

Endonyx toenail onychomycosis caused by *Trichophyton rubrum*: treatment with photodynamic therapy based on methylene blue dye*

Onicomiose endonix podal por *Trichophyton rubrum*: tratamento por terapia fotodinâmica com corante azul de metileno

Linton Wallis Figueiredo Souza¹
Ana Cristina de Carvalho Botelho³

Simone Vilas Trancoso Souza²

DOI: <http://dx.doi.org/10.1590/abd1806-4841.20132180>

Abstract: This study shows the effectiveness of photodynamic therapy based on methylene blue dye for the treatment of endonyx toenail onychomycosis. Four patients with endonyx onychomycosis caused by *Trichophyton rubrum* were treated with 2% methylene blue aqueous solution irradiated with light emission diode at 630 nm and an energy density of 36 J/cm² for 6 months at 2-week intervals. The preliminary study showed the effectiveness of this therapy in the treatment of endonyx onychomycosis, and also indicated that the disease can be caused by *T. rubrum*.

Keywords: Nail diseases; Photochemotherapy; *Trichophyton*

Resumo: O estudo revelou a eficácia da terapia fotodinâmica com corante azul de metileno para o tratamento da onicomiose endonix podal. Quatro pacientes apresentando onicomiose endonix causada pelo *Trichophyton rubrum* foram tratados com solução aquosa de azul de metileno a 2% irradiada com diodo emissor de luz com 630 nm e densidade de energia de 36 J/cm² em sessões quinzenais durante seis meses. O estudo preliminar mostra que essa terapia é eficaz no tratamento da onicomiose endonix e que o *T. rubrum* pode causar a doença.

Palavras-chave: Doenças da unha; Fotoquimioterapia; *Trichophyton*

Fungal nail infections are classified according to the site of fungal invasion. There are 5 different modes of invasion: distal and lateral subungual onychomycosis, proximal subungual onychomycosis, superficial onychomycosis (white or black), endonyx onychomycosis (EO), and mixed onychomycosis (total dystrophic, secondary, and paronychia-associated).¹ EO is characterized by massive fungal invasion of the superficial and deep nail-plate layers with minimal or absent hyperkeratosis.^{1,2} The nail surface has lamellar-like splits, and the end of the nail plate is often friable and split. Dense opacification of the nail plate with milky-white discoloration is unusual. Endothrix dermatophytes cause the clinical peculiari-

ties of EO, usually *Trichophyton soudanense* and in some cases *Trichophyton violaceum*.¹

Photodynamic therapy (PDT) is a medical modality that combines the use of visible light and a photosensitive compound in the presence of oxygen. It is widely used to treat neoplastic skin lesions.³ PDT has been investigated as a noninvasive treatment for onychomycosis which selectively destroys infectious pathogens.⁴ Methylene blue (MB) and other dyes of the same class exhibit intense absorption at the 600–660-nm red light region.³ Studies have demonstrated that MB-light emission diode (MBLED)/PDT is effective and safe, with response rates of approximately 85–100%.^{3,5} Here we investigated the efficacy

Received on 07.10.2012.

Approved by the Advisory Board and accepted for publication on 31.10.2012.

* Work performed at the Clemente Faria University Hospital - Montes Claros State University (HUCF - UNIMONTES) - Montes Claros (MG), Brazil.

Conflict of interest: None

Financial funding: None

¹ Master in Health Sciences – Professor of Dermatology and Research Professor, Department of Clinical Medicine, Center for Infectious Diseases Research - Clemente Faria University Hospital - Montes Claros State University (HUCF - UNIMONTES) - Montes Claros (MG), Brazil.

² Specialist, student in the Postgraduate Program in Health Sciences and Designated Professor - Montes Claros State University (UNIMONTES) - Montes Claros (MG), Brazil.

³ Post-Doctorate in Parasitology - Professor in the Health Sciences Postgraduate Program of the Montes Claros State University (UNIMONTES) - Montes Claros (MG), Brazil.

of MBLED/PDT in patients with toenail EO caused by *Trichophyton rubrum*.

We conducted a preliminary open clinical trial that included 4 immunocompetent patients with toenail EO with clinical and mycological diagnosis. The inclusion criteria were clinical signs of EO confirmed by direct microscopic examination of nail material with 20% potassium hydroxide and by culture on Sabouraud agar with chloramphenicol-cycloheximide and Sabouraud agar with chloramphenicol. None of the patients showed nail changes associated with skin or systemic diseases, nor had used antifungal medications in the previous 4 months. PDT consisted of 6 months of MBLED sessions with an interval of 15 days between sessions. A 2% aqueous MB solution was applied to the lesion followed by irradiation with red light (630 nm, 36 J/cm²) from an LED device with a light intensity output of 3100 mW/cm² and optical intensity of 100 mW/cm² (Multiwaves; Industra, São Carlos, Brazil). Lesions that were not fully penetrated by the dye were treated with nail abrasion, using a rotation abrasive device with a 3-mm diamond tip (Dermoabrasor; Bley Med, Curitiba, Brazil). Patients were evaluated monthly during treatment. The microbiological and clinical outcomes were assessed at the end of treatment. The study was approved by the Ethics Committee of the Montes Claros State University.

