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Fractional CO_2 laser plus topical antifungal versus fractional CO_2 laser versus topical antifungal in the treatment of onychomycosis

Amr Mohamed Zaki | Hamed Mohamed Abdo | Mohamed Anwer Ebadah | Shady Mahmoud Ibrahim

Dermatology and Venereology Department, Al-Azhar Faculty of Medicine, Cairo, Egypt

Correspondence
Shady Mahmoud Ibrahim, Dermatology and Venereology Department, Faculty of Medicine, Al-Azhar University Hospital, Cairo, Egypt.
Email: drshadyaly@yahoo.com, drshadyaly@azhar.edu.eg

Present address
Shady Mahmoud Ibrahim, Department of Dermatology, Al-Hussein University Hospital, Box 11843, Al-Darasa, Cairo, Egypt.

Abstract

Onychomycosis is an important medical disorder affecting both health and quality of life of patients. This study was done to compare the efficacy of CO_2 laser in combination with topical tioconazole versus CO_2 laser only versus topical tioconazole alone in onychomycosis. A total of 120 patients with onychomycosis were randomly assigned to three groups. Group A patients were treated with fractional CO_2 laser followed by topical tioconazole 28% for five sessions with 3 weeks interval. Group B patients were treated with only fractional CO_2 laser for five sessions with 3 weeks interval. Group C patients were treated with only topical tioconazole 28% for 16 weeks. The clinical effect, KOH examination, and culture for the affected nails in the three groups were analyzed. One month after the last session, regarding clinical response, 55% showed complete clinical improvement in Group A versus 30% in Group B versus 25% in Group C with a significant difference in between. There was a significant difference between the three studied groups as regard KOH test and culture after treatment. Fractional CO_2 laser combined with topical antifungal is a safe and effective treatment for onychomycosis.

KEYWORDS
fractional CO_2 laser, onychomycosis, tioconazole

1 | INTRODUCTION

Onychomycosis is an important medical disorder affecting both patients' health and quality of life; it requires prompt and effective treatment. Moreover, early treatment before disease progression to total dystrophic onycholysis (TDO) can also increase the cure rate and therefore avoid the prescription of systemic treatments (Gupta et al., 1998).

Onychomycosis represents up to 50% of all ungual pathologies; high prevalence of the disease together with the limited efficacy of conventional therapies has stimulated the development of new and more effective approaches in treating the disease (Gupta & Simpson, 2012).

Antifungal drugs have been the mainstay of therapy for many years. However potent systemic antimycotics delivered over several months with cure rates of only 40–80% (Bristow, 2014).

Topical therapy would be an alternative approach in the treatment of onychomycosis, as it is found to be capable of overcoming most of the limitations of systemic administration and targeting the drug at its site of action, with minimum interactions and adverse effects (Akhtar, Sharma, & Pathak, 2016). However, topical therapy had limited success, primarily due to poor permeability of the nail plates to the topically applied therapeutics. For effective topical therapy across the nail plate, ungual drug permeation must be enhanced (Saner, Kulkarni, & Pardeshi, 2014).

For a topical agent to be active, it must first traverse the outermost barrier of the nail. Many medications are too large to penetrate this barrier and require systemic therapy. Laser-assisted drug delivery is an evolving modality that may allow for a greater depth of penetration by existing topical medications (Sklar, Burnett, Waibel, Moy, & Ozog, 2014).

The CO_2 laser system is the oldest of the laser therapies for onychomycosis. It is an ablative and therefore can serve as a primary treatment for onychomycosis or as an adjunct to topical antifungals, providing a means of penetration through the nail plate to the nail bed (Lim et al., 2014).

This study was done to compare the efficacy of CO_2 laser in combination with topical tioconazole 28% solution versus CO_2 laser only versus topical tioconazole 28% solution alone for treatment of onychomycosis.

1.1 | Patients and methods

This study was conducted in the Department of Dermatology and Venereology at Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt, from March 2015 to May 2018. The study was approved by the Institutional Review Board of the Faculty of Medicine (DerMed._28Med.Research_Onychomycosis.FractionalCO2laser.Topical.Antifungal_0000028). A written informed consent was obtained from all patients.

