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ORIGINAL ARTICLE

Fractional carbon dioxide laser and topical tioconazole in the treatment of fingernail onychomycosis

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Abstract

Onychomycosis is a common chronic-resistant nail disease. Traditional treatment has its limitations and side effects. This study aimed to evaluate the role of fractional CO_2 laser and topical tioconazole 28% nail lacquer in the treatment of fingernail onychomycosis, as sole treatment modalities and in combination. Thirty patients with culture-proven onychomycosis were included and randomly divided into three equal groups. Laser group received six fractional carbon dioxide (CO_2) laser sessions at monthly intervals; topical group received topical tioconazole 28% nail lacquer twice daily for 6 months, and combined group received six fractional CO_2 laser sessions at monthly intervals with topical tioconazole twice daily for 6 months. Treatment outcome was evaluated through physician's evaluation of improvement using onychomycosis severity index score (OSI), patients' satisfaction, side effect evaluation, and mycological culture (assessed after the end of treatment). At the end of treatment, both laser and combined groups showed significantly better degrees of improvement ($P = 0.036$, 0.024, respectively) and patient's satisfaction ($P = 0.046$, 0.003, respectively) in comparison with topical group. Mycological clearance in fungal cultures was significantly higher in combined group than topical group after the end of treatment ($P = 0.007$). Fractional CO_2 laser is a safe and effective treatment modality for onychomycosis. Its efficacy approximates that of fractional CO_2 laser combined with topical tioconazole 28% nail lacquer and surpasses that of topical tioconazole 28% monotherapy. It is expected to be an excellent choice for patients in whom systemic antifungals are contraindicated or who are unresponsive or intolerant to topical antifungals.

Keywords Fractional Co_2 laser · Onychomycosis · Tioconazole · Topical

Introduction

Onychomycosis is a chronic nail infection caused by dermatophytes, yeasts, and non-dermatophyte molds [1]. It has several risk factors such as trauma, nail psoriasis, aging, diabetes, immunodeficiency, and genetic predisposition to infection [2].

Onychomycosis can be classified into distal lateral subungual onychomycosis (DLSO), superficial onychomycosis, proximal subungual onychomycosis (PSO), endonyx onychomycosis, and total dystrophic onychomycosis (TDO). This classification was extended by Hay and Baran to include mixed and secondary forms of infection [3].

The current therapeutic options for onychomycosis include topical antifungals with longer treatment duration and poor efficacy, oral antifungals with relatively good efficacy, but potential serious side effects restricting its usage, nail avulsion and debridement, iontophoresis, and ultrasound, in addition to laser therapy [4, 5]. Laser therapy for onychomycosis is a new safe and effective treatment modality in which fungal eradication might be mediated through disruption of fungi and spores by the thermal effect of laser pulses [6–8]. Various laser systems have been tried for onychomycosis including carbon dioxide (CO_2) and Nd:YAG lasers [9, 10], in addition to photodynamic [11] and ultraviolet light therapies [12].

This work aimed to evaluate the efficacy of fractional CO_2 laser and tioconazole 28% nail lacquer for the treatment of fingernail onychomycosis as sole treatment modalities and in combination.

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Patients and methods

Thirty adult patients [26 females (86.6%) and 4 males (13.3%)] with fingernail onychomycosis with a mean age of 35 years ± 9.15 (SD) were included. Patients who received systemic or topical antifungal therapy within the preceding 6 weeks and those with other fingernail conditions causing morphological changes or discoloration of the nails were excluded. In addition, diabetic patients, patients with immunocompromising diseases or therapies, pregnant females, nursing mothers, and those with unrealistic expectations were also excluded. All included patients signed a written informed consent before the start of the study, and the study protocol was approved by the institutional review board of the ethical committee of Faculty of Medicine, Tanta University.

Onychomycosis was diagnosed clinically, and diagnosis was confirmed by nail scrapping and direct microscopy using 30% potassium hydroxide (KOH) in addition to culture on Sabouraud dextrose agar medium containing chloramphenicol with and without cycloheximide. Culture plates were then examined both macroscopically and microscopically. They were kept for a minimum of 2 weeks when absence of growth was interpreted as negative. Only those affected nails that were positive for both KOH and culture were included in the study.

