Photobiomodulation for relapsing–remitting multiple-sclerosis management: a nonrandomized controlled trial

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Background
Fatigue and cognitive dysfunctions in multiple sclerosis (MS) are well-established complications that considerably impact patients' independence, yet lack proper medical management.
Purpose
To test the efficacy of low-level laser therapy (LLLT) and broadband ultraviolet B-radiation (BB-UVBR) combination on modulating fatigue and cognitive functions for patients with MS.
Patients and methods
Pretest–post-test nonrandomized clinical trial study. Forty participants were included, nevertheless, 32 completed the study, age 20–45 years old with definite relapsing–remitting MS on monthly cortisone therapy. Then, they were assigned into two groups, control group (n=14) received pulsed LLLT, and study group (n=18) received the same LLLT program in addition to BB-UVBR for 12 sessions. Primary measures were fatigue, Fatigue Severity Scale (FSS) and cognition, a computerized reactive stress tolerance, and percentile ratio for correct answers (PRC). Besides, Expanded Disability Status Scale (EDSS) as a secondary measure.
Results
The two groups were comparable at baseline in FSS, PRC, and EDSS ($P \geq 0.05$). Patients on LLLT group showed post-test high statistically significant improvement of PRC, FSS ($P < 0.001$), and EDSS (P=0.023). Similarly, UVBR and LLLT group showed highly significant improvements of PRC, FSS, and EDSS ($P < 0.001$). However, no significant differences ($P \geq 0.05$) of PRC, FSS, or EDSS were found between the two groups Post-treatment.
Conclusion
The study suggests that there was no added value of UVBR to LLLT. That LLLT program alone has a potent beneficial short-term effect, on modulating fatigue, cognitive functions, and disability status for patients with relapsing–remitting MS.

Keywords:
broadband Ultraviolet B Radiation, cognitive dysfunctions, fatigue, low-level laser therapy, photobiomodulation, relapsing–remitting multiple sclerosis

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. It is The most common cause of neurological disability in adults [1]. MS affects 2.3 million people worldwide and is typically diagnosed with a peak onset between ages 20 and 40 [2,3]. In 2002, the prevalence rate of MS among Egyptians was found to be about 25/100 000 in Cairo, 35/100 000 in Alexandria, while in Upper Egypt was 1.2/100 000 [4].

It has been reported that 45–60% of MS patients are cognitively impaired. However, the measurement of these neuropsychological changes can be difficult, especially in cases of MS, where cognitive dysfunctions are recognized to be heterogeneous in nature [1]. Moreover, cognitive impairment in MS is complex and multifactorial, in which white-matter and gray-matter damage are involved in its pathogenesis [5].

MS-related cognitive impairment has been termed as a 'subcortical dementia'. Unlike cortical, subcortical dementia affects information-processing speed, memory, and executive function. It frequently presents as intense slowing of cognition; referred to as bradyphrenia [6], in addition to psychiatric and personality changes [7], culprit lesions are believed to be located in basal ganglia, thalamus, brain stem, and cerebellum [8].

Another disabling symptom of MS is fatigue, which is considered the most common symptom of MS, affecting nearly 80% of patients [9]. It is defined as 'a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities' [10]. Although the exact cause of fatigue in MS is not well recognized, it is hypothesized to be a consequence of centrally mediated processes inherent to MS, such as demyelination and axonal loss or due to MS-related complications, musculoskeletal, sleep problems, or medications [11,12].

Clinically, fatigue presents as exhaustion, lack of energy, and increased sleepiness [12]. Fatigue has also been connected to increased cognitive impairment and patient's relationships and social integration [13].

Although the exact cause of MS is unknown, a number of genetic and environmental factors are thought to influence MS susceptibility. One potential environmental factor is sunlight and the subsequent production of vitamin D [14]. A number of studies have correlated decreased exposure to ultraviolet radiation (UVR) and low serum 25-hydroxyvitamin D_3 levels with an increased risk for developing MS [15].

Aside of stimulating vitamin-D production, it is believed that UVR is likely suppressing disease activity independent of vitamin-D production, and that vitamin-D supplementation alone may not replace the ability of sunlight to reduce MS susceptibility [16]. Whereas, local application of ultraviolet B (UVB) influences systemic immune reactions and attenuates systemic autoimmunity through induction of skin-derived tolerogenic dendritic cells and T-regulatory cells [17].

