Spasticity is modifiable through phototherapy in patients with relapsing remitting multiple sclerosis: A randomized controlled study

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Background
Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system of unknown reason or definite cure, heavily impacting the patient's mobility and overall quality of life.
Purpose
Through this study the authors propose safe, alternative phototherapies for the early management of MS.
Study design
This is a repeated-measures randomized control trial.
Materials and methods
Twenty-four patients with relapsing remitting MS, of both sexes, aged 25–45 years, completed the study; they were randomly assigned to four groups. Seven patients in the control group (group 1) received monthly intravenous infusion of 1 g solu-medrol therapy for MS; six patients in group 2 received solu-medrol plus low-intensity laser therapy (LILT) at 850 nm; six patients in group 3 received solu-medrol plus broadband ultraviolet B radiation (BB-UVBR) (280–320 nm); five patients in group 4 received solu-medrol and scanner LILT and BB-UVBR. All three groups received a total of 12 sessions over a period of 3 days/week. Expanded disability status scale (EDSS) and H-reflex latency were assessed before treatment, after treatment, and at 3 months' follow-up.
Results
There was statistically significant reduction ($P = 0.009^{**}$) in H-reflex latency but not in H/M ratio ($P \geq 0.05$) in the LILT group (group 2), whereas EDSS was significantly reduced ($P = 0.011^{*}$) by 1 point in the BB-UVBR group (group 3). These results were maintained 3 months after treatment.
Conclusion
This study suggests that LILT can efficiently reduce spasticity in the short term in patients with relapsing remitting MS. While BB-UVBR therapy alone is more efficient in ameliorating the disability status (EDSS), and combining LILT with UVBR, surprisingly, might have an undermining effect.

Keywords:
broadband ultraviolet B radiation, low-intensity laser therapy, multiple sclerosis, phototherapy

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Introduction

Multiple sclerosis (MS) affects 2.3 million people worldwide and is typically diagnosed with a peak onset between ages 20 and 40 [1,2]. MS is a chronic disease of the central nervous system, characterized by dispersed foci of demyelination and clinically multifocal symptoms, with a tendency for remitting and relapsing, which in the end always leads to disability. The cause of the disease is unknown. Immunological mechanisms causing autoaggression toward myelin sheaths in the central nervous system are considered to be responsible for it [3–5].

Muscle spasticity is one of the common complications of MS considerably impacting the patient's mobility [6,7]. Hoffmann reflex (H-reflex) is an electrically induced reflex analogous to the mechanically induced spinal stretch reflex. It is an estimate of α-motor neuron (αMN) excitability when presynaptic inhibition and intrinsic excitability of the αMNs remain constant. Besides being quantifiable (latency and amplitude), the primary difference between the H-reflex and the spinal stretch reflex is that the H-reflex bypasses the muscle spindle and hence is a valuable tool in assessing the modulation of the monosynaptic reflex activity in the spinal cord [8–10].

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Another parameter often adopted as a good index to evaluate spasticity is the H_{max}/M_{max} ratio, which is the ratio between the maximum amplitude of the H-wave (H_{max}) and that of the M-wave (M_{max}). The H_{max} reflects the number of excited αMNs in the anterior horn of the spinal cord, by maximizing the input from group Ia fibers upon electrical stimulation. The M_{max}, on the other hand, shows the amplitude of complex muscle action potential when all the αMNs are excited synchronously [11].

Although the H-reflex can be elicited shortly after central nervous system injury, the H_{max}/M_{max} ratio reaches its maximum in 8–24 weeks and remains stable thereafter. Therefore, it is important to examine patients at least 6 months after disease onset [12]. In previous studies using H-reflex latency and M/H ratio to quantify αMN excitability, it was found that H-reflex latency of spastic patients was shorter than that of normal controls, and the M/H ratio was higher [13–16].

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 [17]. Moreover, ultraviolet radiation, high levels of vitamin D_3 consumption, and skin cancer were found to be inversely correlated with MS development and mortality risk [18–22].

Besides stimulating vitamin D production, it is believed that ultraviolet radiation likely suppresses disease independent of vitamin D production, and that vitamin D supplementation alone may not replace the ability of sunlight to reduce MS susceptibility [23]. However, local ultraviolet B (UVB) influences systemic immune reactions and attenuates systemic autoimmunity through induction of skin-derived dendritic and T-regulatory cells [24].