1.2 | Study design

A randomized, controlled and comparative study was conducted. Patients were randomly assigned to three groups: Fractional CO_2 laser followed by topical antifungal treatment (Group A), fractional CO_2 laser alone (Group B), and topical antifungal treatment alone (Group C). A simple random allocation sequence was created, using computer-based random number generators.

1.3 | Study population

The study included 145 patients with the clinical and mycological diagnosis (culture and KOH) were consistent with onychomycosis but, only 120 patients completed all treatment sessions and follow-up. Patients who refused to take oral antifungal agents and those who did not respond to such agents given for more than 6 months were included. The study excluded patients below14 years old, patients who received any topical antifungals within 1 month or and systemic antifungals during the previous 3 months, onychomycosis associated with paronychia, other diseases causing nail dystrophy such as psoriasis, eczema, and lichen planus and immunodeficiency, for example, HIV-infected patients, patients with organ transplantation and currently on immunosuppressive drugs for long periods, or patients under chemotherapy or radiotherapy. Demographic data, including age, sex, duration of the condition before treatment, and medical history were collected.

1.4 | Treatment protocol

In Group A, the affected nails were treated with a fractional CO2 laser 10,600 nm (SmartXide Square, DEKA, Florence, Italy) was used with parameters: Power of 10–15 W (according to nail thickness), H-Pulse shape, pulse duration of 500 μs, spacing of 700–800 μm and Stack 3 for five sessions at 3-weeks interval plus topical tioconazole 28% solution applied twice per day to the affected nail plates and nail folds for 16 weeks (endpoint). In Group B, fractional CO_2 laser 10,600 nm was used as a treatment for our patients with the same parameters in Group A for five sessions at 3-weeks interval alone for 16 weeks (endpoint). In Group C, the affected nails were treated with daily topical tioconazole 28% solution only twice per day for 16 weeks (endpoint).

1.5 | Outcome assessment

The treatment efficacy was assessed based on clinical and mycological improvement by two blinded dermatologists. Photographs were taken using the same camera settings, lighting, and nail position by the digital camera (Nikon D5300 - Japan) and were obtained at baseline and 8 and 16 weeks after the start of therapy.

Treatment efficacy was determined by comparing the infected area at baseline and 16 weeks. It was analyzed in four grades as follows: complete response (fully normal-appearing nail), significant response (60% normal-appearing nail compared with the area of the initially infected nail), moderate response (20–60% normal-appearing nail), and no response (20% normal-appearing nail). Mycological examination was done 16 weeks after the start of therapy. Direct microscopy: Specimens were collected by scraping of the affected nail sites by a sterile small curette. Specimens were placed on a clean glass slide and a drop of 20% KOH/40% dimethyl sulfoxide (DMSO) mixture was added (DMSO increases sensitivity of the preparation and softens keratin more quickly than KOH alone in the absence of heat). A coverslip was applied with gentle pressure to drain away excess solution. The sample was then examined thoroughly for the presence of filamentous, septate, branched hyphae with or without arthrospores. Cultures on Sabouraud's dextrose agar: the second set of scrapings were inoculated on SDA (two cultured media; with and without cycloheximide) to identify the pathogenic fungal elements and to confirm the fungal infection. Cycloheximide is an antibiotic that inhibits saprophytic fungi but allows for the growth of pathogenic fungi. Observation for growth was done periodically for at least 4 weeks, after which the media were reported as positive or negative. The treatment outcome was evaluated regarding the sex of patients, duration of the disease, clinical type of onychomycosis, involved nails (fingernails or toenails), and degree of severity of onychomycosis.

1.6 | Patients satisfaction assessment

At the end of the study (1 month after the last laser session), the patients' satisfaction will be assessed as very satisfied, satisfied, slightly satisfied, or unsatisfied. Patients will be also asked to report any treatment side effects and pain scores using numerical analog scales from 0 (no pain) to 10 (extremely painful).

1.7 | Sample size and statistical analysis

According to the previously conducted clinical trials, power analysis indicated 40 persons per group and a total of 120 patients were randomized. The presumed lesion-free area difference ratio was 10%,

and the *SD* was 18. The power was considered to be 80%. The data are shown as mean and *SD*. Statistical analyses were carried out using statistical software IBM SPSS software package version 20 (Armonk, NY: IBM Corp.). Data were statistically described in terms of range, mean, median, *SD* (± *SD*), frequencies (number of cases), and relative frequencies (percentages) when appropriate. Analytical tests used included Pearson correlation (*r*), where all the parameters were tested for correlation. Significance (two-tailed) or *p*-value (*p* stands for probability) was used, where *p*-value <.05 was considered to be statistically significant.