On the other hand, low-level laser therapy (LLLT) has a wide range of medical applications, where protection from cell death, stimulation of healing, repair of injuries, reduction of pain, swelling, and inflammation are needed [18]. Photobiostimulation using transcranial LLLT was proved to be a potent treatment of stroke [19,20], with success reports in animal models [21], as well as in clinical trials [22].

Other clinical trials investigating the effect of light therapy in the form of laser application to patients with MS had been previously conducted, showing that objective clinical results were obtained from patients suffering from MS as well as subjective improvement of their mental comfort and motive power. They suggested that laser biostimulation is not only an alternative method of therapy of Patients with MS, but also an effective method of rehabilitation in this so far incurable disease [23].

Phototherapy efficacy in ameliorating fatigue and cognitive deficits suffered by patients with relapsing–remitting MS (RRMS) had never been challenged before in previous clinically applied research work. Therefore, our controlled clinical trial is the first to test the efficacy of both LLLT and broadband ultraviolet B-radiation (BB-UVBR) combined therapy in that domain.

Patients and methods

Forty eligible patients with RRMS were included in this pretest–post-test controlled trial. Patients were recruited from Neurology Department in Kasr Al-Ainy Hospital. Diagnosis of RRMS was based on 2010 McDonald's Criteria [24]. Patients were selected while in remission state. The study was conducted in the outpatient clinic of the Faculty of Physical Therapy, Cairo University, between October 2013 and February 2014. The study followed the Guidelines of Declaration of Helsinki on conduction of human research. All the participants were informed about the clinical importance, nature, and procedures of the study. All patients signed pretreatment written informed consents.

A convenient sample of forty participants were recruited and randomly assigned into control and study groups, 20 patients each. But only 32 patients completed the study. The control group (LLLT group) included 14 patients who received monthly pulse therapy of (1 g) through intravenous infusion of methylprednisolone sodium succinate (Solu-Medrol) as a drug therapy for MS, in addition to GaAlAs diode LLLT on the cervical region for 10 min, 3 days/week (4 weeks) for 12 sessions.

The study group (UVBR group) included 18 patients who received Solu-Medrol and LLLT as in the control group, in addition to BB-UVBR, 280–320 nm on a whole exposed back region for 20 min, 3 days/week (4 weeks) for 12 sessions.

The inclusion criteria were age range 20–45 years of both sexes, in remission with less than or equal to 6 score on Expanded Disability Status Scale (EDSS), free from visual disability, any systemic vascular or blood disease, vasculitis, diabetes, liver disease,

kidney failure, heart failure, traumatic brain injury, cerebrovascular accident, spinal cord injury, HIV, hyperthyroidism, cancer, or in risk of chemical or atomic radiation exposure with skin type of grade 3 or 4 that was free of any local or systemic comorbidity. Patients on antibiotics or photosensitizing drugs were weaned off for 21–30 days before joining the study. Pregnant patients and those allergic to phototherapy in addition to those who missed more than three successive sessions were excluded from the study.

Assessment procedures

(1) EDSS according to Kurtzke [25].
(2) Fatigue Severity Scale (FSS), the questionnaire was interpreted and introduced to patients by the investigators [26].
(3) Computerized Vienna System was used to show the patients' response to visual and auditory stimuli using the computer monitor (Fig. 1). The determination test is used to measure reactive stress tolerance and the associated ability to react. In this study, we used the 6-min adaptive short form of determination test. The test estimates the percentile ratio of correct, incorrect answers, and omitted answers (PRC, PRIC, and PRO, respectively), which reflect patient's stress-reactive tolerance. Patients took the test setting in a quiet room to eliminate any external distractions.

Figure 1

The computerized Vienna system, the monitor, hand, and feet controls.

