Follow-Up Assessment Of Autistic Children 6 Months After Finishing Low Lever Laser Therapy

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Abstract

We recently examined the efficacy of low level laser therapy (LLLT) to treat autistic children and adolescents. Twenty-one of the 40 participants received 5-minute active (test) procedure administrations across a four-week period, while the remaining 19 participants received fake (placebo) procedure administrations. The adjusted mean difference in the baseline to study endpoint change in the ABC Irritability Subscale score between test and placebo participants was 15.17 in favor of the test procedure group. In this paper, we present the results of the 6 months follow up assessment, and we demonstrated that improvement in symptoms continued after 6 months following completion of the LLLT procedure for autistics initially randomized to the active (test) group, with no change at all for placebo subjects. We suggest that LLLT progressively rearranges those neuronal networks related to the complex symptoms in autistics.

INTRODUCTION

Autism spectrum disorder (ASD) is a complicated syndrome of nervous system development characterized clinically by language impairment, dysfunction in social engagement, language, stereotypical movements and behaviors, and various and varied cognitive deficits.(Abbott et al. 2018)

We studied 21 autistic children, to determine the relationship between the anatomic (AC) vs. functional (FC) connectivity, considering short-range and long-range brain networks. AC was assessed by the DW-MRI technique and FC by EEG coherence calculation, in three experimental conditions: basal, watching a popular cartoon with audio and with muted audio track. In recent studies, studying anatomic and functional connectivity. Our experimental design allowed us to demonstrate AC and FC features. explaining, of visual-auditory sensory integration, which is lateralized to the right hemisphere in children with autism. (Machado, Estevez, et al. 2015; Machado et al. 2017; Machado, Rodriguez, et al. 2015)

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.(Lapchak and Boitano 2016; Henderson and Morries 2015; Tedford et al. 2015; Hiwaki and Miyaguchi 2018) Low energy laser passes the skull and a therapeutic effect likely exists. Low energy laser systems employ the so-called quantum optical induced transparency (QIT)-effect This effect, electromagnetically induced transparency (EIT) controls optical properties of dense media and can enhance transparency contrast by a factor of five .(Scherman et al. 2012) Therefore, the skull, spine or joints can be penetrated even with moderate intensity light. Due to the QIT effect, the radiation should reach deep tissue layers in muscles, connective tissue, and even bone, enabling noninvasive transcranial treatments.(Heiskanen and Hamblin 2018; Salehpour et al. 2018; Hamblin 2018)

We recently examined the efficacy of LLLT for the treatment of irritability associated with Autistic Spectrum Disorder (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. The adjusted mean difference in the baseline to study endpoint change in the ABC Irritability Subscale score between test and placebo participants was 15.17 in favor of the test procedure group. in children and adolescents, with positive changes maintained and augmenting over time.(Leisman et al. 2018)

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

In this paper, we present the results of the 6 months follow up assessment of both groups of the 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 in our previous paper. (Leisman et al. 2018) The active procedure group had been treated receiving 5-minute procedure administrations to the base of the brain and temporal areas with the Erchonia® EAL Laser (active) across a four-week period: two procedures per week, each procedure three to four days apart at the investigator's test site.

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. (Kaat, Lecavalier, and Aman 2014)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). (Karabekiroglu and Aman 2009; Brown, Aman, and Havercamp 2002; Rojahn and Helsel 1991; Kaat, Lecavalier, and Aman 2014)

The ABC and CGI-S and CGI-C were assessed in each participant comparing baseline, end-point (4 weeks of LLLT treatment), 8 weeks and after 6 months of treatment. Below is a statistical comparison analysis of the 6-month follow-up data relative to Baseline.

These subjects were followed up at 6 months' post procedure administration completion to gain a sense of duration of treatment effect. All of the originally enrolled 21 test group subjects and 19 placebo group subjects completed the 6-Month follow-up evaluation. Six-month results are evaluated relative to Baseline, Study Endpoint (after finishing all LLLT procedures, 4 weeks), and 8 Weeks Post-Procedure Evaluations.

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.

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, endpoint, 8 weeks post-procedure and 6 months post-procedure was evaluated using analysis of variance (ANOVA) that found the progressive improvement in scores to be statistically significant across all four evaluations for each of the measures ($p<0.0001$) for active test group subjects, with no change evidence for placebo group subjects. For a complete description of the statistical analyses, check our previous publication. (Leisman et al. 2018)

RESULTS

ABC Irritability Score

Table 1 below shows the mean and standard deviation of the ABC Irritability Subscale score across the long-term

evaluation period for subjects in the test and placebo subject groups.

Table 1

Mean and standard deviation of the ABC Irritability Subscale Score

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

Chart 1 below shows the progression of mean ABC Irritability Subscale scores across study duration through 6 months follow-up evaluation for test and placebo group subjects.

