

# Distal and lateral toenail onychomycosis caused by *Trichophyton rubrum*: treatment with photodynamic therapy based on methylene blue dye\*

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**Abstract:** The study showed the effectiveness of photodynamic therapy based on methylene blue to treat severe distal and lateral subungual toenail onychomycosis. 22 patients were divided into two groups: group A consisting of 11 patients with severe toenail onychomycosis and group B consisting of 11 patients with mild-to-moderate toenail onychomycosis. All patients had onychomycosis caused by *Trichophyton rubrum*. The patients were treated with sessions of 2% methylene blue aqueous solution irradiated with light emission diode device with 630 nm and 36 J/cm<sup>2</sup> biweekly for six months. The clinical response was significantly better in patients with mild-to-moderate (100%) onychomycosis compared with patients with severe onychomycosis (63.6%).

Keywords: Nail diseases; Phototherapy; *Trichophyton*

Severe distal-lateral subungual onychomycosis (SDSO) is characterized by fungal invasion of the hyponychium through the distal subungual and lateral nail groove reaching the lunula or nail matrix, or by a 50% nail plate involvement associated with >2 mm subungual hyperkeratosis or dermatophytoma.<sup>1,2</sup> Patients with SDSO are categorized as poor responders or nonresponders to systemic antifungal treatment and are difficult to treat.<sup>3</sup> In severe onychomycosis, the nail surface is likely to retain an abnormal appearance even after mycological cure.<sup>4</sup> The first-line systemic drugs itraconazole and terbinafine promote complete healing in 25% and 35% of severe cases, respectively.<sup>3,4</sup> Therefore the current best treatment option is the use of combination antifungal therapy (systemic + topical + nail avulsion or abrasion) with supplementation, after 3–6 months drug-free.<sup>4</sup> However, a need remains for more effective oral antifungal agents with fewer adverse effects and fewer drug–drug interactions, as well as for more effective topical agents with greater nail penetration.<sup>3,4</sup>

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 nonmelanoma skin cancer.<sup>5</sup> PDT is a noninvasive treatment for onychomycosis and can selectively destroy infectious pathogens.<sup>6</sup> Methylene blue (MB) and other dyes of the same class exhibit intense absorption at the 600–660-nm red light region.<sup>3</sup> Previous studies have demonstrated that MB-light emission diode (MBLED)/PDT is effective and safe, with response rates of approximately 85–100%.<sup>5,7</sup> We here investigated the efficacy of MBLED/PDT in patients with toenail SDSO caused by *Trichophyton rubrum*.

Our open-label controlled clinical trial included 11 immunocompetent patients with toenail SDSO and 11 immunocompetent patients with mild-to-moderate distal and lateral subungual toenail onychomycosis (MDSO) with clinical and mycological diagnosis. The inclusion criteria were clinical signs of onychomycosis confirmed by direct microscopic examination of nail material with 20% potassium hydroxide, and by cul-

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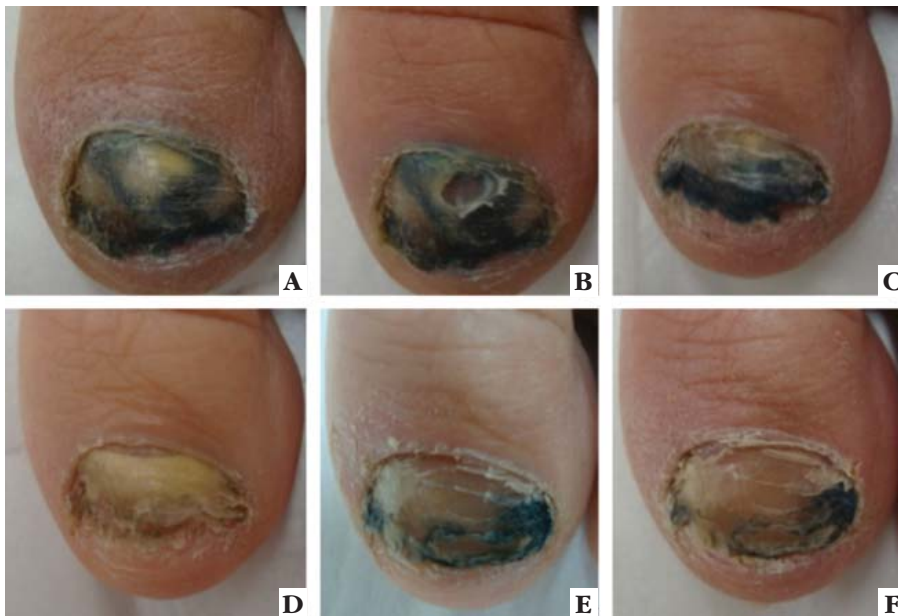
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ture on Sabouraud's agar with chloramphenicol and cycloheximide and Sabouraud's agar with chloramphenicol. None of the patients showed nail changes associated with skin or systemic diseases, nor had used antifungal medications in the previous 4 months. PDT consisted of 6 months of MBLED sessions with a 15-day interval between sessions. A 2% aqueous MB solution was applied to the lesion followed by irradiation with red light (630 nm, 36 J/cm<sup>2</sup>) from an LED device with a light intensity output of 3100 mW/cm<sup>2</sup> and optical intensity of 100 mW/cm<sup>2</sup> (Multiwaves; Industra, São Carlos, Brazil). Patients with hyperkeratotic lesions or dermatophytomas were treated with a rotation abrasive device with a 3-mm diamond tip (Dermoabrasor; Bley Med, Curitiba, Brazil). Patients were evaluated monthly during the treatment period. The microbiological and clinical outcomes were assessed at the end of treatment. The data were described using means (standard deviations), proportions and constructing 95% confidence intervals (CI). This study was approved by the ethics committee of the Montes Claros State University.