Low-intensity laser therapy (LILT) has a wide range of medical applications, when protection from cell death, stimulation of healing and repair of injuries, and reduction of pain, swelling, and inflammation are needed [25]. Previous trials investigating the effect of light therapy in the form of laser application to MS patients were conducted and showed objective clinical results [26].

Therefore, our randomized controlled clinical trial is the first to test the efficacy of combined low-level laser therapy (LILT) and broadband ultraviolet B radiation (BB-UVBR) therapy in the treatment of MS.

Materials and methods

Forty-six patients with Relapsing Remitting Multiple Sclerosis (RRMS) participated in this study, but only 24 patients completed the study. Patients were recruited from the Neurology Department of Kasr Al-Ainy Hospital. Patients were diagnosed with relapsing remitting MS according to McDonald's criteria [27]. Patients were selected while in remission state, and all signed written pretreatment informed consent forms. The study was conducted at the outpatient clinic of the Faculty of Physical Therapy, Cairo University, from September 2013 to October 2014. This study was approved by the ethical committee of The National Institute of Laser Enhanced Sciences on 19/11/2012.

Study design

This was a repeated-measures randomized controlled study. Patients were divided randomly into four groups (a control group and three study groups).

In group 1 (the control group) seven patients received a monthly intravenous infusion of 1 g of methylprednisolone (Solu-medrol) as a drug against MS. In group 2 (the LILT group), six patients received Solu-medrol in addition to scanner LILT (850 nm) gallium aluminum arsenide (GaAlAs) diode laser in the cervical region for 10 min. In group 3 (the UVBR group) six patients received Solu-medrol in addition to broadband BB-UVBR (280–320 nm) on the whole back region for 20 min. In group 4 (the UVBR+LILT group) five patients received Solu-medrol in addition to scanner LILT on the cervical region for 10 min, and then received BB-UVBR (280–320 nm) on the whole back for 20 min (using the same parameters of group 2 and 3). All sessions were for 3 days/week (4 weeks) for a total of 12 sessions.

The inclusion criteria were age 25–45 years (both sexes), being in remission with a score of 6 or less on the expanded disability status scale (EDSS), and being free of any systemic vascular, blood, or neurological diseases such as vasculitis, systemic lupus erythematosus, diabetes, liver disease, kidney failure, heart failure, traumatic brain injury, cerebrovascular accident, spinal cord injury, HIV, hyperthyroidism, or cancer, and risk of chemical or atomic radiation exposure. Patients also had to be of skin type 3 or 4 and free of any local or systemic comorbidity. Patients on antibiotics or photo-sensitizing drugs were weaned off 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 methods

(1) EDSS according to Kurtzke [28].
(2) Electromyography (Nihon Kohden device, Model JB 904 BK, 2007; Tokyo, Japan).

Testing procedures

Expanded disability scale

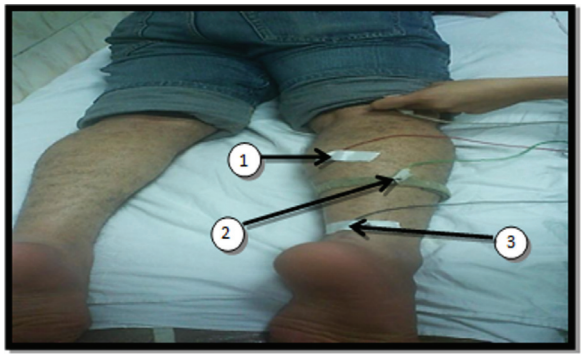
The EDSS quantifies disability on the basis of eight functional systems and allows neurologists to assign a functional system score to each of these functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder functions, visual, mental, and any other neurological findings due to MS [27]. Patients were referred to a neurologist for evaluation.

H-reflex

H-reflexes were obtained from muscles at rest with percutaneous stimulation and surface recording techniques. The stimulating cathode was applied proximally so as to avoid anodal block. Stimulus pulses of long duration (1 ms) were used to activate the large sensory fibers preferentially. Stimulus frequency was 0.2 Hz to allow recovery of postactivation depression of the H-reflex from a prior stimulus.