2 | RESULTS

2.1 | Demographic and clinical findings

A total of 120 patients completed their 16-week follow-up evaluations. Twenty-four patients who did not respond to oral antifungal treatment were included, and 96 patients were not taken an oral antifungal. The total number of affected nails was 364, with an average of 3.6 nails per person. The ages among patients ranged from 14 to 66 years (mean ± *SD* = 33.97 ± 16.85 years). Sex distribution of cases showed that 34 (28.3%) were males while 86 (71.6%) were females. The duration of onychomycosis ranged from 2 months to 4 years. There was no statistically significant difference between the three studied groups as regards the age, sex, and duration. The fingernails were affected more than toenails in the three groups but without significant difference. Regarding types of onychomycosis, distal lateral subungual onychomycosis (DLSO) was more common in all studied groups (75%), followed by TDO (18.3%), proximal subungual onychomycosis 3.3%, and superficial white onychomycosis. Identification of the fungal isolates in this study showed that the commonest isolated fungi were yeast infection by 31%, followed by non-dermatophytes molds (NDMs) infection by 28.5% and dermatophyte infection by 22%, and trichosporon species infection detected by 18.5%.

Regarding clinical response grades, there was a significant difference between the three studied groups ($p < .005$), whereas 55% in Group A showed complete clinical improvement versus 30% in Group B versus 25% in Group C (Table 1) (Figures 1–3). Regarding patient satisfaction, 60% of patients in Group A were very satisfied versus 40% in Group B and 30% in Group C (Table 1).

There was a significant difference between the three studied groups as regards KOH test before and after treatment, whereas

TABLE 1 Comparison of clinical response and patient's satisfaction between treatment groups before and after treatment

	Group A (Combined treatment) *N* = 40	Group B (Fractional CO_2 laser treatment) *N* = 40	Group C (Topical antifungal treatment) *N* = 40	Test of significance
Clinical response *N* (%)				
No response	2 (5.0)	18 (45.0)	10 (25.0)	MC $p < .001$*
Significance	2 (5.0)	4 (10.0)	8 (20.0)	
Moderate	14 (35.0)	6 (15.0)	12 (30.0)	
Complete	22 (55.0)	12 (30.0)	10 (25.0)	
Patient's satisfaction *N* (%)				
Unsatisfied	4 (10.0)	18 (45.0)	14 (35.0)	MC $p = .007$*
Slightly satisfied	4 (10.0)	4 (10.0)	6 (15.0)	
Satisfied	8 (20.0)	2 (5.0)	8 (20.0)	
Very satisfied	24 (60.0)	16 (40.0)	12 (30.0)	

Abbreviations: MC, Monte Carlo test; *p*, probability; *statistically significant if $p < .05$.

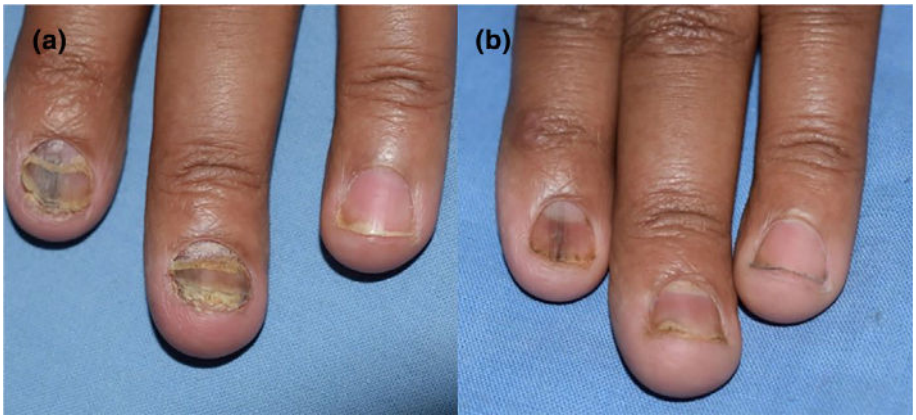

FIGURE 1 "A case of DLSO" (a) Photographs of left-hand index and middle fingernails with moderate DLSO at baseline. (b) 3 months after treatment with CO_2 laser plus topical tioconazole showed a significant clinical response (patient from Group A)