Before treatment, all 22 patients were found positive for *T. rubrum* on mycological examination. Figure 1 shows the stain delimiting the impaired area of the nail plate toward the matrix and the area of subungual hyperkeratosis. The dye did not penetrate the area with fungal biofilm in the nail plate. This noncolored area was subjected to dermabrasion. The nail plate detached from the nail bed during the healing

process because of nail matrix injury. All patients showed clinical improvement with mycological cure (Table 1). The clinical response rate at last visit was significantly better in patients with MDSO (100%; CI 100%) compared with patients with SDSO (63.3%; CI 35-92%). No adverse effects were observed.

This study shows the effectiveness of MBLED/PDT for the treatment of SDSO caused by *T. rubrum*. SDSO is the major cause of treatment failure in patients with onychomycosis.<sup>3</sup> Studies on combined topical and systemic therapies for SDSO reported a mycological cure rate of between 27% and 83%.<sup>4</sup> PDT with MB has been used for several decades to treat cutaneous fungal infections.<sup>5</sup> In this study, MB showed excellent penetration into the nail plate in all patients, including those with nail matrix impairment, unlike other topical antifungals.<sup>4</sup> Another advantage of MBLED/PDT over other treatments is the possibility of delimiting areas with fungal biofilms, found in dermatophytomas and fungal longitudinal streaks, which are determinants of treatment failure.<sup>3</sup> Previous clinical trials and in vitro studies have demonstrated the effectiveness of PDT, but indicated the need for an adequate energy density and concentration of the photosensitive dye.<sup>5,7</sup> Another study showed that the fungicidal activity of PDT can be enhanced by increasing the energy density, which might reduce the number of sessions and the treatment duration.<sup>8</sup> The use of macrocyclic molecules with fewer sessions (3 on average), because of the high cost, has resulted in a clinical



**FIGURE 1:** Severe distal and lateral toenail onychomycosis treated with photodynamic therapy based on methylene blue dye. **A** before treatment; **B** nail abrasion; **C** 2 months; **D** 3 months; **E** 5 months; **F** 6 months.

**TABLE 1:** Baseline demographics, disease characteristics and clinical response in 22 patients with distal and lateral toenail onychomycosis treated with photodynamic therapy.

		Group A (%)* n=11	Group B (%)** n=11
<b>Gender</b>			
Female		4 (36.4)	6 (54.5)
Male		7 (63.6)	5 (45.5)
Age, years, mean + SD		54.2 + 10.8	48.8 + 8.4
Duration, year, mean + SD		4.5 + 2.1	3.8 + 1.7
<b>Clinical response*** - weeks</b>			
Complete	12	-	4 (36.4)
	24	6 (54.5)	11 (100)
	48	7 (63.6)	11 (100)
Marked	12	3 (27.3)	7 (63.6)
	24	5 (45.5)	-
	48	4 (36.4)	-
Moderate	12	3 (27.3)	-
	24	-	-
	48	-	-
Mild	12	5 (45.5)	-
	24	-	-
	48	-	-

**Group A**= severe distal and lateral toenail onychomycosis; **Group B**= Mild / moderate distal and lateral toenail onychomycosis; \***Severe grading** (lunula or matrix involvement, or >50% nail involvement with dermatophytoma or subungual hyperkeratosis >2mm); \*\***Mild/moderate grading** (< 75% nail involvement or < 50% nail involvement with dermatophytoma or subungual hyperkeratosis > 2mm); \*\*\***Clinical response during treatment for 6 months and follow-up: complete** (100%); marked (>75%), moderate (50-75%), Mild (<50%).

cure rate lower than that of azole drugs, probably due to the inadequate number of sessions.<sup>9,10</sup>

The results of this study confirm that MBLED/PDT is safe and effective, with a favorable outcome in the treatment of SDSO caused by *T. rubrum*. Finally, MB facilitates the diagnosis of the

presence of a fungal biofilm in the nail plate and nail bed. Further clinical studies may indicate the optimal energy density needed to improve the therapeutic outcome, and its possible associations with systemic treatments. □

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