Follow-Up Assessment Of Autistic Children 12 Months After Finishing Low Lever Laser Therapy

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Citation

C Machado, Y Machado, M Chinchilla, Y Machado. *Follow-Up Assessment Of Autistic Children 12 Months After Finishing Low Lever Laser Therapy*. The Internet Journal of Neurology. 2020 Volume 21 Number 2.

DOI: 10.5580/IJN.54809

Abstract

We recently examined the efficacy of low-level laser therapy (LLLT) to treat autistic children and adolescents up to 6 months after finishing LLLT therapy. In this paper, we present the follow up assessment up to 12 months after completion of LLLT procedure, demonstrating that improvement in symptoms continued in the patients initially randomized to the active (test) group, with no change at all for placebo subjects. Therefore, we can reaffirm that clinical improvement might be patho-physiologically explained because LLLT progressively rearranges anatomical, functional and effective connectivity, modifying those neuronal networks related to the complex symptoms found in autism.

INTRODUCTION

The diagnosis of autism spectrum disorders (ASD) in children is particularly challenging for clinicians. Overlap in the symptomatology of ASD and the high comorbidity with other disorders complicates the diagnostic process. ASD is a complex nervous system development syndrome, characterized clinically by language impairment, dysfunction in social engagement, language, stereotypical movements and behaviors, and various and varied cognitive deficits.(1-4).

A significant literature exists on the ability of low-level laser therapy (LLLT), a form of photobiomodulation, to penetrate the skull in both diagnostic and therapeutic applications. Low energy laser passes the skull and a therapeutic effect likely exists.(5-13)

We examined the efficacy of LLLT for the treatment of irritability associated with ASD in children and adolescents aged 5 to 17 years. Twenty-one of the 40 participants received 5-minute active procedure administrations to the base of the skull and temporal areas across a four-week period, while the remaining 19 subjects received fake (placebo) treatment administrations: Participants were evaluated using the Aberrant Behavior Checklist, Global Scale and 5 Subscales (Irritability/Agitation, Lethargy/Social Withdrawal; Stereotypic Behavior; Hyperactivity/ Noncompliance and Inappropriate Speech); and the Clinical Global Impressions Severity of Illness (CGI-S) and Improvement/Change (CGI-C) scales at baseline, week 2 (interim), week 4 (endpoint) and week 8 (post-procedure) of the study. Nonetheless, we have recently published a follow-up study after finishing the LLLT, indicating that improvement continues up to 6 months.(12)

Nonetheless, a scientific question arose to know if these positive LLLT treatment effects remained longer, or they were only temporal consequences of the LLLT application.

In this paper, we present the results of the 12 months follow up assessment of both groups of autistics, initially randomized to the active procedure (test) group (those who really received the LLLT treatment), and those randomized to the fake procedure (placebo) group.

METHODS

Subjects initially randomized to the active procedure (test) group at study enrollment were 16 males and 5 females, spanned the age range of 5 to 16 years, with mean participant age of just over 8 years. Subjects initially randomized to the fake procedure (placebo) group at study enrollment were 14 males and 5 females, spanned the age range of 5 to 16 years, with mean participant age of just over 8 years. The inclusion and exclusion criteria are described elsewhere.(5)

Outcome Measures

Outcome measures included the Aberrant Behavior Checklist (ABC). The Global Score and the five subscale scores consisted of: (a) Irritability and Agitation, (b) Lethargy and Social Withdrawal, (c) Stereotypic Behavior, (d) Hyperactivity and Noncompliance and (e) Inappropriate Speech. The Global Score for the ABC was not psychometrically derived, and is not statistically valid. The ABC was designed to be completed by any adult who knows the individual well. The second outcome measure consisted of the Clinical Global Impressions (CGI) Scale that consisted of a Severity of illness scale (CGI-S) and a Global improvement/change scale (CGI-C).(14-16)

The ABC and CGI-S and CGI-C were assessed in each participant comparing baseline, end-point (4 weeks of LLLT treatment), 8 weeks, 6 and 12 months, after treatment completion.

Test Procedures

Participants received 5-minute procedure administrations to the base of the brain and temporal areas with the Erchonia® EAL Laser (active or sham) across a four-week period: two procedures per week, each procedure three to four days apart at the investigator's test site.

