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Low intensity laser therapy with photodynamic therapy in the treatment of onychomycosis

Laserterapia de baixa intensidade com terapia fotodinâmica no tratamento de onicomicose

Terapia láser de baja intensidad con terapia fotodinámica en el tratamiento de la onicomicosis

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ABSTRACT

Objective: to evaluate the results of the application of low-level laser therapy with photodynamic therapy in the treatment of onychomycosis in patients with type 2 Diabetes *Mellitus*. **Method:** case series observational study, performed in a Clinical Podiatrics service in the state of Rio de Janeiro. The population was 11 diabetic patients with onychomycosis who received 5 intervention sessions and evaluated before and after. The study took place from February to March 2021, after approval by the ethics committee. Data were analyzed using descriptive statistics. **Results:** after the intervention, the satisfactory evolution of the clinical aspect of the nail plates was verified in 70% of the sample. Only 30% of the sample showed no change in the appearance of the the blade. **Conclusion:** laser therapy with photodynamic therapy in the treatment of onychomycosis in patients with type 2 Diabetes Mellitus shows promising results with clinical improvement in most cases.
Descriptors: Nursing Care; Podiatry; Low-Level Light Therapy; Diabetes Mellitus; Onychomycosis.

RESUMO

Objetivo: avaliar os resultados da aplicação da laserterapia de baixa intensidade com terapia fotodinâmica no tratamento da onicomicose em pacientes com Diabetes *Mellitus* tipo 2. **Método:** estudo observacional do tipo série de casos, realizado em um serviço de Podiatria Clínica no Estado do Rio de Janeiro. A população foram 11 pacientes diabéticos com onicomicose que receberam 5 sessões de intervenção e avaliados antes e depois. O estudo ocorreu de fevereiro a março de 2021, após aprovação do comitê de ética. Os dados foram analisados através de estatística descritiva. **Resultados:** verificou-se, após aplicação da intervenção, a evolução satisfatória do aspecto clínico das lâminas ungueais em 70% da amostra. Apenas 30% da amostra não apresentou modificação no aspecto da lâmina. **Conclusão:** a laserterapia com terapia fotodinâmica no tratamento da onicomicose em pacientes com Diabetes Mellitus tipo 2 apresenta resultados promissores com melhora clínica da maioria dos casos.
Descritores: Cuidados de Enfermagem; Podiatria; Terapia com Luz de Baixa Intensidade; Diabetes Mellitus; Onicomicose.

RESUMEN

Objetivo: evaluar los resultados de la aplicación de la terapia láser de baja intensidad con terapia fotodinámica en el tratamiento de la onicomicosis en pacientes con Diabetes *Mellitus* tipo 2. **Método:** estudio observacional de serie de casos, realizado en una Clínica Servicio de podología en el estado de Río de Janeiro. La población fue de 11 pacientes diabéticos con onicomicosis que recibieron 5 sesiones de intervención y evaluados antes y después. El estudio se llevó a cabo de febrero a marzo de 2021, previa aprobación del comité de ética. Los datos fueron analizados utilizando estadística descriptiva. **Resultados:** Posterior a la intervención se verificó la evolución satisfactoria del aspecto clínico de las láminas ungueales en el 70% de la muestra. Solo el 30% de la muestra no mostró cambios en la apariencia de las láminas. **Conclusión:** La terapia láser con terapia fotodinámica en el tratamiento de la onicomicosis en pacientes con Diabetes Mellitus tipo 2 muestra resultados prometedores con mejoría clínica en la mayoría de los casos.
Descriptores: Atención de Enfermería; Pediatría; Terapia por Luz de Baja Intensidad; Diabetes Mellitus; Onicomicosis.

INTRODUCTION

The object of this study is Low-Level Laser Therapy (LLLT) with photodynamic therapy (PDT) in the treatment of onychomycosis in patients with Type 2 *Diabetes Mellitus* (DM) in a clinical podiatry service.

The term "*laser*" is the acronym for *Light Amplification by Stimulated Emission of Radiation*. Regarding the physical characteristics, the *laser* light is electromagnetic, unidirectional and monochromatic radiation, capable of transmitting energy packets called photons[1].