Grading of onychomycosis severity was done according to onychomycosis severity index (OSI) where 0 = no onychomycosis, 1–5 = mild onychomycosis, 6–15 = moderate onychomycosis, and 16–35 = severe onychomycosis [13].

Patients were randomly divided into three equal groups: Laser group received six monthly sessions of fractional CO_2 10.600-nm laser (SmartXide DOT®, Deka, Italy), with fluencies in the range of 11–15 W, spacing of 500 μm, dwell time of 500 μs, and stack ranging from 1 to 3. The laser beam was applied in one to three passes to the entire nail plate and the surrounding nail fold. A topical anesthetic cream, 2.5% lidocaine and 2.5% prilocaine (EMLA cream®, AstraZeneca AB, Södertälje, Sweden), was applied 30–60 min before the session. Topical group received topical tioconazole (Fungibacid® 28% nail lacquer, DBK Pharma, Mash Premiere, Egypt) twice daily for 6 months. Combined group received six monthly sessions of fractional CO_2 laser (in the same parameters used in the laser group), combined with topical tioconazole 28% nail lacquer twice daily for 6 months.

Treatment evaluation

Physician's evaluation of treatment Monthly examination and digital photographing of the affected nails were done over a period of 9 months (6 months of treatment and three additional months of follow-up). OSI score of each patient was the mean of the scores given for all the affected nails in this patient. The difference between OSI score at baseline and at the end of the treatment (1 month after the 6 months of therapy) was calculated, and its percentage to baseline OSI was used to assess treatment efficacy. The difference between OSI score at baseline and that after 9 months from study initiation was calculated, and its percentage to baseline OSI was used for evaluation at follow-up. The results were translated as the following: 0–25% change in OSI score = no improvement, 26–50% = mild improvement, 51–75% = moderate improvement, and 76–100% = marked improvement.

Patients' satisfaction By the end of the sixth month of treatment, each patient evaluated his/her satisfaction about treatment outcomes giving a number from 0 to 3 where 0 = not satisfied, 1 = mildly satisfied, 2 = moderately satisfied, and 3 = very satisfied [14].

Evaluation of the side effects and complications of therapy Patients of both laser and combined groups evaluated the level of pain after each laser session on a five-point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = intolerable pain). Other side effects such as oozing or bacterial infections were also reported. Patients using topical nail lacquer were asked to report any side effects of topical tioconazole such as itching, erythema, contact dermatitis, or swelling.

Laboratory evaluation Fungal cultures were repeated 1 month after the end of treatment for detection of mycological clearance.

Statistical analysis

Data were analyzed using IBM SPSS software package version 20 (Armonk, NY, IBM Corp.). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, and standard deviation. Chi-squared test was used to compare the three groups according to categorical variables. ANOVA was used to compare the three groups according to normally distributed quantitative variables, while Kruskal-Wallis test was used for abnormally distributed quantitative variables and post hoc (Dunn's multiple comparisons test) for pairwise comparisons. Friedman test was used for abnormally distributed quantitative variables, to compare between the three groups at different periods or stages. Significance of the obtained results (P value) was judged at the 5% level.

Results

Baseline characteristics

The duration of onychomycosis in included patients ranged from 9 to 72 months with a mean of 30.4 ± 17.3 (SD). The study included a total of 69 onychomycotic nails (range between single to six affected nails per patient). Of patients, 76.67% had DLSO, 13.33% had PSO, and 10% had TDO. The OSI score before treatment ranged from 4 to 35. Cultures done at baseline were all positive for dermatophytes. The baseline clinical and laboratory data of included patients are summarized in Table 1.

Clinical efficacy

Table 2 shows the median values of OSI scores of patients of the three studied groups at baseline, at the end of treatment (1 month after the six months of treatment), and at follow-up after nine months of study initiation. Only patients of laser and combined groups showed a significant decrease in their OSI scores at the end of treatment in comparison with baseline ($P < 0.001$). At the end of treatment, the mean improvement in the percentage of OSI score in laser group was 61.7 ± 38.1 (SD), while in topical group, it was 26.7 ± 25.6% (SD), and in combined group, it was 64.9 ± 34.5% (SD) (Table 1). Both laser and combined groups showed significantly better degrees of improvement than topical group ($P = 0.036$, 0.024, respectively), while there was no significant difference between laser and combined groups ($P = 0.879$) (Table 1).