Chart 1

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

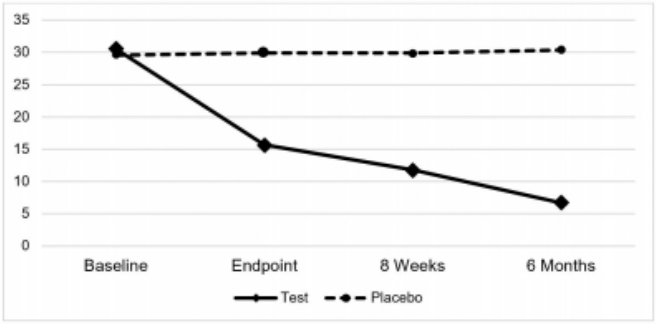

Table 1 and Chart 1 above illustrate the continuing progressive reduction of irritable behaviors in subjects treated with the active Erchonia® HLS Laser prevailing through the long-term 6-month evaluation visit, occurring 6 months after procedure administration completion and having improved an additional 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 6-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 6-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	Endpoint	8 Weeks	6 Months
Test	107.29 (20.31)	63.76 (30.52)	48.81 (25.05)	28.95 (27.73)
Placebo	109.95 (19.38)	110.68 (18.76)	110.53 (18.84)	110.53 (18.84)
Lethargy & Social Withdrawal Mean (Standard deviation)	Baseline	Endpoint	8 Weeks	6 Months
Test	23.05 (9.32)	13.76 (8.76)	10.67 (9.78)	6.81 (6.56)
Placebo	24.68 (5.12)	24.74 (5.12)	24.74 (5.12)	25.58 (5.75)
Stereotypic Behavior Mean (Standard deviation)	Baseline	Endpoint	8 Weeks	6 Months
Test	13.71 (4.10)	8.24 (5.08)	6.86(5.11)	3.95 (4.43)
Placebo	12.32 (5.61)	12.32 (5.61)	12.63 (5.70)	12.53 (5.86)
Hyperactivity & Noncompliance Mean (Standard deviation)	Baseline	Endpoint	8 Weeks	6 Months
Test	32.81 (7.82)	21.14 (9,50)	16.00 (10.45)	9.14 (9.48)
Placebo	36.89 (7.88)	37.26 (7.43)	37.26 (7.43)	37.42 (8.14)
Inappropriate Speech Mean (Standard deviation)	Baseline	Endpoint	8 Weeks	6 Months
Test	7.19 (3.12)	4.90 (2.36)	3.48 (2,23)	2.43 (2.63)
Placebo	6.42 (3.86)	6.42 (3.79)	6.47 (3.82)	6.42 (3.98)

Chart 2 below illustrates the change in each of the ABC Global and remaining subscale scores from week 8 post-procedure evaluation to 6 months post-procedure evaluation.

Chart 2

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

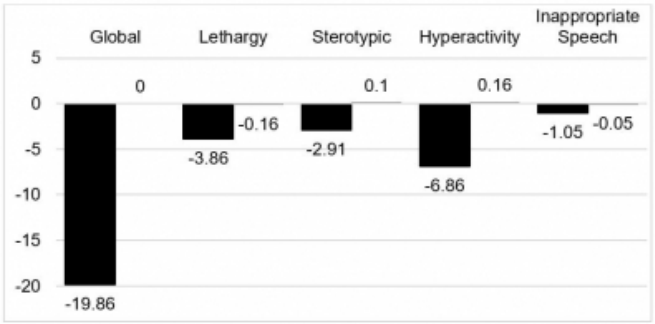

Table 2 and Chart 2 above illustrate the continuing progressive reduction of key characteristic behavioral symptoms of autism, with all symptom expression continuing to improve between the 8-week and 6-month post-procedure evaluations in subjects treated with the active Erchonia® HLS Laser, but not for subjects treated with the fake (placebo) Laser.

CGI-S Ratings

Table 3 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 3

CGI-S ratings across study long-term evaluation

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

CGI-S ratings continued to progressively improve 6 months after procedure administration end for subjects in the test group. Overall, 17 of the 21 test subjects (81%) received CGI-S ratings or '4: Moderate' or better at 6-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 6 months post-procedure.

Table 4 below shows the number of subjects within each CGI-C category across the long-term evaluation period for subjects in the test group.

Table 4

CGI-C ratings across study long-term evaluation

CGI-C Rating	Week 2	Week 4	Week 8	6 Months
1: Very Much Improved	-	5	10	12
2: Much Improved	9	12	8	6
3: Minimally Improved	11	3	3	2
4: No Change	1	1	-	-
5: Minimally Worse	-	-	-	1
6: Much Worse	-	-	-	-
7: Very Much Worse	-	-	-	-

As with CGI-S ratings, CGI-C ratings continued to progressively improve 6 months post-procedure administration for test group subjects. Two (2) additional subjects improved their CGI-C rating from '2: Much Improved' at 2 weeks post-procedure evaluation to '1: Very Much improved' at 6 months post-procedure evaluation. At 6 months post-procedure evaluation, 12 of the 17 test subjects (71%) were rated as '1: Very Much Improved' compared with none (0%) of the test subjects at interim week 2 evaluation.