It is known that LLLT has proved to be a therapeutic resource widely used in the clinical practice and has a range of effects on living tissues, such as improving the quality of healing, stimulation of microcirculation and anti-inflammatory, anti-edematous, analgesic and infection control effects[2].

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Regarding applicability of the laser therapy in the control of infections, its ability to promote destruction of bacteria and fungi is noted, through the transfer of electrons, leading to the production of free radicals by energy transfer to oxygen, inducing the production of a reactive molecule called singlet oxygen, a free radical that promotes death of microorganisms, a condition that can be potentiated when PDT is used[3].

PDT comprises the application of a photosensitizer, a non-toxic dye, together with selective laser therapy of a target lesion (fungi and bacteria), aiming to provide localized oxidative photoinjury. The *laser* activates the photosensitizers, transferring energy to molecular oxygen and, with immediate death of the microorganism as a result of this combination[4,5].

Applied to the treatment of fungal infections, such as onychomycosis, PDT has shown encouraging results. A number of studies on *laser* have shown preliminary evidence of clinical improvement and growth in nails, with a reduction of the dystrophies caused by onychomycosis[6].

Onychomycosis is a chronic fungal infection in the nails caused by dermatophytes, mainly *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Candida albicans*[5]. It is responsible for nearly 40% to 50% of all the diseases attacking the nail region and affects one out of ten individuals, representing a global public health problem[7].

Among diabetic patients, the prevalence of onychomycosis and the incidence of secondary infections are up to 2.5 and 2.8 times higher, respectively. It is added that onychomycosis can cause skin injuries that become gateways for other pathogens[8].

Onychomycosis is a health problem, especially for diabetic patients, as it represents an additional risk factor for the occurrence of foot ulcers, cellulitis, osteomyelitis and gangrene – complications that constitute the main causes of hospitalizations, amputations and loss of health-related quality of life[8].

Treatment of this pathology includes topical and oral therapies. In general, topical drug treatments are not very successful, as they cannot penetrate the nail plate. In turn, oral antifungals can produce side effects due to the significant possibility of hepatic and renal toxicity. Given this reality, using LLLT emerges as s promising possibility[8].

It is noted that LLLT with PDT has no potential for drug interactions and does not produce renal or hepatic toxicity, in addition to requiring less treatment time, having low occurrence of local adverse effects and absence of systemic adverse effects, which makes it eligible for patients with chronic diseases, such as diabetes[9].

In this scenario, LLLT with PDT is considered as a relevant therapeutic possibility for the treatment of onychomycosis, displaying excellent results in the treatment of this and other infections[5].

LLLT with PDT is effective in inactivating fungi. In a study using LLLT with 660 nm wavelength and methylene blue dye, inactivation of the species of yeasts belonging to genus *Candida* was evidenced. PDT is a technique that can bridge failures found in the conventional treatment of onychomycosis[9]. The fact that it is a well-tolerated alternative treatment that can achieve significant cure rates for patients who have contraindications to oral or standard medications that have failed[5] is added to the above.

It is noted that the use of LLLT by nurses is an activity regulated by the Federal Nursing Council (*Conselho Federal de Enfermagem*, COFEN) through COFEN opinion numbers 114/2021 and 013/2018 and widely used especially in Clinical Podiatry, which is a recent specialty of Nursing, focused on the care of the lower limbs and within the scope of promotion, prevention, treatment and rehabilitation, which, for this purpose, leverages the benefits of photobiomodulation produced by LLLT as a complementary therapy.

However, it is to be noted the scarcity of studies on its use as a complementary therapy in the treatment of onychomycosis in diabetic patients and its results in the clinical practice.

The objective of this study was to assess the results of applying LLLT with PDT in the treatment of onychomycosis in patients with Type 2 DM.

METHOD

This is an observational study of the case-series type, conducted in a Clinical Podiatry service in the state of Rio de Janeiro. The sample consisted of 11 patients with Type 2 DM referred by the medical team with nail changes compatible with onychomycosis, treated at the referred service between February and March 2021, selected for convenience, after declaring availability to attend the service to undergo the therapy, considering the following criteria: not being undergoing or having undergone treatment with systemic or topical antifungals in the last three months and being in due conditions to perform hygiene care with feet, nails and shoes. Patients with peripheral obstructive arterial disease were excluded, as well as those with diabetic retinopathy and pregnant women.