Ethics

The study received an approval: from the Helsinki Committee of the Institute for Neurology and Neurosurgery in Havana, Cuba, and was registered with the NIH (identifier: NCT03379662). Informed written consent was obtained: from the parent or guardian of each participant after a full explanation of the procedures to be undertaken. The informed consent forms, research protocol, and approvals are available for inspection in the Office of Research Integrity at the Institute of Neurology and Neurosurgery in Havana, Cuba.(5, 11, 12)

Statistical Analysis

For the continuous primary efficacy measure of score on the ABC irritability and agitation subscale as well as the secondary measures of scores on the ABC Global scale and the remaining 4 subscales, change across baseline, 8 weeks post-procedure, 6- and 12-months post-procedure, was evaluated using analysis of variance (ANOVA). A Tukey HSD Analyses was applied to evaluate the specific statistically significant changes between and across individual evaluations.

For a complete description of the methodology, check our previous publication.(5)

RESULTS

ABC Irritability Score

Table 1 below shows the mean and standard deviation of the ABC Irritability Subscale score.

Table 1

Mean and standard deviation of the ABC Irritability Subscale Score

ABC Irritability Score Mean (standard deviation)	Baseline	Endpoint	8 Weeks	6 Months	12 Months
Test	30.52 (6.73)	15.71 (9.94)	11.81 (9.98)	6.71 (7.91)	9,42 (9.68)
Placebo	29.58 (6.83)	29.89 (7.50)	29.89 (6.55)	30.37 (6.94)	31.37 (7.94)

Chart 1 below shows the progression of mean ABC Irritability Subscale scores across study duration through 12 months follow-up evaluation for test and placebo group subjects.

Chart 1

ABC Irritability Subscale Score Across Long-Term Follow-Up Evaluation

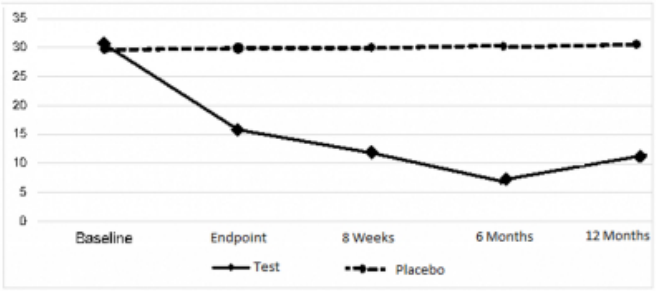

Table 1 and Chart 1 above illustrate the continuing progressive reduction of irritable behaviors in subjects treated with the active Erchonia® HLS Laser prevailing through the long-term evaluation visit, occurring up to 12 months after procedure administration completion, and having improved an additional 5.1 points since the prior 8 weeks post-procedure evaluation. A **t-test for 2 independent samples** found this 5.1-point change to be statistically significant: t=+3.31; df=20; p=0.0035 (p<0.005). Conversely, there was no change across the 12-month evaluation period for placebo subjects (p>0.05).

ABC Global and Remaining Subscale Scores

Table 2 below shows the mean and standard deviation of the ABC Global and remaining Subscale scores across the long-term 12-month evaluation period, for subjects in the test and placebo groups.

Table 2

ABC Global and Remaining Subscale Scores

Global Score Mean (Standard deviation)	Baseline	8 Weeks	6 Months	12 Months
Test	107.29 (20.31)	48.81 (25.05)	28.95 (27.73)	34.67 (25.52)
Placebo	109.95 (19.38)	110.53 (18.84)	110.53 (18.84)	108.99 (15.554)
Irritability				
Test	31.14 (6.39)	13.24(11.37)	6.71 (7.91)	9.43 (9.68)
Placebo	32.13 (7.12)	31.99 (10.50)	30.98 (11.11)	31.12 (10.55)
Lethargy & Social Withdrawal Mean (Standard deviation)	Baseline	8 Weeks	6 Months	12 Months
Test	23.05 (9.32)	10.67 (9.78)	6.81 (6.56)	5.90 (4.49)
Placebo	24.68 (5.12)	24.74 (5.12)	25.58 (5.75)	24.76 (5,50)
Stereotypic Behavior Mean (Standard deviation)	Baseline	8 Weeks	6 Months	12 Months
Test	13.71 (4.10)	6.86(5.11)	3.95 (4.43)	4.76 (4.74)
Placebo	12.32 (5.61)	12.63 (5.70)	12.53 (5.86)	12.48 (5.60)
Hyperactivity & Noncompliance Mean (Standard deviation)	Baseline	8 Weeks	6 Months	12 Months
Test	32.81 (7.82)	16.00 (10.45)	9.14 (9.48)	11.95 (10.45)
Placebo	36.89 (7.88)	37.26 (7.43)	37.42 (8.14)	37.34 (8.23)
Inappropriate Speech Mean (Standard deviation)	Baseline	8 Weeks	6 Months	12 Months
Test	7.19 (3.12)	3.48 (2,23)	2.43 (2.63)	2.62 (2,52)
Placebo	6.42 (3.86)	6.47 (3.82)	6.42 (3.98)	6.41 (3.88)

Chart 2 below illustrates the change in each of the ABC Global and remaining subscale scores from week 8 post-procedure evaluation to 12 months post-procedure evaluation.