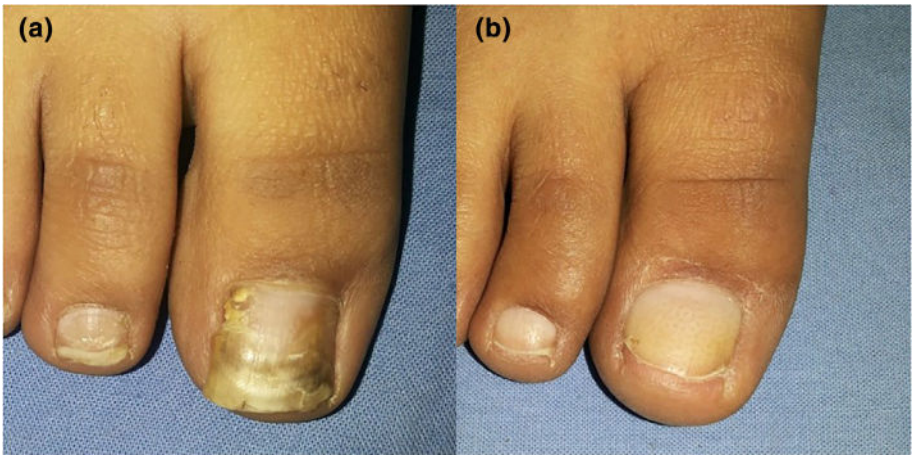

FIGURE 2 "A case of DLSO" (a) Photographs of right big toe with moderate DLSO at baseline. (b) 3 months after treatment with CO_2 laser only, showed a complete clinical response (patient from Group B)

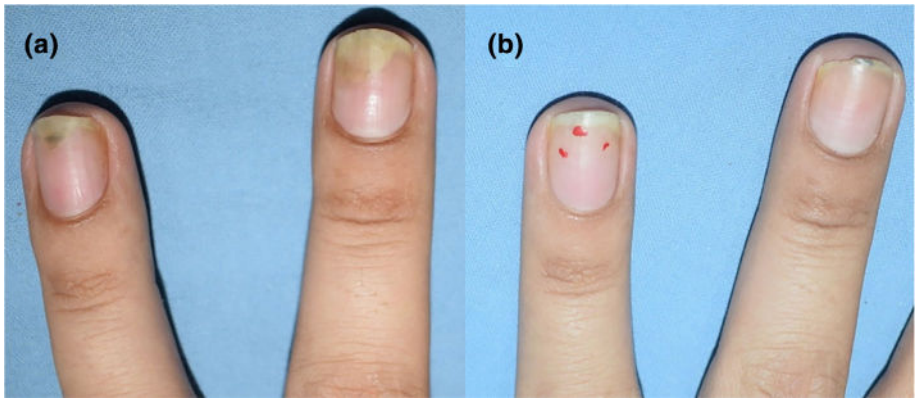

FIGURE 3 "A case of DLSO" (a) Photographs of left middle and ring fingernails with mild DLSO. (b) 3 months after treatment with topical tioconazole alone, showed a significant clinical response (patient from Group C)

TABLE 2 Comparison of KOH results between treatment groups before and after treatment

	Group A (Combined treatment)		Group B (Fractional CO_2 laser treatment)		Group C (Topical antifungal treatment)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
KOH						
Negative	0 (0.0)	32 (80.0)	0 (0.0)	24 (60.0)	0 (0.0)	22 (55.0)
Positive	40 (100.0)	8 (20.0)	40 (100.0)	16 (40.0)	40 (100.0)	18 (45.0)
MC Nemar test *p* =	<.001**		<.001**		.001**	

Abbreviations: *p*, probability; *Statistically significant if $p < .05$; **High statistically significant if $p < .01$.

KOH test was turned negative in 80% of patients in Group A versus 60% of patients in Group B versus 55% of patients in Group C (*p*-value = .001) (Table 2).

There was a statistically significant difference between the three studied groups as regard culture result before and after treatment (with and without cycloheximide) (*p*-value <0.001), whereas the culture without cycloheximide turned negative by 70% of patients in Group A, 50% of patients in Group B, and 30% of patients in Group C, while the culture with cycloheximide turned negative by 90% of patients in Group A, 90% of patients in Group B, and 90% of patients in Group C (Table 3).