Treatment procedures

Low-level laser therapy

Patients were positioned in a comfortable leaning-forward sitting position, with foreheads rested on their hands to ensure straight cervical position. Then, the cervical region was rubbed by alcohol to minimize laser-light reflection. LLLT was applied using a calibrated ASA laser-scanning device (He–Ne red laser 632.8 nm, 15 mW power as an aiming beam, and GaAlAs diode laser), emitting near-infrared (NIR) wavelength 850 nm, with total beam area (a)=0.5 cm^2 (incident beam area=0.01 cm^2×50 mm total width of the scanning beam). PW, PD 50 ns, frequency 2084 Hz, maximum power (P_{Max}) 10 W, and calculated average power 0.00104 W. Radiant power 0.00208 W/cm^2, radiant energy (Q) 2 J, and radiant exposure $(E/a)_{act}$ 4 J/cm^2.

The application site is determined by three points, one on C7 spinous process, and the two other points were situated 2.5 cm lateral to the C7 spinous process bilaterally. The LLLT scanning started at the horizontal occipital line and ended at the C7 spinous process with a medium-speed level. And 20±5 cm perpendicular distance from the laser aperture, while the patient is in a sitting–leaning-forward position.

Ultraviolet B radiation (broadband ultraviolet B-radiation)

Using a calibrated Dr Kern Quattro, BB (280–320-nm) UVB device, patients were placed in a side-lying position, with their back facing the UVBR device. The back region was rubbed by alcohol to reduce UVR reflection. The BB-UVBR (280–320 nm) was applied with a radiant power=0.396 W/cm^2, and total suberythemal dose=470 mJ/cm^2 on the whole back region from below the neck till the iliac crests from 100-cm distance perpendicularly from side lying, for 20 min [starting at 50% of the total dose (235 mJ/cm^2≈10 min for the first session), with an incremental increase of 10% of the total dose (47 mJ/cm^2≈1-min increase/session).

Primary outcome measures were FSS and PRC and the secondary outcome measures were EDSS, PRIC, and PRO.

Statistical analysis

Power analysis was calculated using G*power software, version (3.1.9.2), t tests – means:

Wilcoxon–Mann–Whitney test (two groups), two-tailed, a priori: compute the required sample size, parent distribution=Laplace, effect size d=0.8, α-error prob.=0.05, power (1-β error prob.)=0.80, allocation ratio N2/N1=1, and sample size 36 participants.

Data were analyzed using IBM SPSS Advanced Statistics, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Numerical data were expressed as mean and SD or median and interquartile range as appropriate. The measured scales were tested for normality of distribution (Shapiro–Wilk test); all variables were found to be not normally distributed. Thus, two-way analysis was not done. Comparison between two groups was done using Mann–Whitney test. Wilcoxon signed ranks test was used to compare pretest and posttest measures in each group separately. Spearman–rho method was used to test the correlation between numerical variables. A P value less than 0.05 was considered significant. Percent of change also was calculated to depict clinical significance within and between the two groups.

Results

The two study groups were comparable at baseline regarding age (P=0.116), BMI (P=0.561), and disease duration (P=0.955) (Table 1). Table 2 shows that pretreatment, there were no significant difference between the two groups in all. Patients in the control (LLLT) group showed significant improvement of EDSS (P=0.023), FSS (P=0.002), and PRC (P=0.001). Patients in the study group showed significant improvement of EDSS, FSS, and PRC (P=0.002, 0.001, and 0.001, respectively). Post-treatment, there were no statistically significant differences between the two groups in EDSS, FSS, and PRC (P=0.301, 0.180, 0.206, and 0.122, respectively).

Also, patients in the control group showed significant improvement of PRO (P=0.021), However PRIC did not change significantly (P=0.549). While patients in the study group showed significant improvement of PRIC and PRO (P=0.001, 0.031, and 0.002, respectively) (Table 2).

Percentages of change for all measures in both the study and control groups are represented in Fig. 2. The study group showed considerable percentages of change in all measures. Whereas, in the control group, were minimal in comparison.

Discussion

Photobiomodulation using light in the NIR range (630–1100 nm) with low-energy lasers has shown a therapeutic effect in various clinical conditions, with a penetration depth up to 50 mm [27,28]. The mechanism of action is believed to be through activation of a cellular photoreceptor, cytochrome-C oxidase that is localized in the mitochondrial respiratory chain, which is a key molecule in the electron-transport chain, leading to production of ATP, and the subsequent activation of transcription factors, leading to improved energy metabolism and mitochondrial function [29–32].