For calf H-reflexes, the posterior tibial nerve is stimulated in the popliteal fossa. Using bipolar stimulation, the recordings were made from the soleus muscle. A standard and convenient location for the active electrode medial to the tibia at a point that is half the distance between the stimulation site and the medial malleolus was used, with the reference electrode placed on the Achilles tendon (Fig. 1).

Figure 1



H-reflex examination of the lower limb for the tibial nerve. First, the recording electrode was placed on the soleus muscle, then the ground electrode was placed between the recording and reference electrodes, and finally the reference electrode was placed on the Achilles tendon.

Treatment procedures

Low-intensity laser therapy

Patients were positioned in a comfortable leaning-forward sitting position, with foreheads resting on their hands to ensure a straight cervical position. The cervical region was then rubbed with alcohol to minimize the laser light reflection. LILT was applied using a calibrated ASA laser scanning device [He-Ne red laser 632.8 nm; 15 mW power as aiming beam. And GaAlAs diode laser which emits near infrared beam at wavelength of 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); in pulsed wave, pulse duration 50 ns, frequency 2084 Hz, maximum power (P_{max}) 10 W, 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 3 points, one on the C7 spinous process, and the two other points were situated 2.5 cm lateral to the C7 spinous process bilaterally. The LILT 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 leaning-forward sitting position.

Broadband ultraviolet B radiation

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

Follow-up

All examinations were conducted once before the beginning of the treatment, once at the end of the study time, and 3 months after the end of the study. Primary outcome measures were H-R latency and H/M ratio. Secondary outcome was EDSS.

Statistical analysis

Data were analyzed using IBM SPSS Advanced Statistics, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were used for numerical data and were expressed as mean, SD, and range. The

measured scales were tested for normality of distribution (using the Shapiro–Wilk test); all variables were found to be non-normally distributed. Thus, nonparametric statistical tests were used to analyze the data. The Kruskal–Wallis Test was used for between-group analysis of variables, and the Friedman test was used for within-group analysis.

Results

Patient characteristics in the four groups were comparable at baseline with respect to age ($P=0.482$), BMI ($P=0.775$), duration of disease, and sex (Table 1).

Within-group results

Expanded disability status scale

In the control group (group 1) mean values of the EDSS showed no significant difference ($P=0.135$) from baseline (3.4 ± 1.6) to post-treatment (3.4 ± 1.6) and follow-up (3.5 ± 1.6). In the LILT group also (group 2), the mean values of the EDSS showed no significant difference ($P=0.135$) from baseline (3 ± 1.5) to post-treatment (2.8 ± 1.7) and follow-up (2.8 ± 1.7). However, in the UVBR group (group 3), the mean values of the EDSS showed significant decrease ($P=0.011$) from baseline (2.7 ± 1.4) to post-treatment (2 ± 1.2) to follow-up (1.8 ± 1.1). In the LILT+UVBR group (group 4), the mean values of the EDSS showed nonsignificant improvement, though close ($P=0.068$), from the baseline (3 ± 1.7) to post-treatment (2.6 ± 1.9) and follow-up (2.4 ± 1.8) (Fig. 2).

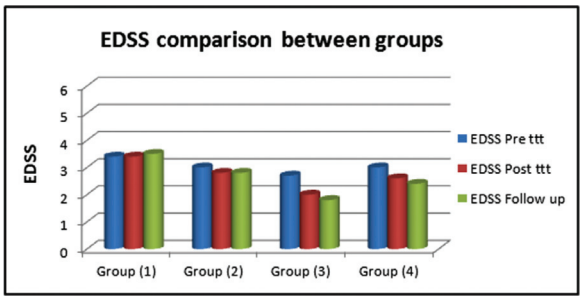
Bilateral H-reflex latency

Results of the control group (group 1): The mean H-reflex latencies of the right tibial nerve showed significant decrease ($P=0.02$) from 30 ± 3.1 before treatment to 29 ± 3.0 after treatment to 28.1 ± 4.1 at follow-up. In contrast, the left tibial nerve showed no significant difference ($P=0.08$), as it was 28.7 ± 3.8 before treatment, 27.7 ± 4.4 after treatment, and 27 ± 4.3 at follow-up (Table 2).