Our study reported that there were five factors that could influence the treatment outcome: sex of patients, duration of the disease, clinical type of onychomycosis, involved nails (fingernails or toenails), and degree of severity of onychomycosis. The clinical outcome was significantly higher in female patients, with duration of the disease less than 1 year, in nails with a clinical type of DLSO, and more in fingernails and with mild to moderate degree of severity.

There were statistically significant correlations between the clinical response and type of onychomycosis (*p*-value = .002) and degree of severity (*p*-value = .024) in Group A. There were statistically significant correlations between the clinical response and type of nails

TABLE 3 Comparison of culture without and with cycloheximide between treatment groups before and after treatment

	Group A (Combined treatment) *N* = 40 *n* (%)		Group B (Fractional CO_2 laser treatment) *N* = 40 *n* (%)		Group C (Topical antifungal treatment) *N* = 40 *n* (%)	
Culture	**Pretreatment**	**Posttreatment**	**Pretreatment**	**Posttreatment**	**Pretreatment**	**Posttreatment**
With cycloheximide						
Positive	40 (100.0)	12 (30.0)	38 (95.0)	20 (50.0)	40 (100.0)	28 (70.0)
Negative	0 (0.0)	28 (70.0)	2 (5.0)	20 (50.0)	0 (0.0)	12 (30.0)
MC Nemar test *p* =	<.001**		.001**		.03*	
With cycloheximide						
Positive	40 (100.0)	4 (10.0)	32 (80.0)	4 (10.0)	38 (95.0)	6 (15.0)
Negative	0 (0.0)	36 (90.0)	8 (20.0)	36 (90.0)	2 (5.0)	34 (85.0)
MC Nemar test *p* =	<.001**		<.001**		<.001**	

Abbreviations: *p*, probability; *Statistically significant if $p < .05$; **high statistically significant if $p < .01$.

affected (fingernails or toenails) (*p*-value = .013), degree of severity (*p*-value = 0.014), and duration of the disease (*p*-value = 0.03) in Group B. There were statistically significant correlations between the clinical response and sex of patients (*p*-value = .03) and degree of severity (*p*-value = .009) in all the studied groups in Group C.

3 | DISCUSSION

Antifungal drugs have been the mainstay of therapy for many years; however, it is limited by low efficacy because of subtherapeutic concentrations reaching the nail bed. Laser or light systems that have been tried for onychomycosis include CO_2 laser, ND-YAG laser, diode, and photodynamic therapy.

In our study, onychomycosis was found to be more common in females representing 71.7% versus males who represent 28.3% of cases, similar results were reported by many studies such as Zhou et al. (2016), Shi et al. (2017)), and (Afshar, Khodavaisy, Kalhori, Ghasemi, & Razavyoon (2014). This can be attributed to the fact that females do household wet work like laundry and house cleaning with repeated trauma to the nails facilitating easy entry of fungal pathogens. Females also are more concerned about the cosmetic appearance of their nails.

In the present study, fingernails were more affected than toenails (70 vs. 30%, respectively), which might be because hands (fingernails) are more prone to trauma. Moreover, fingernail infection can harm the patient's life and disfigurement in nails can affect their self-esteem, thereby compelling them to report to a doctor early. This finding is in agreement with many studies that showed that fingernail onychomycosis is more common than toenail onychomycosis (Kaur, Kashy, & Makkar, 2008; Neupane, Pokhrel, & Pokhrel, 2009). In contrast, other studies show that toenail onychomycosis is more common than fingernail onychomycosis (Haneke, 1991; Perea et al., 2000). The low incidence of toenail onychomycosis in our study may be attributed to the use of open footwear and lesser concern for the appearance of the feet and toenails.

In this work, the commonest clinical type was DLSO; seen in 90 patients (75%) followed by TDO in 22 patients (18.3%). The same findings were detected in the study of Bhatta, Keyal, Huang, & Zhao (2016) who reported that DLSO was found in 36 patients (48%) followed by TDO in 27 (36%).