Chart 2

ABC Global and Remaining Subscale Scores From 8 Weeks to 6 Months Follow-Up Evaluation

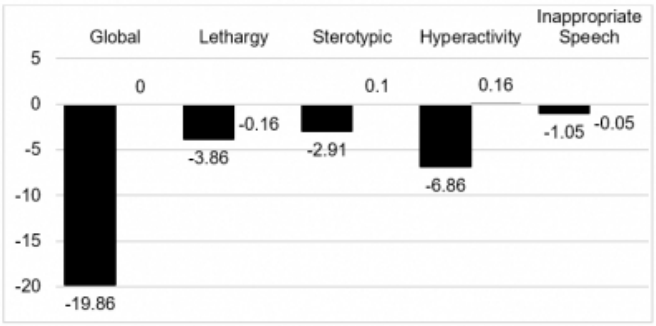

Table 2 and Chart 2 above illustrate the continuing progressive reduction of key characteristic behavioral symptoms of autism, with all symptom expression continuing to improve between the 8-week and 12-month post-procedure evaluations in subjects treated with the active Erchonia® HLS Laser.

A series of **One-Way ANOVAs for 4 correlated samples** was performed to evaluate the mean change across and between baseline, 8-weeks post-treatment, 6-months post-treatment and 12-months post-treatment for the ABC Global Score, and each of the subscale sores for the initial test group subjects. Each change was found to be **statistically significant**, at p<0.0001, as shown in Table 3 below.

Table 3a

ANOVA Results Across the 4 Evaluations for ABC Global and Subscale Scores

ABC Global Scale and Subscales	F	df	p
Global Score	70.42	3	<0.0001
Irritability	69.20	3	<0.0001
Lethargy and Social Withdrawal	34.70	3	<0.0001
Stereotypic Behavior	34.26	3	<0.0001
Hyperactivity and Noncompliance	44.94	3	<0.0001
Inappropriate Speech	23.58	3	<0.0001

Subsequent Tukey HSD analyses, to evaluate the specific statistically significant changes between and across individual evaluations, found statistically significant changes in means ABC Global and Subscale scores occurring consistently between baseline and each of the 3 subsequent evaluations of 8 weeks, 6 months and 12 months post-treatment (p<0.01) in the test group subjects. Statistically significant mean changes occasionally occurred between 8 weeks and 6 months evaluations and between 8 weeks and 12 months assessments. Specific statistically significant changes are shown in Table 4 below.

Table 3b

Test Group: Tukey HSD Analysis Results Across the 4 Evaluations for ABC Global and Subscale Scores

ABC Global Scale and Subscales p-values	Baseline to 8W Post	Baseline to 6M Post	Baseline to 12M Post	8W to 6M Post	8W to 12M Post	6M to 12M Post
Global Score	<0.01	<0.01	<0.01	NS*	<0.05	NS
Irritability	<0.01	<0.01	<0.01	<0.01	NS	NS
Lethargy and Social Withdrawal	<0.01	<0.01	<0.01	NS	<0.05	NS
Stereotypic Behavior	<0.01	<0.01	<0.01	NS	NS	NS
Hyperactivity and Noncompliance	<0.01	<0.01	<0.01	NS	NS	NS
Inappropriate Speech	<0.01	<0.01	<0.01	NS	NS	NS

** NS = not statistically significant (p>0.05)*

CGI-S Ratings

Table 4 below shows the number of subjects within each CGI-S category across the long-term evaluation period for subjects in the test and placebo groups.

Table 4

CGI-S ratings across study long-term evaluation

CGI-S	Baseline		Week 4		Week 8		6 Months		12 Months	
	Test	Placebo	Test	Placebo	Test	Placebo	Test	Placebo	Test	Placebo
7: Amongst most extreme	3	-	-	-	-	2	1	-	-	-
6: Severe	14	15	2	16	3	14	2	15	2	2
5: Marked	4	4	1	3	1	3	-	4	2	-
4: Moderate	-	-	13	-	1	-	9	-	4	9
3: Mild	-	-	4	-	10	-	6	-	6	7
2: Borderline	-	-	1	-	3	-	3	-	4	-
1. Normal	-	-	-	-	-	-	-	-	3	1

CGI-S ratings continued to progressively improve 12 months after procedure administration end for subjects in the test group. Overall, 17 of the 21 test subjects (81%) received CGI-S ratings of "4: Moderate" or better at 12-months post-procedure evaluation. Three (3) subjects had attained a CGI-S rating of "1: Normal". There was essentially no change across the evaluation period in CGI-S ratings for subjects in the placebo group, and in fact, 2 placebo subjects demonstrated worsening of the CGI-S rating from 8 weeks to 12months post-procedure.

