg was now almost back to normal gait. Most remarkable was the fact that the mother reported that her daughter began speaking in full sentences and her memory had returned. She no longer needed to walk with a cane. The patient was followed up intermittently over a 2-year period and no regression was observed.

Case 4. A 48-year-old woman referred because of a fall and cervical spine injury. X-ray showed severe herniation of C2 (Atlas) vertebra. Symptoms were inability to walk (wheelchair bound) and 50% loss of vision. Chiropractic was initiated and the stroke PBM protocol was performed. In addition, the occipital area was also illuminated. Four treatments were needed to increase her mobility utilizing a cane, and 90% of her vision was restored. The patient continued to receive chiropractic for maintenance due to the severity of the cervical spine injury. PBM with laser was no longer required.

4. Discussion

PBM is now becoming more mainstream due to expanding clinical studies and many more published papers in recent years [5]. Of all the different organ systems that have been shown to respond very well to PBM therapy, perhaps the most important to patients is the brain [17]. The cost savings to the healthcare system and families can be significant when considering the need for skilled nursing facilities for patients with brain damage or post-stroke disability. Various groups have reported significant benefits from PBM treatment for many brain disorders including Alzheimer's disease [18]. A group including Berman and Huang has described a helmet with 1100 LEDs emitting 1060 - 1080 nm light pulsed at 10 Hz with a 50% duty cycle. PBM was administered for 6 minutes daily over 28 consecutive days in a pilot trial of 11 patients. A non-significant improvement was seen in the active compared to the placebo group with respect to MME and ADAS-Cog scores [19]. The same group then went on to recruit a much larger group of fifty-seven patients [20]. Significant improvements were seen in the active group with respect to MMSE, Logical Memory Tests I and II, Trail Making Tests A and B, Boston Naming Test, and Auditory Verbal Learning Tests. A further analysis revealed no difference between the responses of male and female patients [19]. Additional case studies have reported the benefits in Alzheimer's disease patients using PBM alone [21] [22], or PBM combined with a ketogenic diet [23]. Guiterezz *et al.* discussed several areas of research that need to be carried out for treatment of disorders in the psychological arena [24]. A case series recently published by our group reporting treatment of ADHD with super-pulsed laser PBM, underlines the need for funding a formal clinical study in this area of medicine [25].

PBM has been intensively investigated in human patients who had suffered an acute stroke in the three NEST trials. The NEST-1 clinical trial had 120 ischemic stroke patients (79 active and 41 placebo) [26]. The PBM therapy consisted of the application of a transcranial 808 nm laser to 20 specified locations on the shaved scalp for 2 minutes at each site. The mean time between stroke and PBM therapy was 16 h (range 2 - 24 h). The results from the active treatment group showed more patients with improved NIHSS scores (70%) as compared to the placebo group (51%) [26]. The NEST-2 clinical trial was a prospective, double-blind, randomized, sham-controlled, multicenter study involving 660 acute stroke patients (331 active, 327 placebo, and 2 dropouts) [27]. One hundred twenty patients (36.3%) in the active treatment group showed improved mRS scores versus 101 patients (30.9%) in the placebo group [27]. The NEST-3 double-blind, sham-controlled, randomized, multicenter trial involved 630 acute stroke patients (314 active and 316 placebo) [28]. An interim analysis of 566 completed patients revealed no significant difference in the primary endpoint (active PBM with 140/282 [49.6%] versus placebo PBM with 140/284 [49.3%]) and the trial was terminated for futility. The reasons for the eventual failure of NEST-3 have been proposed to be insufficient light penetration, varying thickness of different patient's skulls, only a single irradiation session (rather than repeated daily treatment), inappropriate stroke severity measurement scale, too long an interval between stroke onset and PBM therapy, and irradiation areas which were not optimized for the location of damage in individual patients [29].

Compared to acute stroke, PBM has not been much investigated for treatment of chronic stroke. In 2012, Boonswang *et al.* [30] reported a case study of a 29-year-old woman diagnosed with a brainstem stroke. She suffered acute infarctions involving the medulla, superior aspect of the cervical spinal cord and bilateral cerebellar hemispheres. The PBM protocol consisted of combined 660 and

850 nm LED irradiation on a total of 32 locations, including the cerebral cortices, brainstem, cervical spine (8 locations), and the body musculature and lymphatics (24 locations), while the patient sat in her wheelchair. After 8 weeks of treatment, the patient's mood became much less melancholic and she was less anxious and fearful as well as more alert and aware of her environment. It is interesting to note that the improvements at 8 weeks post-treatment were maintained for the next 12 months [30].

In 2017, Yang *et al.* [31] reported a case study of a 77-year-old man who had suffered a stroke. The patient was diagnosed with progressive weakness of left limbs, underwent repeated falls, choking, and slow responses, based on clinical examination. MRI showed an infarction in the right anterior cerebral artery. CT of the brain also revealed low density over the right anterior cerebral artery. The PBM protocol consisted of 632.8 nm intravascular laser irradiation for 60 minute over 10 consecutive days. The patient underwent 3 different SPECT procedures, before and after PBM therapy, as well as at 63 days post-stroke. Comparison of the 2 regional perfusion SPECT images revealed that the blood perfusion in the right cerebellar hemisphere became more similar to the left cerebellar hemisphere in the second SPECT after PBM therapy. The SPECT data also showed that the crossed cerebellar diaschisis (CCD) was decreased in the patient after treatment. Furthermore, the patient appeared to be more energetic, and his muscle power and functional ability were improved as measured by the Barthel index.

It is well established that rehabilitation after a stroke depends strongly on the stimulation of neuroplasticity within the injured brain [32]. The brain has the capacity to rearrange or "rewire" itself to develop new neural pathways that can take over the function of lost pathways caused by brain damage after a stroke [33]. However this rewiring process is often a lengthy process requiring months of intensive physiotherapy or speech therapy [34] [35].

We believe that the benefits of PBM for chronic stroke could be due to its remarkable ability to stimulate neuroplasticity and synaptogenesis in the brain [36]. Moreover PBM can also stimulate neurogenesis, or the formation of new neurons from neuroprogenitor cells in the hippocampus [14] [37]. The benefits of PBM-induced neuroplasticity can also be inferred from its ability to improve opiate addiction [38] and autism spectrum disorder [39] in patients.

5. Conclusion

The use of PBM in stroke rehabilitation deserves to be tested in controlled clinical trials, because this common condition has no approved pharmaceutical treatment at present.

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Conflicts of Interest

LJB is the proprietor of Laser Innovations, Amherst, NY. MRH declares the following potential conflicts of interest. Scientific Advisory Boards: Transdermal Cap Inc, Cleveland, OH; Hologenix Inc. Santa Monica, CA; Vielight, Toronto, Canada; JOOVV Inc, Minneapolis-St. Paul MN; Sunlighten, Kansas City, MO; Consulting; USHIO Corp, Japan; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany; Klox Asia, Guangzhou, China. Stockholding: Niraxx Light Therapeutics, Inc, Irvine CA; JelikaLite Corp, New York NY.

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