De Souza LB, Lazzarin MC, De Oliveira F. Low Level Laser Therapy as an adjuvant therapy for Duchenne muscular dystrophy. J Rehab Therapy.2020;2(2):27-31

Journal of Rehabilitation Therapy

Mini review Open Access

Low Level Laser Therapy as an adjuvant therapy for Duchenne muscular dystrophy

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Article Info

Article Notes
Received: June 08, 2020
Accepted: July 05, 2020

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Keywords:
mdx mice
Low Level Laser Therapy
Duchenne muscular dystrophy
Rehabilitation

Abstract

Duchenne muscular dystrophy (DMD) is a rare disease caused by mutations or rearrangements in the dystrophin gene, leading to progressive muscle lesion. There is no curative treatment for DMD, however, there is evidence that treatment with LLLT acts to decrease inflammation, oxidative stress, pain and stimulate muscle repair. The aim of this review was to discuss the effects of LLLT as a helpful alternative therapy to be associated with other treatments for DMD. To this end, a systematic research in PubMed database was conducted including the following terms: "Duchenne muscular dystrophy" and "low level laser therapy" or "mdx mice" and "low level laser therapy". After prospecting scientific articles, 5 were selected. As a result, it was found that there is a lack of information about the use of LLLT on DMD patients because all of the studies were preclinical. The selected articles showed that mdx mice were chosen as the experimental model and although they describe the positive effects of LLLT, the studies were performed with different mice ages, parameters of irradiation, treatment duration and muscle chosen. In conclusion, according to this review both preclinical animal experiments and human clinical studies with LLLT use should be expanded to the benefits of patients in this translational research answer.

Introduction

Duchenne muscular dystrophy (DMD) is a recessive disease associated with the X chromosome, caused by mutations or rearrangements in the dystrophin gene, a structural protein belonging to the dystrophin-glycoprotein complex[1], and the global DMD birth prevalence is 1 per 100,000 live male births[2]. The dystrophin-glycoprotein complex is responsible for stabilizing the cytoskeleton of muscle fibers with the extracellular matrix[3]. The absence of dystrophin leads the muscle to lesions characterized by progressive degeneration, inflammatory infiltration and fibrosis[4]. The sarcolemma's fragility due to the absence of dystrophin worsens with physiological events such as calcium influx and oxidative stress[5]. In addition, with the progression of the disease, repeated degenerative- regenerative cycles impaired regeneration, resulting in the replacement of muscle fibers by connective tissue[6]. The loss of muscle regenerative capacity is accompanied by an increased fibrogenesis leading to muscular tissue to be replaced by fibrotic tissue[7]. Among the various pathophysiological mechanisms proposed in DMD, evidence suggests the involvement of inflammation[8] and oxidative stress to explain the dystrophic process[9,10].

Low Level Laser Therapy (LLLT) has non-thermal therapeutic effects and has been used in some inflammatory diseases in order to provide a non-invasive treatment strategy due to the photochemical

effects, which act on the cell membrane, being able to alter cellular functions in irradiated cells[11,12]. It has been shown that the phototherapy can promote the biochemical adaptation of the mitochondria with changes in the redox state, leading to a conversion of electromagnetic energy into biochemistry, consequently, increasing oxygen consumption, ATP production and respiratory rate[13,11]. Evidence from experimental investigations suggests that LLLT promotes skeletal muscle regeneration by reducing the duration of acute inflammation and accelerating tissue repair[11]. According to Ferraresi et al.[14] the use of LLLT has expanded to cover areas of medicine. Besides the usual applications in wound healing and inflammatory orthopedic conditions, the ability of LLLT for reducing or repairing the consequences of muscle fatigue, stimulate muscle repair in addition to reduce inflammation and oxidative stress, should be expanded. Furthermore, LLLT represents a cost-effective therapy for musculoskeletal pain[15].

There is no curative treatment for Duchenne muscular dystrophy. However, there is evidence that treatment with LLLT acts to decrease inflammation, oxidative stress, pain and stimulate muscle repair. In this context, the aim of this review was to discuss the effects of LLLT as a helpful alternative therapy to be associated with other treatment for DMD.