The mean H/M ratio for the right tibial nerve increased significantly ($P=0.028$), indicating increased spasticity, from 50 ± 29.1 before treatment to 52.5 ± 32.3 after treatment and 59 ± 36 at follow-up. Also the left tibial nerve showed a highly significant ($P=0.005$) increase in H/M ratio from 52.7 ± 46 before treatment to 52.7 ± 46.3 after treatment and 58.5 ± 47 at follow-up (Table 3).

Results of the LILT group (group 2): The mean H-reflex latencies of the right tibial nerve showed a highly significant increase ($P=0.009$) from 28.9 ± 2.5 before treatment to 29.3 ± 2.7 after treatment and 30.8 ± 2.1 at follow-up. In contrast, the left tibial nerve showed no significant difference ($P=0.119$), as it was 28.2 ± 4.3 before treatment and increased to 29.6 ± 1.9 after treatment to 30.4 ± 1.9 at follow-up (Table 4).

Figure 2



The differences of means of expanded disability status scale (EDSS) values between the four groups before treatment, after treatment, and at follow-up.

Table 1 Demographic characteristics of patients

Variables	Groups	N	X±SD	Min-Max	*P*-value
Age (years)	Group (1)	7	31±5.7	25–43	0.482
	Group (2)	6	31.3±7.2	25–45	
	Group (3)	6	30.8±3.6	25–34	
	Group (4)	5	35.4±6.9	26–44	
Duration (years)	Group (1)	7	7.5±4.5	2–15	—
	Group (2)	6	6.5±4.2	1–12	
	Group (3)	6	6.5±5.7	1–15	
	Group (4)	5	6.7±6.6	1–16	
BMI	Group (1)	7	25±3.3	20–31	0.775
	Group (2)	6	25.2±4.7	19–32	
	Group (3)	6	26.3±5.6	19–33	
	Group (4)	5	23±2.8	20–26	
Sex No. (Male/Female)	Group (1)	7	4/3	—	—
	Group (2)	6	2/4		
	Group (3)	6	2/4		
	Group (4)	5	2/3		

Table 2 Mean values of H-Reflex latencies of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (1)

H-R Latency (ms)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	30±3.1	25–34	29±3.0	23–32	28.1±4.1	22–35	0.02*
Left TN	28.7±3.8	22–33	27.7±4.4	20–35	27±4.3	19.5–32	0.08**

Max=maximum value, Min=minimum value, ms=millisecond, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

Table 3 Mean values of H/M ratios of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (1)

H/M Ratio (%)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	50±29.1	7.3–103	52.5±32.3	6.6–110	59±36	10.4–124	.028*
Left TN	52.7±46	7.8–129	52.7±46.3	6.6–127	58.5±47	8.9–134	.005**

Max=maximum value, Min=minimum value, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

Table 4 Mean values of H-Reflex latencies of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (2)

H-R Latency (ms)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	28.9±2.5	24.5–31.5	29.3±2.7	26–32	30.8±2.1	28–33	.009**
Left TN	28.2±4.3	20.5–31.5	29.6±1.9	26–31	30.4±1.9	27–32.5	.119*

Max=maximum value, Min=minimum value, ms=millisecond, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

Table 5 Mean values of H/M ratios of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (2)

H/M Ratio (%)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	26.6±16.9	2.9–50.2	26±14.3	3.9–47.8	23±12.8	5.2–41.8	.846*
Left TN	38.6±49	5.5-136	34.2±46.9	3.1-127	28.8±39.3	3.6-106	.115**

Max=maximum value, Min=minimum value, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

In contrast, the mean values of H/M ratio of the right tibial nerve decreased, though nonsignificantly ($P=0.846$), from 26.6 ± 16.9 before treatment to 26 ± 14.3 after treatment and 23 ± 12.8 at follow-up. Also the left tibial nerve did not show significant ($P=0.115$) decrease in H/M ratio, which was 38.6 ± 49 before treatment and became 34.2 ± 46.9 after treatment and 28.8 ± 39.3 at follow-up (Table 5).

