ORIGINAL ARTICLE

Photodynamic Therapy Versus Its Combination with Fractional Carbon Dioxide Laser in The Treatment of Onychomycosis: A Randomized Controlled Trial

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Abstract

This study explores an alternative approach to managing onychomycosis, a persistent fungal nail infection often resistant to conventional treatments due to prolonged therapy duration, potential liver toxicity, and limited drug penetration into the nail. The research assesses the efficacy of combining photodynamic therapy (PDT) with fractional CO2 laser treatment. A total of 20 patients were categorized into two groups: one receiving PDT alone, and the other undergoing a combination of PDT and Fractional CO2 treatments. The combined approach yielded the most favorable outcomes in achieving complete nail clearance. These findings suggest that integrating PDT with fractional CO2 laser therapy may enhance treatment effectiveness compared to PDT alone, though additional studies are necessary to determine long-term outcomes.

Keywords: Onychomycosis; Photodynamic therapy; Fractional CO2 laser; Nail, Combination therapy; Mycology

1. Introduction

The nail, though an inert appendage of the skin, plays an essential role in reflecting metabolic and genetic changes within the body.[1] Onychomycosis, a fungal infection affecting the nails, can lead to pain, paresthesia, difficulty in daily activities, and social discomfort, potentially impacting both personal and professional life .[2]

Treating onychomycosis remains challenging, often requiring up to 18 months for complete resolution, yet 20–25% of patients fail to achieve a cure 3. Additionally, the condition has a high relapse rate due to residual fungal spores or hyphae, with recurrence reported in 53% of cases .[4]

To overcome these limitations, researchers are exploring alternative treatment modalities that bypass the drawbacks of conventional systemic and topical therapies. Physical interventions such as photodynamic therapy (PDT), laser therapy, laser-assisted drug delivery, and combination approaches are under investigation to enhance treatment efficacy .[5]

PDT has demonstrated antifungal activity and is considered a promising alternative therapy. Initially identified in 1900 for its antimicrobial effects, it gained recognition as a potential antifungal treatment in the 1980s .[6]

Similarly, laser therapy has been approved by the FDA for managing fungal nail infections, though its regulatory approval primarily permits use for aesthetic purposes, such as improving nail clarity, rather than achieving a mycological or complete cure.[5]

Research indicates that both PDT and laser-assisted PDT can effectively treat onychomycosis. Moreover, studies suggest patient satisfaction may be higher with combination therapy due to more rapid clinical improvement .[7]

The aim of this work was to the efficacy of combining photodynamic therapy (PDT) with fractional CO2 laser treatment.

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2. Patients and methods

Between December 2023 and October 2024, 20 patients with onychomycosis were recruited from the Mycology unit at Al-Hussein University Hospital. Exclusion criteria included age under 18, recent use of topical or systemic antifungals, other nail disorders, immunosuppressive conditions, and methylene blue allergy. All participants provided informed consent.

Patients were randomly divided into two groups: Group A underwent weekly PDT with 2% methylene blue and red light after 72-hour urea (40%) pretreatment. Group B received combined therapy, starting with fractional CO2 laser followed by PDT every two weeks.

Efficacy was assessed through clinical and mycological evaluations. Standardized digital photographs were taken at baseline and 16 weeks post-treatment. Severity was graded in four grades, Complete response (fully normal-appearing nail), Significant response (more than 60% improvement), Moderate response (20%-60% improvement), and No response (less than 20% improvement), with outcomes compared at 16 weeks.

The mycological evaluation involved KOH (20%) and DMSO (40%) wet mounts of subungual debris, and examined microscopically for fungal structures. Nail scrapings were cultured on Sabouraud Dextrose Agar (SDA) with and without cycloheximide, and then incubated at 28°C and 35°C for up to four weeks. Fungal species were identified based on growth rate, colony morphology, and microscopic features using lactophenol cotton blue staining.

3. Results

The study cohort had an average age of 36 years, with a predominantly male population (75%), while females accounted for 25%. Group B had a slightly higher proportion of males (30%) compared to Group A, where males comprised only15%.

Risk factors were similar across all groups, with chronic illnesses and frequent exposure to moisture and trauma being the most prevalent contributors. The clinical presentation varied, with distal lateral subungual onychomycosis (DLSO) being the most frequent (60%), followed by total dystrophic onychomycosis (TDO) (18%), endonyx onychomycosis (EO) (10%), proximal subungual onychomycosis (PSO) (10%), mixed patterns (4%), and superficial white onychomycosis (SWO) (2%).

A total of 25 fungal species were identified, with no significant differences in distribution among groups. Yeasts were the most frequently isolated (35%), followed by Aspergillus and Trichophyton rubrum, Fusarium, and Trichosporon. Less common isolates included T. sudanense, Neoscytalidium Dimitatum, and Rhodotorula, each representing 5% of cases.

Both groups showed a significant reduction in KOH positivity post-treatment, with the highest reduction in the combined therapy group (Table 1).

Table 1. Koh test before and after treatment

KOH TEST	TREATMENT			
	Group A PDT (n=20)		GROUP B COMBINED (N=20)	
	No.	%	No.	%
BEFORE TREATMENT				
NEGATIVE	0	0.0	0	0.0
POSITIVE	30	100.0	30	100.0
AFTER TREATMENT				
NEGATIVE	15	75	18	90
POSITIVE	5	25	2	10
P_1	<0.001*		<0.001*	

The significant clinical response was most notable in the combined group, where severe cases dropped to the moderate category. The PDT showed downward trends in severity, but these were not statistically significant (Table 2).

