

The association of fractional CO₂ laser 10.600nm and photodynamic therapy in the treatment of onychomycosis*

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Abstract: BACKGROUND: Onychomycosis is a fungal infection of the nails caused in most cases by dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Despite numerous available antifungal drugs for therapy of this infection, the cure rate is low, with high rates of relapse after treatment and side effects.

OBJECTIVES: To present a new option for the treatment of onychomycosis, in search of a more effective and rapid method than conventional ones.

METHODS: Patients underwent two sessions of CO₂ fractional laser 10.600nm associated with photodynamic therapy. Mycological and digital photography were performed before and after the treatment.

RESULTS: McNemar test with continuity correction and degrees of freedom = 1: for clinical cure rate, 13.06, with $p=0.00005$; for mycological cure, 17.05, with $p=0.00005$; 72% felt fully satisfied with the procedure.

CONCLUSIONS: The use of fractional CO₂ laser 10.600nm associated with photodynamic therapy can be effective in the treatment of onychomycosis, decreasing the risk of systemic lesions that may be triggered with prolonged use of oral antifungals.

Keywords: Nail diseases; Nails; Onychomycosis

INTRODUCTION

Onychomycosis is a fungal infection of the nails caused, in 80 to 90% of cases, by the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*, affecting from 10 to 30% of the global population.^{1,2,3} Clinically, there are five different modalities: distal and lateral subungual onychomycosis, proximal subungual onychomycosis, superficial onychomycosis, endonyx onychomycosis and mixed onychomycosis.⁴

The most used conventional treatments include oral (OAF) and topical (TAF) antifungals. Despite the numerous antifungal medications available in the market, the cure rate is low, with high rates of relapse after treatment.^{3,5} In addition, due to the peculiarities of the unguis system and speed of fungal reproduction, oral antifungals may require a long treatment, which would increase costs for the patient, besides enhancing the possibility of adverse effects.^{6,7}

Therefore, there is a growing need to seek a more efficient method that may diminish relapses

and have a smaller chance of adverse effects.⁸ In this context, some non conventional treatments for onychomycosis, like laser and photodynamic therapy, have shown effectiveness in combating this infection.^{2,3,4,9,10,11}

The objective of this study was to present to patients with a recurring clinical picture a topical therapy for the treatment of onychomycosis, more effective and faster than conventional methods, using fractional CO₂ laser 10.600nm associated with photodynamic therapy in the same session.

MATERIALS AND METHODS

This is a study that had as object cases selected from our Outpatient Hair and Nails Clinic, in the period between August and October 2012, which were clinically followed-up for one year after the last session. All of the patients presented alterations in the nail plate clinically suggestive of onychomycosis and underwent mycological examination by culture and microcultivation to determine the etiologic agents at the Special Laboratory of Clinical Microbiology of

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the Mycology Department. These examinations were carried out at three occasions: before the sessions, 30 days after the second session and 1 year after the second session. Prior to the beginning of the study the patients were oriented not to use any TAF or OAF for one month before the collection date. None of the patients used any TAF or OAF during the follow-up period of the study.

The inclusion criteria of the study were: patients who had tried previous treatment with TAF or OAF without therapeutic success and with recurrence of the clinical picture, patients with onychomycosis of long progression or patients with chronic diseases in whom the long-term use of OAF would have a chance of causing systemic alterations. Those patients with collagenoses and patients with photosensitive disease who presented onychomycosis by nondermatophyte agents in the prior examination were excluded.

Two sessions were conducted with each study patient, with a 60-day interval between them. The sessions were carried out with fractional CO₂ laser 10.600nm, 3rd overlap, 1.600mJ energy and 0.6mm density between the points over the affected nail areas. Subsequently methyl aminolevulinate hydrochloride 16% was applied over the area and the product remained under occlusion by opaque material for 2 hours. Then Light-Emitting Diode (LED) for photodynamic therapy was applied for 15 minutes. Both sessions were carried out in the same manner. None of the patients used any OAF or TAF during follow-up.

In order to conduct the case study the patients were evaluated at moment zero, before the sessions began, for mycological test and digital photograph; at moment one, 30 days after the second session, for mycological test; and at a late moment, one year after the second session, for mycological test and digital photograph. The nails were divided into four quadrants with the back of fingers in a non anatomic position (medial distal nail plate, lateral distal nail plate, medial proximal nail plate and lateral proximal nail plate) through a vertical imaginary line and another horizontal imaginary line at the mean point of each side of the plate. After this division, the number of clinically involved and not involved quadrants was determined (1 quadrant, 2 quadrants, 3 quadrants and 4 quadrants) before and after therapy (late moment) by digital photography. The statistical analysis of this correlated paired sample was done with the Microsoft Excel program through McNemar test with continuity correction, significance level 5% (alpha level = 0.05 for rejection of the null hypothesis) and 1 degree of freedom. The number of failures is considered as "a", because it goes from an absence of disease to a presence of disease, and "d" is the number of successes, because

it goes from a presence to an absence of disease, according to the formula below:

$$Q2 = (|a-d| - 1)2 / a+d$$

The clinical cure is based on the diminution of the number of quadrants without clinical lesion after 1 year of follow-up. The mycological cure was determined by the mycological test results, using culture and microcultivation at moment one and late moment.

The Degree of Satisfaction of the patients was investigated by questionnaire with scores from 0 to 4, with the following parameters: 0 – dissatisfied, as the condition worsened; 1 – dissatisfied, as nothing changed; 2 – satisfied, but would like more; and 3 – fully satisfied. The questionnaire was applied after one year of follow-up. Data analysis was carried out using simple percentages.