Results of the UVBR group (group 3): The mean H-reflex latencies of the right tibial nerve showed a nonsignificant decrease ($P=0.607$) from 30.1 ± 4.8 before treatment to 28.8 ± 2.4 after treatment, and rose again to 30.6 ± 3.3 at follow-up. Also, the values of the left tibial nerve showed a nonsignificant difference ($P=0.311$), as it was 28.7 ± 7.2 before treatment and did not change (28.6 ± 4.6) after treatment but rose to 30 ± 4.7 at follow-up (Table 6).

The mean H/M ratio for the right tibial nerve decreased, although nonsignificantly ($P=0.135$), from 46.3 ± 27.6 before treatment to 41 ± 22.3 after treatment and 26.8 ± 13.8 at follow-up. Also the left tibial nerve did not show significant ($P=0.309$) decrease in H/M ratio, from 43 ± 40.7 before treatment to 43 ± 35.8 after treatment and 23.4 ± 20.7 at follow-up (Table 7).

Results of the LILT+UVBR group (group 4): The mean H-reflex latencies of the right tibial nerve showed a nonsignificant difference ($P=0.819$) from 27.4 ± 3 before treatment to 28.4 ± 3.5 after treatment but rose again to 28.3 ± 3 at follow-up. Also, the values of the left tibial nerve showed a nonsignificant difference ($P=0.819$), as it was 29 ± 2.5 before treatment and did not change (29.2 ± 3.1) after treatment or at follow-up (28 ± 1.8) (Table 8).

The mean H/M ratio for the right tibial nerve decreased, although nonsignificantly ($P=0.074$), from 86.3 ± 62.6 before treatment to 54.2 ± 40.8 after treatment and 35 ± 22.7 at follow-up. Also, the left tibial nerve did not show significant ($P=0.165$) decrease in H/M ratio, from 52.8 ± 58.5 before

Table 6 Mean values of H-Reflex latencies both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (3)

H-R Latency (ms)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	30.1±4.8	21.4-35	28.8±2.4	27–32.3	30.6±3.3	26.5-34	.607*
Left TN	28.7±7.2	17.2–35.7	28.6±4.6	20.4–33.3	30±4.7	23–36.7	.311**

Max=maximum value, Min=minimum value, ms=millisecond, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

Table 7 Mean values of H/M ratios of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (3)

H/M Ratio (%)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	46.3±27.6	8.5–79.4	41±22.3	14.7-72	26.8±13.8	16.5-47	.135*
Left TN	43±40.7	2.4–90.1	43±35.8	2.5–89.3	23.4±20.7	5.5–57.5	.309**

Max=maximum value, Min=minimum value, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

Table 8 Mean values of H-Reflex latencies of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (4)

H-R Latency (ms)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	27.4±3	23.5–30.7	28.4±3.5	23.9-33	28.3±3	25.7–33.5	.819*
Left TN	29±2.5	25.8-31	29.2±3.1	26-34	28±1.8	26.4–30.5	.819**

Max=maximum value, Min=minimum value, ms=millisecond, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

Table 9 Mean values of H/M ratios of both Tibial nerves, pre-treatment, post-treatment, and at follow up for group (4)

H/M Ratio (%)	Pre-treatment		Post-treatment		Follow up		*P*-value
	X±SD	Min-Max	X±SD	Min-Max	X±SD	Min-Max	
Right TN	86.3±62.6	9.3-148	54.2±40.8	6.8-106	35±22.7	10–55.4	.074*
Left TN	52.8±58.5	2.7-146	33.5±43.6	6.5-110	28±17.7	12-53	.165**

Max=maximum value, Min=minimum value, SD=standard deviation, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$).

treatment to 33.5 ± 43.6 after treatment and 28 ± 17.7 at follow-up (Table 9).

Between-group results

Bilateral tibial nerve H-reflex latency

The mean H-R latencies of the right tibial nerve in the four groups were not significantly different before treatment ($P=0.37$), after treatment ($P=0.97$), or at follow-up ($P=0.37$). The H-R latencies of the left tibial nerve did not show any significant difference between groups either before treatment ($P=0.94$), after treatment ($P=0.53$), or at follow-up ($P=0.46$) (Table 10).