Table 2: clinical response after treatment

CLINICAL RESPONSE	TREATMENT				X^2	MC_P
	Group A PDT (n=20)		Group B Combined (n=20)			
	No.	%	No.	%		
COMPLETE	6	30	12	60		
SIGNIFICANT	6	30	4	20		
MODERATENO	5	25	2	10	3.89	0.274
	3	15	2	10		

Figure 1. Patient with TDO (a) Before treatment (b) After treatment with photodynamic therapy only (c) Gross morphology of Rhodotorula species showing coral pink, smooth, and moist to mucoid, yeast-like colonies (d) Microscopic morphology of Rhodotorula species showing spherical to elongate budding yeast-like cells or blastoconidia (LCB mount×400).

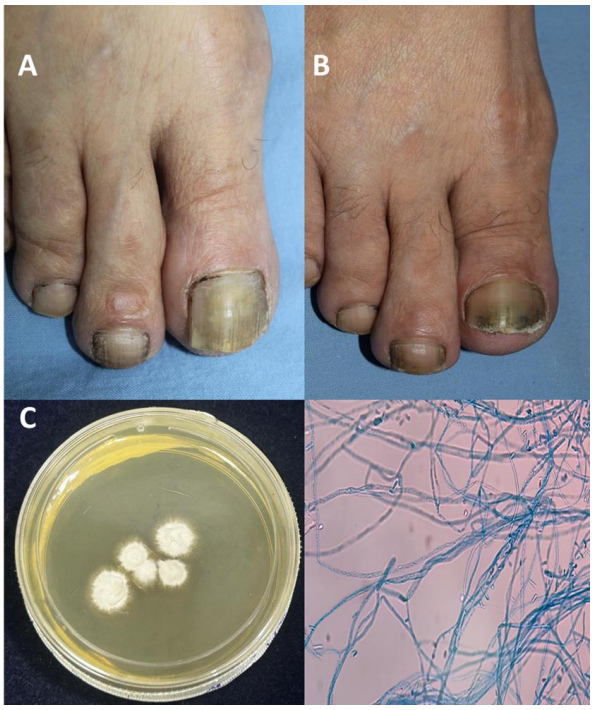

Figure 3. Patient with DLSO (a) Before treatment (b) After treatment with Photodynamic therapy and fractional CO2 (c) Culture on SDA without cycloheximide showing downy to suede-like white colonies characteristic of trichophyton species (d) Microscopic morphology of the colonies showing slender clavate microconidia and cigar-shaped macroconidia, some with terminal appendages (LCB mount×400).

4. Discussion

Onychomycosis is one of the most common nail disorders. It results from an infection of the nail bed, plate, or both and leads to discoloration, subungual hyperkeratosis, and nail dystrophy 8-9. Relying solely on clinical examination can be misleading; therefore, laboratory testing is essential for accurate diagnosis and to rule out other nail conditions .[10]

Treatment challenges stem from the fungus's deep penetration into the nail, prolonged therapy duration, poor adherence, and high recurrence rates.[11] Expanding therapeutic options is crucial to improving treatment response and minimizing relapse and side effects associated with systemic antifungals. Device-based therapies, including lasers, intense pulsed light, iontophoresis, and PDT, offer potential solutions to these limitations.[12]

This study evaluates the safety and efficacy of PDT and its combination with fractional CO_2 laser in managing onychomycosis.

Although onychomycosis is typically more prevalent in the older age group, this study found a higher incidence in the 21–40 age group, with an average patient age of 36 years.

Similar to earlier studies indicating male predominance, this research observed a higher prevalence in males. Male patients are more susceptible to fungal infection of nails as they are more exposed to frequent trauma.

Aging and chronic illness emerged as the most common risk factors, aligning with the high male prevalence and toenail involvement. This result is consistent with previous research that highlighted aging and poor peripheral circulation as primary risk factors .[13]

Distal lateral subungual onychomycosis (DLSO) was the most common clinical type (60%), consistent with a previous study followed by total dystrophic onychomycosis (TDO) in 18% of cases, indicating disease chronicity in some patients.

Dermatophytes are usually considered the primary cause of onychomycosis; this research found Candida species to be the predominant pathogens. Recent studies in tropical and subtropical areas concluded that Candida is the most frequent pathogen in fungal nail infections.[14]

When evaluating treatment efficacy across groups, we observed that PDT alone resulted in a significant mycological cure in most cases. The extended pretreatment with 40% urea (three days) may have contributed to better outcomes, as high-concentration urea enhances photosensitizer penetration.

Unlike the PDT group, the combination therapy group demonstrated significant clinical and mycological responses. This suggests that the laser effectively generates sufficient heat to eliminate fungal elements and may add value to PDT; however, a Fractional Laser may also cause nail bed damage, limiting the final clinical results if used at high power.

4. Conclusion

In summary, combining PDT with fractional CO_2-assisted drug delivery proves to be a safe and effective approach for onychomycosis, yielding superior results compared to PDT treatment alone. This method enhances mycological clearance, clinical outcomes, and patient satisfaction. Its integration into clinical practice could improve the management of onychomycosis.

Disclosure

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