LILT of 670 nm, 5 J/cm^2 for 3 min, at a power intensity of 28 mW/cm^2, showed more sustained effectiveness in ameliorating disease severity of EAE in C57BL/6 mice through the downregulation of proinflammatory cytokines (interferon-c, tumor-necrosis factor-a) and upregulation of anti-inflammatory cytokines (interleukin-4, interleukin-

Table 1 Age, BMI, and disease duration of the two studied groups

	LLLT group (n=14)	UVBR group (n=18)	P value
Age (years)	30.7±6.4	33.1±6.4	0.116
BMI (kg/m^2)	23.6±2.9	24.2±4.3	0.561
Disease duration (years)	4.0 (1.0–12.0)	5.0 (1.0–16.0)	0.955

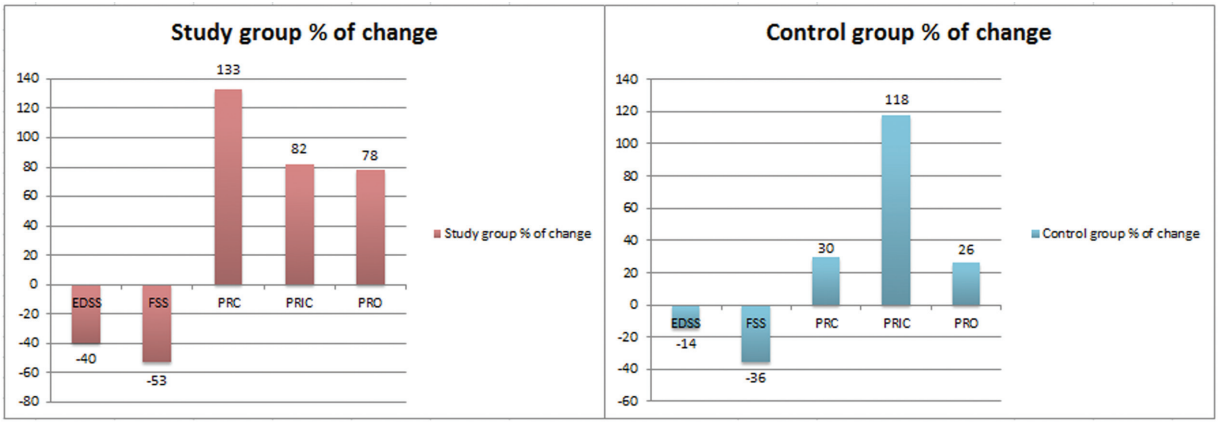
LLLT, low-level laser therapy; UVBR, ultraviolet B-radiation.

Table 2 Pretreatment and post-treatment values of scales of disability, fatigue, and stress-reactive tolerance of the two studied groups

Measures	Pretreatment		P value	Posttreatment		P value
	Control group (n=14)	Study group (n=18)		Control group (n=14)	Study group (n=18)	
EDSS	3.5 (1.5–6.0)	2.5 (1.5–6.0)	0.206	3.0 (1.0–6.0)	1.5 (1.0–6.0)	0.301
FSS	45.0 (9.0–51.0)	47.0 (23.0–54.0)	0.896	29.0 (9.0–39.0)	22.0 (9.0–33.0)	0.180
PRC	10.0 (1.0–22.0)	3.0 (1.0–16.0)	0.135	13.0 (4.0–36.0)	7.0 (2.0–22.0)	0.122
PRIC	17.0 (9.0–88.0)	28.0 (11.0–63.0)	0.779	37.0 (12.0–56.0)	51.0 (9.0–82.0)	0.338
PRO	19.0 (2.0–28.0)	18.0 (4.0–28.0)	0.377	24.0 (3.0–54.0)	32.0 (4.0–71.0)	0.419

EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; PRC, percentile ratio of correct answers; PRIC, percentile ratio of incorrect answers; PRO, percentile ratio of omitted answers.

Figure 2



Percent of change in all measures within each group. Shows greater percent of change in the study group (LLLT+UVBR) in all measures compared with the control group (LLLT). With much higher percent of omitted answers (PRO) and less percent of incorrect answers in the study group compared with the control group. LLLT, low-level laser therapy; UVBR, ultraviolet B-radiation.