Our study showed that yeast (31%) was the commonest fungal species causing onychomycosis in all studied groups followed by NDM (28.5%), dermatophytes were detected in (22%) and trichosporon species infection detected in 18.5% of cases. A similar result had been reported in India by Wajid, Khaleel, & Begum Amirunnisa (2016) who reported that Candida species was the most common isolates in 65 patients (43.3%) followed by NDM. Similar results were reported in a study from Egypt by Abd El-Aal, Abdo, Ibrahim, & Eldestawy (2019) who revealed that the commonest isolated fungi were yeast infection by 37% followed by NDMs infection by 22.5% and trichosporon species infection by 18% and dermatophyte infection was only detected in 10%. In contrast, other studies showed that the most common fungal isolate was dermatophyte (mainly *Trichophyton rubrum*) followed by yeast (mainly *Candida albicans*) (Kaur et al., 2008; Matos & Mariano, 2010). Overall, the predominance of causative agents varies depending on ethnicity and different environmental factors such as climate, humidity, occupation, and different lifestyles and upon geographical location and temporal distribution.

Our study showed that combined treatment was effective to treat onychomycosis with complete clinical response found in 22 patients (55%). Combined therapy had a higher efficacy than fractional CO_2 laser treatment alone or topical antifungal whereas complete clinical response observed in 12 patients (30%) in Group B (fractional CO_2 alone) and 10 patients (25%) in Group C (topical tioconazole 28% solution alone). However, there were no significant differences in the clinical efficacy rates in the groups treated with fractional CO_2 laser only and/or tioconazole 28% solution alone. Similar results were found by Zhou et al. (2016) who reported that fractional CO_2 laser combined with luliconazole 1% cream was effective to treat infected nails and had a higher efficacy than fractional CO_2 laser treatment

alone. Zhang et al. (2016) reported that the combination therapy with the fractional 2,940-nm Er:YAG laser and amorolfine showed a much better effect than the use of amorolfine alone.

Regarding the patient satisfaction, it was concordant with the clinical results and was documented as the patients were very much satisfied with the combination fractional CO_2 laser with topical antifungal therapy (60%; 24 patients) more than other modalities. The percentage of very much satisfied patients in this study for the combination therapy was similar to that of Lim et al. (2014) (59%; 14 patients), Bhatta et al. (2016) (66.67%; 50 patients), while slightly higher than Zhou et al. (2016) (41.4%; 21 patients).

In the current study, KOH test showed negative mycological results in 80% of patients (32 out of 40), also negative culture results were found in 36 (90%), and in 28 patients (70%) by culture (with and without cycloheximide) in Group A. This coincides with Bhatta et al. (2016) who used a total of three sessions of fractional CO_2 laser combined with topical terbinafine cream to treat 75 patients. There were about 71 patients (94.66%) with a negative KOH result and 69 patients (92%) with negative culture after 3 months of treatment (Bhatta et al., 2016).

Our study reported that Group B who received fractional CO_2 laser as monotherapy showed negative mycological results, as the KOH test was negative in 60% of patients with negative culture results in 36 (90%) and 20 patients (50%) by culture (with and without cycloheximide). Our finding was similar to those of Zhou et al. (2016) who reported mycological clearance using fungal microscopy (KOH only), after 3 months of treatment in the CO_2 laser group, was 42 nails (38.9%). So, fractional CO_2 laser as a monotherapy can improve nail with onychomycosis due to the ablative and thermal effect of the microthermal zones induced by fractional CO_2 laser. There were not any reported side effects or intolerable pain during laser sessions in the current study.

Also, in this work, Group C who treated with topical tioconazole solution 28% alone as monotherapy, showed negative mycological results, as KOH test was negative in 55% of patients with negative culture in 34 (85%) and 12 patients (30%) by culture (with and without cycloheximide). This finding is higher than those of Hay, Mackie, & Clayton (1985) who investigated the efficacy of topical tioconazole 28% solution for onychomycosis in 27 patients, resulted in negative direct microscopy in 22% of patients. Antifungal drugs as monotherapy for onychomycosis have been effective treatment with minimum interactions and adverse effects compared to systemic antifungal therapy.

3.1 | Limitations

The length of follow up is only 16 weeks in this study.

4 | CONCLUSIONS

Fractional CO_2 laser combined with topical antifungal is a safe and effective treatment for onychomycosis, and its efficacy is superior to fractional CO_2 laser treatment alone or topical antifungal alone.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Shady Mahmoud Ibrahim https://orcid.org/0000-0001-7616-267X

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