Material And Methods

Search strategy

During the searches of this study, was conducted systematic research in the PubMed database (National Library of Medicine and National Institutes of Health). The MeSH terms used as keywords were: “Duchenne muscular dystrophy” and “low level laser therapy” or “mdx mice” and “low level laser therapy”.

As an inclusion criterion, during the search, the title and summary were read and verified according to the aim of this study. The following duplications articles or not therapeutic use of laser or literature review, were not included in the present investigation.

Selection of studies

Original research articles and written in English were included. No geographical exclusion criteria were imposed. Selected articles were from the period between 2014 and 2018, due to the lack of studies before 2014. The presentation of the results followed the criteria of the publication’s chronological order: from the oldest to the most recent. Finally, the discussion of the articles was based on the clinical importance of the LLLT in Duchenne muscular dystrophy.

Results

After prospecting scientific articles using the descriptors already mentioned for this review, 6 articles were found. Out of 6 screened scientific publications, 5 were selected and fully reviewed. All selected studies were preclinical, with mdx mice. The only scientific article excluded was a literature review.

No clinical study was found with DMD and LLLT and, although no geographical exclusion criteria have been imposed in this research, most of studies have been carried out in Brazil, except the study by Oron et al.[17], carried out in Israel. Due to a variety of information found about aim of study, LLLT parameters and mice age, the results were distributed in a Table, according to the mice age, descriptions of irradiation parameters, study aim and main conclusion (**Table 1**).

Discussion

In DMD disease, considering that there is no effective therapy available, there are many treatments aiming to improve patients’ quality of life and delaying the progression of the disease, such as induced pluripotent stem cells as a powerful technology in drug discovery[21], pharmacological agents that slow the progression of the disease[22] and motor physical therapy[23]. Numerous pre-clinical models, such as mice, rats, dogs, pigs and rabbit have advantages and disadvantages[24], but it is important to highlight that, although the contribution of different treatment strategies to prolong ambulation and provide improvements in quality of life and life expectancy, they do not provide a definitive cure. The most used experimental preclinical model for investigating the pathophysiology of DMD is the mouse of the mdx lineage (X-chromosome linked muscular dystrophy). In mdx mice, the mutation occurs due to a premature stop codon, resulting in termination in exon 23 of the dystrophin gene[25].

Taken together, the aim of this review was to discuss the effects of LLLT as an adjuvant therapy to improve quality of life in DMD. Although the positive effects of LLLT intervention on the inflammation and oxidative stress, there is a lack of information about the interaction of LLLT on Duchenne muscular dystrophy in humans because the majority of studies are preclinical. The only study with laser therapy in humans with DMD seen was by Abdel et al.[26] that verified the role of He-Ne laser irradiation in ameliorating blood oxidative stress in DMD patients vs. controls. It is important to highlight that, in this study, the blood DMD samples were irradiated with He-Ne laser, but not skeletal muscle.

The selected articles for this review showed that mdx mice were chosen as experimental model and in different ages. This is an important point in mdx model because signs

Table 1. Main information about the use of LLLT in Duchenne muscular dystrophy.