DISCUSSION

Our findings powerfully support our previous publication, evaluating the LLLT long-term effects up to 12 months. Hence, the Erchonia® HLS laser effect a sizable, statistically significant and clinically meaningful improvement in all of the key evaluable behaviors characteristic of ASD in children and adolescents, but it endures to affect a progressive and eloquent improvement in symptoms for up to 12 months following completion of the procedure administration protocol.(12)

We had demonstrated that LLLT can be an effective tool for reducing irritability and other symptoms and behaviors associated with ASD in children and adolescents. It is necessary to discuss now the pathophysiology to explain that improvement continued increasing over time until 12 months, after finishing LLLT treatment.(5, 12)

Several authors have suggested that applying near-infrared light to the head of animals that have suffered TBI produces improvement in neurological functioning, lessens the size of the brain lesion, reduces neuroinflammation, and stimulates the formation of new neurons.(17-19) Other authors have emphasized that photobiomodulation using LLLT has been demonstrated to be as safe and effective technique in significantly improving the memory, attention, and mood performance in for patients with chronic traumatic brain injury.(9, 10, 12, 17, 20-22)

We have discussed that LLLT can achieve a therapeutic effect by employing non-ionizing light, including lasers, light-emitting diodes or broadband light in the visible red (600-700 nm) and near-infrared (780-1100 nm) spectra.(5, 12) LLLT is a non-thermal process beginning when a chromophore molecule is exposed to a suitable wavelength of light. Chromophores are responsible for the color associated with biological compounds such as hemoglobin, myoglobin, and cytochromes. When a chromophore absorbs a photon of light an electron transits to an excited state. The physiologic effects of LLLT occurs when photons dissociate the inhibitory signaling molecule, nitric oxide (NO), from cytochrome-C-oxidase, increasing: electron transport, mitochondrial membrane potentials production of mitochondrial products such as ATP, NADH, RNA, and cellular respiration. The leading hypothesis is that the photons dissociate inhibitory nitric oxide from the enzyme, leading to an increase in electron transport, mitochondrial membrane potential and ATP production. Another hypothesis concerns light-sensitive ion channels that can be activated allowing calcium to enter the cell. After the initial photon absorption events, numerous signaling pathways are activated via reactive oxygen species, cyclic AMP, NO and Ca2+, leading to activation of transcription factors. These transcription factors can lead to increased expression of genes related to protein synthesis, cell migration and proliferation, anti-inflammatory signaling, anti-apoptotic proteins, antioxidant enzymes.(21-24) Stem cells and progenitor cells appear to be particularly susceptible to LLLT.(25-27)

It has been argued that LLLT promotes cell and neuronal repair and brain network rearrangement in many neurologic disorders. LLLT fast tracks wound-healing as mitochondria respond to light in the red and near infrared (NIR) spectrum. (9, 10, 12, 17, 20-22) It has been demonstrated that weak light directs the leading edge of growth cones of a nerve. Some authors have demonstrated that is capable of enhancing peripheral nerve regeneration following a crush injury. (28-31) Reports are now emerging that LLL T and photobíomodulation significantly upregulate brain-derived neurotrophic factor (BDNF), a factor highly associated with dendritic sprouting, neuroplasticity, and brain connectivity.(5, 21, 22, 32) In summary, nerve cells appear to thrive and grown in the presence of low energy light, and we think that the effect seen here is associated with rearrangements of neuronal connectivity.(5, 12, 33, 34)

Therefore, we can reaffirm that clinical improvement of the key evaluable behaviors characteristic of autism disorder in children and adolescents, for up to 12 months after following treatment completion, might be patho-physiologically supported with the fact that LLLT progressively rearranges anatomical, functional and effective connectivity, modifying those neuronal networks related to the complex symptoms in autistics.(5, 12, 13, 33)

We conclude that LLLT is a promising and non-invasive tool to treat ASD patients, offering the possibility of clinical improvements in a syndrome where current treatment methods are scarce and not effective.

ACKNOWLEDGMENTS

The project was supported by Erchonia Corp., Melboume, FL, the producers of the equipment emp1oyed in this study. The authors would also like to thank Ms. Elvira Cawthon for her assistance with the statistical analysis and research methodology.

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