Bilateral tibial nerve H/M ratio (amplitude)

The mean H/M ratios of the right tibial nerve between the four groups were not significantly different before treatment ($P=0.22$), after treatment ($P=0.35$), or at follow-up ($P=0.14$). The mean H/M ratios of the left tibial nerve did not show any significant difference between the groups before treatment ($P=0.91$), after treatment ($P=0.73$), or at follow-up ($P=0.27$) (Table 11).

Discussion

This study was conducted to investigate the efficacy of the combined therapy of low-level laser therapy and UVBR at original and premeditated energy doses to achieve the targeted depth and photochemical responses required to tackle the underlying etiologies (autoimmunity triggered by vitamin D_3 deficiency, and vascular deficits that cause decreased total cerebral blood volume) of relapsing remitting MS. This form of therapy could impact the neurophysiological functions of the central nervous system, modulate spasticity, and improve the patient's disability status and overall quality of life.

For these purposes, electrophysiological studies [H-reflex (H-R latency–H/M ratio) of the tibial nerves] and the EDSS were used.

In the current study we used a long wavelength in near infrared zone (850 nm), and pulsed wave, with radiant exposure (E/a) act of 4 J/cm^2 (Bio-stimulating dose) from

Table 10 Comparison between mean values of the four groups for H-Reflex Latencies of both Tibial Nerves, pre-treatment, post-treatment, and at follow up

H-R Latency	Pre-treatment					Post treatment					Follow Up				
N	G (1) X ms (7)	G (2) X ms (6)	G (3) X ms (6)	G (4) X ms (5)	*P*	G (1) X ms (7)	G (2) X ms (6)	G (3) X ms (6)	G (4) X ms (5)	*P*	G (1) X ms (7)	G (2) X ms (6)	G (3) X ms (6)	G (4) X ms (5)	*P*
R. TN	30	28.9	30.1	27.4	.37	29	29.3	28.8	28.4	.97	28.1	30.8	30.6	28.3	.37*
L. TN	28.7	28.2	28.7	29	.94	27.7	29.6	28.6	29.2	.53	27	30.4	30	28	.27**

ms=milliseconds, TN=tibial nerve, X=Mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$). G (1)=(Control group), G (2)=(LILT group), G (3)=(UVBR group), G (4)=(LILT+UVBR group).

Table 11 Comparison between mean values of the four groups for H/M ratios of both Tibial nerves, pre-treatment, post-treatment, and at follow up

H/M Ratio %	Pre-treatment					Post treatment					Follow Up				
N	G (1) X (7)	G (2) X (6)	G (3) X (6)	G (4) X (5)	*P*	G (1) X (7)	G (2) X (6)	G (3) X (6)	G (4) X (5)	*P*	G (1) X (7)	G (2) X (6)	G (3) X (6)	G (4) X (5)	*P*
R. TN	50	26.6	46.3	86.3	.22	52.5	26	41	54.2	.35	59	23	26.8	35	.14*
L. TN	52.7	38.6	43	52.8	.91	52.7	34.2	43	33.5	.73	58.5	28.8	23.4	28	.27**

ms=milliseconds, TN=tibial nerve, X=mean. *= Significant difference ($P<0.05$), **= highly significant difference ($P<0.000$). G (1)=(Control group), G (2)=(LILT group), G (3)=(UVBR group), G (4)=(LILT+UVBR group).

a device of 10 W (P_{max}) maximum power to ensure deeper penetration with minimum attenuation of the applied energy as to reach the vertebral arteries in the cervical region and induce the targeted photochemical reaction and biostimulation by LILT to improve cerebral blood flow, and supply plenty of energy ATP to neural tissues to promote its fast recovery [29–31], and to benefit from the possibility of the bioresonance occurring between the frequency of the light pulses and the neuronal electromagnetic frequency, which in some way may explain a number of the beneficial results with LILT using true pulsed light [32].

We also used another type of phototherapy commonly used in dermatology, which is the BB-UVBR, with wavelengths of 290–315 nm. BB-UVBR with a peak at 298 nm can supply 90–95% of the body's requirement of vitamin D, compared with dietary supplements [33,34]. Also it has the potential to reduce the morbidity associated with systemic immune disorders including MS. It is not dependent on circulating levels of 25(OH)D, which supports the fact that vitamin D_3 synthesis is not essential for mediating the immunosuppressive effects of UVBR [35,36].