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It is noted that no laboratory tests were performed for fungal identification of the nail plates due to unavailability of the method in the outpatient complex in which the service is located, admitting the clinical aspects related to the nail alterations presented.

The intervention protocol included application of five consecutive sessions of LLLT associated with PDT, with 7-day intervals.

In the first session, an evaluation of the nail plate and photographic record were performed using a Nikon Coolpix® P510-4.3-180 mm photographic camera, 10 cm apart, with no flash. Everyone received written guidelines about foot and shoe hygiene at their homes, in addition to other specific and important care measures during treatment of onychomycosis. For being diabetic patients, capillary glycaemia was checked before initiating each of the five sessions, in order to obtain a glycemic control overview. Subsequently, podoprophylaxis, thinning and sanding of the nail plate with a micromotor, cutters and diamond drills were performed in order to remove dystrophic areas that prevent penetration of the photosensitizer.

Subsequently, a solution of methylene blue at a concentration of 0.1% was applied to the nail plate. We waited 5 minutes for nail impregnation and we subsequently applied LLLT with the Easy-Laser® model *laser* equipment, patented by the Ricardo Trajano Institute in 2009 and registered at the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) under number 80030819009.

The equipment has 100 mw power, with simultaneous emission of red and infrared *lasers*. The red and infrared *laser* beams have wavelengths of 808 nm and 660 nm, respectively. Transmission through optical fiber allows emission of a collimated and highly targeted light beam to the tissue.

To perform LLLT with PDT, irradiation of the nail plate was used, with a red 660 nm (nanometers) wavelength *laser* and 12 Joules/cm^2 dosimetry, point by point.

The evaluation after the intervention was carried out 6 months after the last application, with a new photographic record to verify involution of the nail changes initially found before the intervention. The 6-month period is justified by the growth time of the nail plate of the feet, which varies a mean of 1 to 1.5 mm per month. During this period, to minimize reinfections, maintenance of the foot hygiene control measures was recommended, with daily brushing of the nail plates (soap and water), constant use of shoes and cleaning them with 70% alcohol, weekly.

The presence of thickening, longitudinal stretch marks or dermatophytomas and nail plate fragility, as well as presence of wet maceration of the hyponychium, subungual callus and nail plate detachment were evaluated. Total recovery of the nail plate and improvement or reduction of the alterations found in the initial evaluation were considered as cure.

It is clarified that, after reviewing the literature on the topic, no validated clinical protocols for the treatment of onychomycosis with LLLT were found. This clinical protocol was established based on the authors' *expertise* acquired in the service.

After carrying out the LLLT post-application evaluation, the data were organized in a database using Microsoft Excel® 2010, and subsequently analyzed by means of descriptive statistics.

The research meets the required ethical standards, having been approved by the institution's Research Ethics Committee and having documented its due institutional permission. All the individuals signed the Free and Informed Consent Form (FICF).

RESULTS

A total of 18 patients were selected after applying the inclusion criteria. However, after the study had been initiated, seven patients were removed: six due to non-attendance to the scheduled sessions and one due to death. Thus, 11 patients were obtained who underwent the entire protocol established in the study. The reduced sample was justified due to the pandemic period caused by the Severe Acute Respiratory Syndrome related to the Coronavirus type 2 (SARS-CoV-2), which contributed to the fact that the patients belonging to the risk group did not commute to the service.

Of the 11 patients, nine had onychomycosis in the nail plate of both feet and two had onychomycosis in one foot. Thus, the study consisted of a total sample of 20 affected nail plates, treated by means of LLLT with PDT and subsequently analyzed.

Regarding the patients' characteristics, most of the study sample consisted of aged people (over 65 years old), representing 82% (n=9), while the adults represented only 18% (n=2). The mean age remained around 66 years old, the mode

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was 72 and the median was 67. In addition, most of the study sample consisted of female patients, representing 82% (n=9) and there were only two male patients, representing 18%.

Blood glucose measurement in each session varied from 108 mg/dL to 211 mg/dL, with a mean of 196 mg/dL.

Regarding the changes in the patients' nail plate, presence of the following changes was identified: nail plate thickening (n=14; 70%), longitudinal streaks or dermatophytomas (n=8; 40%), subungual callus (n=8; 40%), nail plate fragility (n=6; 30%), presence of wet maceration of the hyponychium (n=4; 20%) and nail plate detachment (n=3; 15%).