DISCUSSION

Collectively, our findings strongly illustrate that not only does application of the Erchonia® HLS Laser effect a sizable, statistically significant and clinically meaningful improvement in all of the key evaluable behaviors characteristic of autism disorder in children and adolescents, but it continues to affect a progressive and meaningful improvement in symptoms for up to 6 months following completion of the procedure administration protocol, during which time no procedure administrations were applied with the Erchonia® HLS Laser and with no change in subjects' non-study medication and/or therapy use to treat autistic symptoms. This means that we demonstrated the continuous primary efficacy measure of score of all scales and subscales change across baseline, endpoint, 8 weeks post-procedure and 6 monthss' post-procedure.

In our previous publication we demonstrated that LLLT can be an effective tool for reducing irritability and other symptoms and behaviors associated with ASD in children and adolescents, with positive changes maintained and augmenting over time, until an 8 weeks patient's assessment. It is necessary to discuss now the pathophysiology to explain that improvement continued increasing over time until 6 months, after finishing LLLT treatment. (Leisman et al. 2018)

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. (Xuan et al. 2014; Huang et al. 2012) 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 .(Poiani et al. 2018; Hamblin 2018; Naeser et al. 2016; Morries, Cassano, and Henderson 2015; Henderson and Morries 2015)

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. (de Freitas and Hamblin 2016) 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, [Cotler et al., 2014]. 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.(Freitas et al. 2017; de Freitas and Hamblin 2016; Demirtas-Tatlidede et al. 2012; Poiani et al. 2018) Stem cells and progenitor cells appear to be particularly susceptible to LLLT.(Emelyanov and Kiryanova 2015; Primo et al. 2011)

In a way of manipulating network function it has been demonstrated 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. (Poiani et al. 2018; Leisman et al. 2018; Hamblin 2018; de Freitas and Hamblin 2016; Morries, Cassano, and Henderson 2015; Khuman et al. 2012; Demirtas-Tatlidede et al. 2012) It has been demonstrated that weak light directs the leading edge of growth cones of a nerve. Therefore, when a light beam is positioned in front of a region of a nerve's leading edge, the neuron will move in the direction of the light and has been reported to grow in length.(Poiani et al. 2018; Leisman et al. 2018; Hamblin 2018; de Freitas and Hamblin 2016; Morries, Cassano, and Henderson 2015; Khuman et al. 2012; Demirtas-Tatlidede et al. 2012; Shen et al. 2013; Shen, Yang, and Liu 2013; Moreira et al. 2011; Rochkind et al. 2002). Some authors have demonstrated that is capable of enhancing peripheral nerve regeneration following a crush injury.(Stevens and Tomlinson 1995) 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. 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 connectivities. (Hamblin 2018)

Brain connectivity assessment, both anatomical (AC) and functional (FC), is fundamental to diagnose and follow-up with intervention in ASD.(Jiang et al. 2018; Wu et al. 2018; Raj and Powell 2018; Batista-Garcia-Ramo and Fernandez-Verdecia 2018; Kotkowski et al. 2018; Vassal et al. 2018; Stone et al. 2017; Ranasinghe et al. 2017) Many studies assess either AC or FC, but literature regarding the correlation between both types of connectivity in autism is lacking. We studied children with autism, determining the relationship between AC and FC, with consideration of short-range and long-range brain networks. AC was assessed by the DW-MRI technique and FC by EEG coherence calculation. We found correlations among AC and FC measurements, and concluded that an impaired audiovisual interaction in the right-brain hemisphere might be the cause. Moreover, our data in individuals with ASD from ages 4-7 shows a disruption of long-range connections involving the superior longitudinal fasciculus (SLF) and uncinate fasciculus. SLF is associated with spatial working memory and the integration of the auditory and speech areas of the brain. The left SLF is important for information exchange between Broca's and Wernicke's areas. Thus, abnormal connectivity in SLF may underpin the neurobiological basis of language deficits in ASD. On the other hand, the uncinate fasciculus has traditionally been considered to be a part of the limbic system and is known for its involvement in human emotion processing, memory and language. (Machado, Estevez, et al. 2015; Machado et al. 2017; Machado, Rodriguez, et al. 2015; Machado and Bachevalier 2003). We concluded that a dominant finding with respect to the anatomical connectivity in ASD is that there is a combined pattern of local over-connectivity and long distance under-connectivity. Hence, the study of brain connectivity should be a tool to assess ASD in present and future research.(Machado, Estevez, et al. 2015; Machado et al. 2017; Machado, Rodriguez, et al. 2015)

Therefore, we can suggest that our results presented in this study showing that clinical improvement of the key evaluable behaviors characteristic of autism disorder in children and adolescents, in symptoms for up to 6 months after following treatment completion, might be patho-physiologically supported with the fact that LLLT progressively rearrange anatomical, functional and effective connectivity, modifying those neuronal networks related to the complex symptoms in autistics, characterized clinically by language impairment, dysfunction in social engagement, stereotypical movements and behaviors, and various and varied cognitive deficits.(Leisman et al. 2018; Machado,

Estevez, et al. 2015; Machado et al. 2017; Machado, Rodriguez, et al. 2015)

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.

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