Within the limitations of this study, clinically, the severity of EDSS in group 1 showed nonsignificant ($P=0.135$) differences from baseline to post-treatment and follow-up. Also, in group 2 there was no significant improvement ($P=0.135$) in the EDSS from baseline to post-treatment and follow-up. This may be attributed to the inadequate follow-up period or the small sample size, which were not enough to show significance as reported by Peszyñski-Drews *et al.* (2003) [26]. They reported a significant 1 point decrease in EDSS after LILT for patients with primary and secondary progressive MS.

In group 3 the EDSS showed significant improvement ($P=0.011$) from baseline to post-treatment, which was sustained throughout the follow-up period, probably because of UVBR immunomodulatory and anti-inflammatory effects [37–40]. Group 4 also showed improvement in the EDSS, although nonsignificant ($P=0.068$), from baseline to post-treatment and at follow-up, which may indicate the possible undermining role of the combination of LILT and UVBR.

Moving to the electrophysiological results, the H-reflex latencies of the right tibial nerve in the control group (group 1) showed significant decrease ($P=0.02$) from pretreatment to post-treatment and follow-up, but no significant difference was found for the left tibial nerve ($P=0.08$). The percentage of patients with prolonged (>32 ms) or shortened (<28 ms) H-reflex latencies of both tibial nerves did not change except for the percentage of patients with less than 28 ms H-reflex latencies of the right tibial nerve at follow-up, which increased from 28.6% before treatment to 42.9% after treatment. This indicates increased spasticity as the H-R latency below 28 ms [41] and increased H/M ratio of at least 50% refer to increased excitability of αMNs due to loss of supraspinal inhibition, which is manifested as muscle spasticity [13–16].

Unlike group 1, in group 2 the H-R latency of the right tibial nerve increased significantly ($P=0.009$) from pretreatment to post-treatment and more at follow-up. The percentage of patients with latencies greater than 32 ms increased from 0% before treatment to 33.3% after treatment and 50% at follow-up. And there were no longer patients with less than 28 ms latencies post treatment or at follow up. These findings reflect spasticity reduction induced by the LILT program.

In contrast, the left tibial nerve showed a nonsignificant increase ($P=0.119$) from baseline to post-treatment and follow-up, which may be attributed to considerably damaged neural tissues that may need more time to show improvement. That was more evidently proved by the increased percentages of H-R latencies greater than 32 ms from 0% at baseline to 16.7% after treatment and at follow-up. The less than 28 ms percentages decreased from 33.3% at baseline to 16.7% after treatment and at follow-up.

Regarding the mean H-reflex latencies for group 3, the right and left tibial nerves showed nonsignificant differences ($P=0.607$, 0.311, respectively) from baseline to post-treatment and follow-up. Moreover, the percentages of patients with H-R latencies >32 ms of the right tibial nerve dropped from 50% at baseline to 16.7% after treatment and rose again to 50% at follow-up. The percentage of less than 28 ms latencies increased from 16.7% at baseline to 50% after treatment and dropped again to 33.3% at follow-up, indicating a transit decrease in spasticity after treatment that was not sustained during the follow-up period; this was due to independent UVB-induced systemic immunosuppression through postulated mediators in the form of some soluble products released by skin cells like keratinocytes and mast cells that remotely modulate T and B cells' autoimmune activities [42–45].

Likewise, the mean H-reflex latencies of group 4 did not show significant differences ($P=0.009$) for both tibial nerves. Whereas, the percentage of patients with post-treatment H-reflex latencies of the right tibial nerve less than 28 ms was the same (40%) and the percentage with H-reflex latencies greater than 32 ms rose to 20%. At follow up, 60% had H-R latencies less than 28 ms and 20% had H-R latencies greater than 32 ms. Regarding the left tibial nerve, 40% had H-R latencies less than 28 ms with no changes after treatment or at follow-up. No patient (0%) had H-R latencies greater than 32 ms before treatment, but this figure rose to 20% after treatment, and dropped again to 0% at follow-up. The results were of a similar pattern to that of group 3, reflecting a transient decrease in spasticity after treatment that suggests no beneficial value of adding LILT to UVBR on modulating spasticity in the long term.