The most common changes found in the plates evaluated were thickening (n=14; 70%), followed by striations and subungual callus (n=8; 40%).

After the intervention protocol has been applied through LLLT with PDT, the nail plates were evaluated 6 months later and, when comparing the changes found in the evaluation before the intervention, the following was identified: absence of changes in the nail plate (n=3; 15%), improvement of the changes found in the nail plate (n=11; 55%) and persistence of the changes found (n=6; 30%).

Based on the results obtained after the intervention, it was possible to verify that most of the nail plates analyzed presented a satisfactory evolution of the clinical aspect, after being submitted to the treatment protocol with application of LLLT with PDT; 70% of them presented involution in one or more parameters in the previously existing changes: presence of thickening, longitudinal streaks, dermatophytomas, nail plate fragility, presence of wet maceration of the hyponychium, subungual callus and plate detachment – evaluated by clinical comparison of such variables and photographic record of the aspect of the changes found in the nail plates. Of this percentage, 55% (n=11) of the treated nail plates showed improvement in the changes produced by onychomycosis after the therapy, as exemplified in Figure 1.

FIGURE 1: Nail plate with improvement of the alterations found before the intervention (n=11). Rio de Janeiro, RJ, Brazil, 2021.

Also with regard to involution of the changes, 15% (n=3) evolved with no changes in the nail plate, that is, there was total recovery of the plate, as can be seen in Figure 2.

FIGURE 2: Nail plate showing full recovery after Low-Level Laser Therapy with photodynamic therapy (n=3). Rio de Janeiro, RJ, Brazil, 2021.

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However, of the 20 nail plates submitted to treatment, 30% (n=6) showed no improvement with the method. In these cases, the nail plate maintained or increased the clinical alterations presented at treatment initiation, as shown in Figure 3.

FIGURE 3: Nail plate showing maintenance of the changes (n=6). Rio de Janeiro, RJ, Brazil, 2021.

DISCUSSION

The predominance of patients over 60 years of age in the study can be explained by the fact that onychomycosis is a common pathology in older adults. The proportion between onychomycosis and age reveals that, the higher the age, the higher the prevalence of the disease, a fact influenced by several factors, such as decreased nail growth, trauma and diseases that predispose its development, such as the high incidence of DM among older adults[7,10,11].

Epidemiological data indicate that nearly 10% of the general population is affected by onychomycosis and that, within this context, 20% are over 60 years old and 50% are over 70. Regarding diabetic patients, nearly one third are affected by onychomycosis[7].

It is noted that the study consists of patients with Type 2 DM affected by onychomycosis, a fact that contributes to a sample mostly comprised by aged and female patients, when considering the prevalence of DM. In both men and women, the prevalence of Type 2 DM increases from the age of 50, and this increase is more pronounced in women, which can be possibly explained by menopause, strengthening the higher frequency of this population segment in this research, which is also found in other studies[3,12-14].

It is noted that female patients are mostly found in some health services due to greater concern of this population with health, which leads to the search for care more frequently than among men. Another factor is that the prevalence of females is pointed out in a Clinical Podiatry service, specialized in the care of diabetic patients with lower limb injuries[3].

Higher prevalence of onychomycosis in females has also been described, so that women are more affected by superficial mycoses, mainly represented by onychomycosis, with toenails as the most affected[7,15].

To evaluate the blood glucose levels and glycemic control of the study participants, it is necessary to consider the recommended glycemic goals. According to the *American Diabetes Association,* the expected glycemic goals should remain between 70 and 130 mg/dL in the fasting state and below 180 mg/dL postprandially[16]. However, what was observed was a mean above the recommended, which shows ineffective control of the glycemic levels among the participants.

It is important to highlight that individuals with diabetes not treated or keeping glycemic indices off target develop more micro- and macro-vascular complications, in addition to infections. In this context, it is important to maintain glycemic control, aiming to reduce the risk of developing such complications[17].

Among such complications we should mention the high prevalence of onychomycosis and the incidence of secondary infections, which are up to three times more frequent in diabetic patients than in the non-diabetic population, which occurs due to the decrease in the individual's circulation and immune response[17].