10) in vitro and in vivo [33]. This was also confirmed in vitro in 2012 by Song *et al.* trial [34].

Moreover, LLLT exerts both local and systemic circulatory and neuroprotective effects, as it increases blood flow both locally and remotely from the application site through manipulating the autonomic nervous system and maintaining homeostasis of the internal environment [35,36].

Cerebral blood perfusion was reported to be reduced in MS patients [37]. This often occurs in the basal ganglia and thalamus and has been related to fatigue [38,39].

A Polish study reported objective improvement of disability in one-third of MS patients with EDSS more than or equal to 5.5 under treatment with LLLT in addition to subjective improvement in another one-third [23].

In the current study, we used a longer-wavelength NIR (850 nm), in PW, 50 ns PD, 2084-Hz frequency, radiant power 0.00208 W/cm^2, radiant energy (Q) 2 J, and radiant exposure $(E/a)_{act}$ 4 J/cm^2 from maximum-power (P_{Max}) 10 W device to ensure deeper penetration with minimum attenuated energy level [28], to reach the vertebral arteries in the cervical region to induce a photochemical reaction of LLLT to improve cerebral blood flow and supply more energy ATP to neural tissues promoting its recovery [40–42]. And benefiting from the bioresonance occurring between the frequency of the LLLT pulses and the neuronal electromagnetic frequency provided using true pulsed LLLT [43].

Our study showed beneficial effect of LLLT on the disability status, cognitive dysfunction, and fatigue in patients with RRMS, EDSS less than or equal to 6 during remission state. Treatment for 12 sessions (three sessions/week), on cervical region for 10 min significantly decreased patients' disability-status EDSS by half point from 3.5 to 3.0, FSS to less than or equal to 36 points indicating no disabling fatigue [26]. In addition, LLLT resulted in increased PRC answers of Vienna determination test, which is a measure of reactive stress tolerance. However, these positive effects were not potentiated with the addition of UVBR.

Moreover, treatment with LLLT in the control group significantly improved the PRO showing the ability to maintain attention under stress. Meanwhile, PRIC that measures the ability to concentrate on simple tasks for a relatively long period of time did not improve significantly (P=0.549). This may be attributed to either the small group size or the short time between the intervention and reevaluation that did not allow enough time for the CNS to recover from the damage caused by MS to both white and gray matters primarily inducing fatigue and cognitive dysfunctions [43].

Another commonly used type of phototherapy is BB-UVBR with wavelengths of 290–315 nm, with a peak at 298 nm, which can supply 90–95% of body requirements of vitamin D_3, other than diet supplements [44]. Evidently, UVBR showed potential benefits in reducing the morbidity associated with systemic immune disorders, including MS. It is not dependent on circulating

levels of 25(OH)D; thus, vitamin-D_3 synthesis is not essential for mediating the immunosuppressive effects of UVBR [45–48].Like in the control group (LLLT), patients in the study (LLLT +UVBR) group showed significant improvement of all measures: EDSS, FSS, PRC, PRIC, and PRO. Nevertheless, there were no statistical significant differences between the two groups in Post-treatment values. Interestingly, percentages of change in all measures within the study group were substantially larger than in the control group, with much higher PRO and less PRIC in the study group compared with the control group, indicating that clinically significant cognitive improvement for the study group although was not statistically evident. Thus, the effect of UVBR on patients with MS might become significant with a larger sample size and longer follow-up periods, at least 3 months. Compliance of participants with the treatment was high with no relapsing or any side effects noted, however, dropouts were high due to logistic and socioeconomic causes and the inability to recruit more participants was limited by the 3-month winter period (December–February), the best but narrow therapeutic window for the UVB therapy [49].

Conclusion

The study suggests that photobiomodulation using our devised LLLT program solely, with no added value of the UVBR therapy, can provide quick relief of fatigue and cognitive dysfunctions, and improvement of the disability status on the short term. That can accordingly improve the quality of life for patients with RRMS immensely. And calls for larger follow-up research work to confirm the long-term results for future clinical application.

Implementations

The cost-effective and safe LLLT can be clinically used as an effective adjuvant therapy for the mainstream RRMS management.

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Conflicts of interest

There are no conflicts of interest.

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