RESULTS

The epidemiological profile of this case study had seven patients, four male and three female, with ages varying between 41 and 65 years. All of the patients had undergone previous therapy, both topical and systemic, with recurrence and treatment failure. The time of progression of the disease varied from 1 to 12 years, with median of 10 years before the patient looked for another type of treatment. None of them had used technology in the approach to onychomycosis treatment.

Of the seven nail lesion scrapings, after culture and microcultivation evaluations, six presented *Trichophyton rubrum* and one *Epidermophyton floccosum* as etiologic agents. After identification of the species, two sessions of fractional CO₂ laser 10.600nm were performed on the affected nail, followed by Photodynamic Therapy, with a 60-day interval between them.

The total of quadrants analyzed was 28, as each of the seven nail plates were divided into four, as described in the methodology. The analysis of the digital photographs with the description of the number of affected and not affected quadrants before and one year after the last session are shown in table 1. Of the 19 affected quadrants, 15 presented clinical therapeutic success ("d") and of the 9 quadrants not affected, none presented therapeutic failure ("a"). McNemar Test with continuity correction for clinical cure was 13.06, with p = 0.00005. The digital photographs are shown in figures 1 to 7.

At moment one and at the late moment, after one year of follow-up, all of the patients presented negative mycological test results, with mycological cure in every case. Of the 19 affected quadrants, all achieved mycological therapeutic success ("d") and of the 9 quadrants that were not affected, none

TABLE 1: Distribution of affected and non affected quadrants, before and after treatment

	Number of affected quadrants	Number of non affected quadrants	Total
Before treatment	19	9	28
After treatment	4	24	28



FIGURES 1 TO 7:
A. Before treatment;
B. One year after treatment

presented therapeutic failure (“a”). McNemar Test with continuity correction for mycological cure was 17.05, with $p = 0.00005$.

The Degree of Satisfaction of the patients is shown in table 2, with 72% declaring they were fully satisfied with the outcome, mainly because there were no relapses. The only two patients who were not fully satisfied were those who did not present total clinical cure, according to analysis of digital photographs.

DISCUSSION

Despite the numerous antifungal medications available for onychomycosis therapy, the cure rate is low, with high relapse rates after treatment.^{3,5} Light therapy was shown to be a promising treatment for this nosology for its ability to act in a small area of the affected region, which would limit the systemic adverse effects. In addition, the high concentration of energy released by means of this technique allows deeper penetration into the nail plate, eradicating all fungal residues.^{2,3,9,12}

Fractional CO₂ laser 10.600nm immediately destroys, at the moment of application, the area affected by fungi, allowing the elimination of the damaged nail and a deeper penetration of the methyl aminolevulinate hydrochloride 16% to optimize the action of light in photodynamic therapy.¹³ This photochemical reaction is able to selectively destroy a tissue. This methodology represents a complex system that requires three factors to interact concomitantly: a photosensitizer, such as the 5-aminolevulinic acid; a light source and oxygen.^{14,15} In cases that involve superficial cutaneous fungal infections, many in vitro studies demonstrated, in culture media, the effectiveness of photodynamic therapy to combat the *Trichophyton rubrum*.^{10,11}

In this study, the mycological cure was achieved in all of the patients at two distinct moments, with statistically significant outcomes ($p < 0.005$), without observing any relapse of the infection in the follow-up period. These results are superior to those already observed after treatment with conventional antifungals, when the cure rate is low, with high

TABLE 2: Degree of patient satisfaction and clinical improvement

	Degree of Satisfaction	Clinical Improvement
PATIENT 1	3	Total
PATIENT 2	3	Total
PATIENT 3	2	Partial
PATIENT 4	3	Total
PATIENT 5	3	Total
PATIENT 6	2	Partial
PATIENT 7	3	Total

relapse rates after treatment.^{3,5} However, it should be emphasized that negative mycological tests may not prove that healing was achieved, since over 40% of cases may be false negatives. An example of this may be found in figure 2, which presented persistent chromonychia. Together with this mycological cure is associated the absence of onycholysis relapse and nail pain one year after the end of treatment. In addition to this mycological cure, the improved clinical aspect was also statistically significant, with $p < 0.005$ when each of the 28 quadrants is compared. However, when the entire nail plate is compared before and after the treatment, only 43% presented total lightening of lesions. This was a selection bias of the study, as the patients included were those with a recurrent clinical picture or of long progression, that is, onychomycosis pictures more resistant to traditional therapy. In any case, the patients presented favorable outcomes after 12 months of follow-up, with no need for topical or systemic antifungal therapy for any of the patients

during this follow-up period, reaching the maximum degree of satisfaction in 72% of the cases. In the long term, this reflects in a decreased risk of adverse effects for the patients, contrary to what is observed in treatment with oral antifungals.^{6,7}

CONCLUSION

Our conclusion is that the use of fractional CO₂ laser 10.600nm associated with photodynamic therapy may be effective in the treatment of recurrent onychomycosis of difficult treatment, as well as diminish the risk for systemic lesions that may be triggered with prolonged use of oral antifungals. However, further studies and longer follow-up are necessary to corroborate our observation.

We consider this emerging treatment important not only as an individual therapy, but mainly as combined therapy, since there was clinical improvement that could be increased by association with other topical or systemic antifungal therapies. □

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