Before treatment, all 4 patients were found positive for *T. rubrum* on mycological examination (Table 1). In 2 patients, a second culture was needed for etiological confirmation. Figure 1A shows nail plate impairment without subungual hyperkeratosis, and the presence of undulation and distal split. Figure 1B shows the rapid clinical response after 8 weeks of treatment and the presence of lamellar scaling and a nail plate distal split. Complete clinical response was evident, with mycological cure in all cases. No patient showed dense opacification of the nail plate (Figure 1). No adverse effects were observed.

This preliminary MBLED/PDT trial showed the effectiveness of the method for treating onychomycosis caused by *T. rubrum*. EO caused by endothrixdermatophytes (mainly *T. soudanense*) differs from distal and lateral subungual onychomycosis (mainly caused by *T. rubrum*), essentially by the absent or minimal subungual hyperkeratosis.^{1,2} From



FIGURE 1: Endonyx toenail onychomycosis treated with photodynamic therapy based on methylene blue. (a) before treatment; (b) 2 months; (c) 4 months; (d) 6 months of treatment

TABLE 1: Clinical data of patients with endonyx toenail onychomycosis treated with photodynamic therapy based on methylene blue dye

Patient	Gender	Age years	Duration months	MSH	Contributing factors	Clinical response*	
						3 months	6months
1	F	43	18	+	sport trauma	>75%	>99%
2	M	65	15	+	claw toe	>75%	>99%
3	M	39	22	-	sport trauma	>75%	>99%
4	F	28	12	-	sport trauma	>99%	>99%

F= female; M= male; MSH= minimum subungual hyperkeratosis; >75%= marked improvement; >99%= complete improvement; * Clinical response and treatment duration.

the genetic standpoint, *T. rubrum* and *T. soudanense* are the same species.⁶ *T. rubrum* was believed to be exclusively ectothrix but is currently known to be either ectothrix or endothrix.^{7,8}

MB/PDT has been used for several decades for the treatment of cutaneous mycosis.³ Previous clinical trials and in vitro studies have demonstrated the effectiveness of PDT, but indicated the need for adequate energy density and concentration of the photosensitive dye.^{3,8} The increased energy density used in this study might reduce the number of sessions and the treatment duration due to the increased PDT fungicidal activity.⁸ The use of macrocyclic molecules with fewer sessions (3 on average), because of the

high cost, has resulted in a clinical cure rate lower than that ofazole drugs, probably due to the inadequate number of sessions.^{9,10}

In conclusion, onychomycosis remains a therapeutic challenge. The preliminary results of this study confirm that MBLED/PDT is safe and effective, promoting a favorable outcome in the treatment of EO caused by *T. rubrum*. New clinical studies may indicate the suitable energy density for improving the therapeutic outcome and potential associations with systemic treatments. Finally, this study shows that, besides *T. soudanense* and *T. violaceum*, other fungi of the *T. rubrum* complex can cause endonyx onychomycosis. □

REFERENCES

1. Baran R, de Berker D, Holzberg M, Thomas L. Baran&Dawber Disease of the nails and their management. 4th ed. Chichester: Wiley-Blackwell; 2012.
2. Tosti A, Baran R, Piraccini BM, Fantl PA. ``Endonyx'' Onychomycosis: A New Modality of Nail Invasion by Dermatophytes. *ActaDermVenereol.* 1999;79:52-3.
3. Tardivo JP, Del Giglio A, Oliveira CS, Gabrielli DS, Junqueira HC, Tada DB, Severino D. Methylene blue in photodynamic therapy: From basic mechanisms to clinical applications. *PhotodiagnPhotodynTher.* 2005;2:175-91.
4. Zeina B, Greenman J, Corry D, Purcell WM. Antimicrobial photodynamic therapy: assessment of genotoxic effects on keratinocytes in vitro. *Br J Dermatol.* 2003;148:229-32.
5. Scwingel AR, Barcessat AR, Núñez SC, Ribeiro MS. Antimicrobial photodynamic therapy in the treatment of oral candidiasis in HIV-infected patients. *Photomed Laser Surg.* 2012;30:429-32.
6. Reiss E, Shadomi HJ, Lyon GM. *Fundamental medical mycology.* Chichester: Wiley-Blackwell; 2011.
7. Mann MW, Berk DR, Popkin DL, Bayliss SJ. *Handbook of Dermatology.* Chichester: Wiley-Blackwell; 2009.
8. Amorim JC, Soares BM, Alves OA, Ferreira MV, Sousa GR, Silveira Lde B, et al. Phototoxic action of light emitting diode in the in vitro viability of *Trichophyton rubrum*. *An Bras Dermatol.* 2012;87:250-5.
9. Smijs TG, Pavel S. The susceptibility of dermatophytes to photodynamic treatment with special focus on *Trichophyton rubrum*. *PhotochemPhotobiol.* 2011;87:2-13.
10. Sotiriou E, Koussidou-Eremonti T, Chaidemenos G, Apalla Z, Ioannides D. Photodynamic therapy for distal and lateral subungual toenail onychomycosis caused by *Trichophyton rubrum*: Preliminary results of a single-centre open trial. *ActaDermVenereol.* 2010;90:216-7.

MAILING ADDRESS:

Linton Wallis Figueiredo Souza
Avenida Cula Mangabeira, 562
Sto Expedito
39401-001 - Montes Claros - MG
Brazil
E-mail: wallis@uai.com.br

How to cite this article: Souza LWF, Souza SVT, Botelho ACC. Endonyx toenail onychomycosis caused by *Trichophyton rubrum*: treatment with photodynamic therapy based on methylene blue dye. *An Bras Dermatol.* 2013;88(6):1019-21.