Author/ experimental model, age	LLLT parameters	Study Aim	Main Conclusion
Leal-Júnior et al.[16] / mdx mice/six weeks	Superpulsed LLLT administered using a wavelength of 904 nm, light density 52W/cm^2, 10,4W power and dose of 1 J on successive days, 5 times per week for 14 weeks	To evaluate effects of preventive treatment with LLLT on progression of dystrophy in mdx mice, assessing skeletal muscle morphology, skeletal muscle damage and inflammation.	LLLT effects ameliorated morphological changes, skeletal muscle damage and inflammation in mdx mice. This suggests that LLLT may decrease progression of DMD.
Oron et al. [17]/ mdx mice,1 week	Ga-Al-As diode laser (810 nm), applied at a power density of 10 mW/cm^2 to the surface (area of 0.0255 cm^2) of hindlimb muscle for 120 sec (fluence of 1.2 J/cm^2) once a week for 4 consecutive weeks.	To determine whether low-level laser therapy (LLLT) at early stages post-partum could affect regeneration and degenerative processes in skeletal muscles of the dystrophic mdx mouse.	LLLT applied to mdx mice during postnatal development may have a significant beneficial effect in the induction of regenerative capacity and reduction of degenerative muscle foci in these mice, with possible direct clinical relevance.
Silva et al.[18]/ mdx mice,1 week	LLLT administered using a wavelength of 808 nm, output power 30mW, power density 1071W/cm^2, spot size 0.028cm^2 and and dose of 3 J, 3 consecutive days.	To verify whether the levels of oxidative stress markers could be influenced by LLLT in mdx mice subjected to high-intensity exercise training on an electric treadmill.	LLLT was able to reduce oxidative stress markers these markers even in conditions of muscle fatigue; LLLT also reduced the levels of antioxidant enzyme markers significantly; LLLT had a beneficial effect on the skeletal muscle of mdx mice and improved the performance of these animals. However, the single application of LLLT and the dose parameters used were not able to cause changes in the morphology of dystrophic muscles.
Macedo et al.[19]/ Primary cultures of mdx skeletal muscle cells	Aluminum Gallium Arsenide (AlGaAs) diode, 830 nm wavelength at 5 J/cm² fluence, continuous emission during 20 seconds, 30mW output cm^2 power and 0.07 For after 24h and 48h.	Evaluated LLLT effects on some physiological pathways that may lead to muscle damage or regeneration capacity in dystrophin-deficient muscle cells of mdx mice, the experimental model of DMD.	LLLT improved regenerative capacity and decreased inflammatory response and oxidative stress in dystrophic muscle cells culture.
Albuquerque- Pontes et al.[20]/ mdx mice, 6 weeks	Photobiomodulati on Therapy (PBMT) with doses of 1 J , 3 J, and 10 J. PBMT was performed employing a cluster probe with 9 diodes (1 x 905nm super- pulsed laser diode; 4 x 875nm infrared LEDs; and 4 x 640nm red LEDs, 3 times a week for 14 weeks	To test the effects of different doses of PBMT on muscle morphology, gene and protein expression of dystrophin, and on functional performance of DMDmdx mice.	PBMT had positive effects on dystrophic skeletal muscle and delayed disease progression. This therapy may have a protective effect when applied at the onset of DMD.

such as necrosis, central nuclei cells and inflammatory infiltrate of muscle degeneration and regeneration, vary according to the animal age. Considering that, the histopathological events change, and the more serious stage occurs with 26 weeks[27]. In addition to differences in age criteria, several methods were used for irradiation parameters, number of irradiation points, treatment duration and muscle chosen.

It is well known that the most part of LLLT studies is in local and acute inflammation process. The biggest challenge of LLLT treatment in DMD is the chronic and systemic condition, i.e., although the preclinical studies show the effects of LLLT in specific skeletal muscles, DMD affects the muscular system. In this way, which muscle to choose? Maybe muscles related to locomotion, but, how many points are necessary to apply in groups of locomotion muscle? For LLLT to be effective, the irradiation parameters need to be within certain ranges according to the treatment goal. Ferraresi et al.[14] presented a literature review about the use of LLLT on human muscle tissue and showed clinical trials with acute or chronic responses and numerous parameters that answer these questions and, in conclusion of review, they encourage researchers to investigate the effects of LLLT on patients with Duchenne muscular dystrophy. The concept of translational research reinforces this idea. According to Callard et al.[28] translational research aims to translate findings from basic research more quickly and

efficiently into clinical and health-care practice: in other words, such research is intended to ease the path from laboratory experiments through to clinical trials to patient.

Regarding possible adverse effects in LLLT, according to Cotler el al.[15] "The North American Association for Laser Therapy conference in 2010" held a consensus meeting on safety and contraindications. The study summarizes main contraindications such as exposure of the eyes, carcinogenesis in patients, pregnancy, epileptic and photosensitivity. Therefore, a careful evaluation history is fundamental to the LLLT pre-use in DMD patients.

In conclusion, based on positive effects LLLT verified in preclinical studies and the importance of laboratory experiments through to clinical trials to interventions, studies about LLLT in human DMD patients are necessary for the contribution of different treatment strategies to prolong ambulation and provide improvements in quality of life in DMD patients. Therefore, according to this review both preclinical animal experiments and human clinical studies with LLLT should be expanded to the benefits of patients in this translational research answer.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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