Onychomycosis is a risk factor for diabetic foot development, which can cause lower limb amputation. This is a clinical condition that must be diagnosed and treated early in time, allowing actions to avoid further complications and prevent such outcome[7,14,18].

The presence of nail fungal infection is repeatedly present through nail plate destruction, thickening, stretch marks and subungual callus, a fact that can be associated with severity of the infection[19].

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Among the changes caused by the pathology, we can mention the presence of dermatophytomas and subungual hyperkeratosis, used to define the severity of onychomycosis through the Onychomycosis Severity Index (OSI)[19]. The significant increase in the region affected by microorganisms, generating thickening, is one of the main characteristics of the disease[20].

The penetration of antifungal drugs in dermatophytomas is considered limited. This change is presented in the nail plate as a longitudinal yellow, white or orange band or as a round yellow fragment. Thickening of the corneal extract in response to fungal infection generates hyperkeratosis, which is also considered a complicating factor for treatment, as it hinders penetration of the antifungal therapy, especially when it is greater than 2 mm thick[19].

Other alterations that can also manifest in onychomycosis are changes in color, partial or total onycholysis and onychodystrophy, generating fragility of the affected plate, making it thin, disfigured and dyschromic[11,20].

As an alternative to traditional antifungal treatment, photodynamic inactivation is proposed, a therapy performed with low-level therapeutic *laser*, although it can also use another light source[20]. PDT has shown great potential for treatment, being an efficient and economical method[21].

The treatment of fungal infections with photosensitizing agents has gained attention as a viable alternative to conventional treatments, as PDT with low-level *laser* is effective in inactivating fungi[22].

It is a technique that uses the triad consisting of non-toxic photosensitizing dye, oxygen and light at an appropriate wavelength, aiming to provide localized oxidative photoinjury, jointly generating singlet oxygen and other cytotoxic radicals, which induce microbial cells to severe damage, leading to their death, with the basic principle of generating chemical photosensitivity in a target tissue[4,23].

Regarding the results achieved with this technique, it was identified that it was satisfactory in 70% of the sample of this study that received PDT with laser therapy. In line with these results, there are several studies that were successful in the treatment, as is the case of achieving cure rates of 80% in 12 months in one study[21]. Other percentages cited by a number of research studies indicate negative cultures in 67% of the patients in whom PDT was used, as well as complete cure rates of 63.6% in severe and moderate onychomycosis[24,25].

Lower rates are also mentioned, as is the case of clinical and microbiological cure achieved by a study in 43.3% and no apparent clinical signs in 16.6%[21]. In another, 36.6% of clinical cure in 18 months is mentioned[21,24]. The causes for treatment failure were not established in the studies. It is noted that, in this study, there may be a relationship with the lack of glycemic control, which was very common and is associated with the emergence of several complications, due to the changes they cause in the body.

Despite advances in the treatment of onychomycosis, non-response to the conventional treatment is nearly 40% to 70% and, in this study, 30% non-response to PDT with *laser* was found, which strengthens the need to develop and investigate this and other new therapeutic options[21].

Study limitations

The limitations found in this study refer to the small sample size, not allowing generalization of the results. In addition to that, not performing tests to identify or not the presence of the fungus may limit the results, considering that only the local analysis of the clinical aspect of the nail plate was used to evaluate the results. Thus, it is suggested that larger studies be carried out, with larger samples and using tests to better explore the results of PDT with *laser*.

Another limitation found was that no validated tool was used in this study to monitor the clinical evolution of the nail plate before and after treatment, which could provide a more objective analysis, through scores and, consequently, more reliable.

CONCLUSION

Photodynamic therapy with laser therapy proves to be a very promising technique for the treatment of onychomycosis, having shown a rate of 70% of beneficial effect, highlighting the advantages of its use in diabetic patients, for not presenting any potential for drug interactions and for the absence of systemic adverse effects when compared to the traditional treatment.

Despite all the advances, there are still few clinical studies on the use of low-level *laser* with photodynamic therapy for the treatment of onychomycosis, especially for defining dosimetry and concentrations of photosensitizing substances. Thus, there is a need for larger studies to be carried out and for treatment protocols to be established, in order to improve the technique and achieve better results.

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