The mean H/M ratio for the right and left tibial nerves in group 1 increased significantly ($P=0.028$, 0.005, respectively), indicating increased spasticity. H/M ratios more than 50% reflect αMN hyperexcitability and muscle spasticity [13–16]. But in group 2 no significant improvements ($P=0.846$, 0.115) were found in both right and left tibial nerves between baseline, post-treatment, and follow-up periods. However; the percentage of patients with evident spasticity of the right tibial nerve was only 16.7% with H/M ratios of at least 50% before treatment, but no one showed H/M ratios of at least 50% after treatment or at follow-up. In contrast, for the left tibial nerve 16.7% of patients had H/M ratios of at least 50% before treatment that did not change after treatment or at follow-up, showing that patients did not have spasticity at baseline. Thus, although there was a decrease in H/M ratio it was not representative of a real change in spasticity influenced by the LILT program.

Likewise, group 3 did not show significant improvements ($P=0.135$, 0.309) in the H/M ratios of the right and left tibial nerves from pretreatment to post-treatment, or at follow-up. Although the percentage of patients with evident spasticity (H/M ratios≥50%) of the right tibial nerve was 50 and 33.3% had H/M ratios of at least 50% after treatment, no one had H/M ratios of at least 50% at follow-up. However, for the left tibial nerve 50% of patients had H/M ratios of at least 50% that did not change after treatment but decreased to 16.7% at follow-up. Such findings reflect the relatively long-term potential of UVBR to reduce spasticity, although larger-sized studies are needed to show significance.

In group 4, even though there was a considerable drop in mean values from baseline to post-treatment and follow-up, there were no significant ($P=0.074$, 0.165) improvements regarding H/M ratios of the right and left tibial nerves. Nevertheless, the percentage of patients with evident spasticity (H/M ratios≥50%) of the right tibial nerve was 60% before treatment and after treatment, but only 40% had H/M ratios of 50% or more at follow-up. Likewise, for the left tibial nerve 40% had H/M ratios of 50% or more that dropped to only 20% after treatment and at follow-up. That may be attributed to the effect of UVBR rather than LILT as the results were more in concordance

with the UVBR group than with the LILT group. LILT did not potentiate the effect of UVBR.

The body of evidence lacks, and requires, randomized controlled clinical studies to propose safe and efficient doses of UVB for long-term use in clinical practice to induce systemic immunosuppression for patients with RRMS in order to avoid the unsubstantiated carcinogenicity risk occurring from skin application of both narrow and broad band UVB in the long term. However, there were no cases of long-term melanoma cancer correlated to either type of UVBR so far [46].

Our study offered two novel supplemental phototherapy programs that gave fast and short-term relief from MS symptoms; and hopefully better work endurance with less fatigue, spasticity, and poor visual acuity, and eventually improved the quality of life of patients with RRMS, for which no sole pharmacological intervention (immunosuppressants, immunomodulating drugs, or amantadine) is efficient enough without conjoint rehabilitation (exercise, energy, or fatigue self-management education), not to mention the adverse effects of some symptomatic treatments (e.g. anti-cholinergic and antispasticity drugs) on increasing the severity of fatigue [39,47–49].

Conclusion

Our study suggests that LILT can efficiently reduce spasticity in the short term in patients with relapsing remitting MS. While, BB-UVBR therapy alone is more efficient in ameliorating the disability status (EDSS), and combining UVBR with LILT, surprisingly, might have an undermining effect. Also, larger randomized controlled studies using the same doses of UVBR and LILT or other modified doses for different skin types are needed for more conclusive results and for clinical implementation.

Implementations

(1) The findings of the current study suggest that UVBR or LILT treatment should be considered for the treatment of individuals with relapsing remitting MS as a supplemental immunomodulatory therapy.
(2) The findings of the current study also suggest that UVBR has a potent and relatively fast ameliorating effect on disability that consequently improves the activities of daily life and physical work capacity. And that LILT can efficiently reduce spasticity, with the high potential of UVB, which needs further studies to confirm its significance.

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Conflicts of interest

There are no conflicts of interest.

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