After the additional 3 months of follow-up, the mean improvement in the percentage of OSI score in laser group was 67.55 ± 38.89 (SD), while in topical group, it was 25.15 ± 20.52 (SD), and in combined group, it was 74.9 ± 36.49 (SD). Both laser and combined groups were still showing significantly better degrees of improvement than topical group ($P = 0.018$, 0.006, respectively), while there was no significant difference between laser and combined groups ($P = 0.699$) (Table 1). Figures 1, 2, and 3 demonstrate the clinical results of some patients of the three studied groups.

Both laser and combined groups showed significantly better patients' satisfaction than topical group ($P = 0.046$, 0.003, respectively) while there was no significant difference between laser and combined groups.

A statistically significant better incidence of mycological cure in culture was detected in the combined group than the topical group, while the difference between the laser and combined groups was statistically insignificant.

Table 3 summarizes the side effects reported by onychomycosis patients of the three studied groups. Most of the reported side effects where transient, minimal, and did not affect the patient compliance to continue treatment protocols.

Discussion

Laser efficacy for treatment of onychomycosis is still a matter of debate, and reports about the applicability of fractional CO_2 laser for onychomycosis treatment are still sparse. In the current study, topical group showed a mean improvement of OSI score of only 26.7 ± 25.6%. Actually, none of the patients showed clinical cure or even marked improvement either at the end of treatment or after 3 months of follow-up. Mycological clearance in fungal culture was detected in only 20% of patients at the end of treatment. This low efficacy of topical antifungal monotherapy is expected and has been previously attributed to the low penetration of the lacquer to the nail plate. It should be noted, however, that even cases with mild DSO did not benefit so much from the use of topical tioconazole 28% as a sole treatment in our study. The poor patient compliance to the twice daily lacquer application and to the strict avoidance of excessive water use might be the cause.

Hay et al. [15] also investigated the efficacy of topical tioconazole 28% solution on 27 patients with onychomycosis for up to 12 months. They achieved cure (defined as a completely normal nail and negative direct microscopy) in only 22% of patients. Other studies evaluating monotherapy of other topical antifungals for onychomycosis also showed disappointing results except in very mild cases [16–18].

Lim et al. [9] studied the efficacy of fractional CO_2 laser (three sessions at 4-week interval) combined with a topical amorolfine cream once daily to treat 24 patients with onychomycosis. They reported that 71% of patients got fully or more than 60% normal-appearing nails. All patients with fully normal-appearing nails (50%) had a negative fungal microscopic result. Another trial was done by Bhatta et al. [19] using a total of three sessions of fractional CO_2 laser at 4-week interval combined with once-daily application of terbinafine cream to treat 75 onychomycosis patients. In their study, 73.32% of patients had fully or more than 60% normal-appearing nails after 3 months from the last treatment, 94.66% had negative fungal microscopy, and 92% had negative culture. The patients who did not show mycologic cure were mostly those who had *Candida albicans* grown in the culture. They attributed their results to the poor efficacy of terbinafine against *Candida*. Zhou et al. [20] included 60 patients into two groups: laser only group who received 12 sessions of fractional CO_2 laser treatment at 2-week intervals and combined group who received 12 sessions of laser treatment at 2-week intervals combined with luliconazole 1% cream once daily.

Table 1 Baseline clinical and laboratory characteristics of onychomycosis patients of the three studied groups and their post-treatment and follow-up results

Patient characteristics	Laser group (n = 10)	Topical group (n = 10)	Combined group (n = 10)	Statistical test	P value
Age (years), mean ± SD	37 ± 8.69	35 ± 9.15	35.9 ± 8.71	ANOVA; 0.13	0.88
Disease duration (month), mean ± SD	31.9 ± 21.87	32.9 ± 21.52	28 ± 15.49	Kruskal-Wallis test; 0.034	0.983
Number of affected fingers, mean ± SD	2.3 ± 1.42	2.1 ± 1.45	1.7 ± 1.16	Kruskal-Wallis test; 4.44	0.109
Clinical types of onychomycosis, n (%)				Chi-squared test; 1.19	0.64
DLSO	7 (70%)	8 (80%)	8 (80%)		
PSO	2 (20%)	1 (10%)	1 (10%)		
TDO	1 (10%)	1 (10%)	1 (10%)		
OSI scores before treatment, mean ± SD	21 ± 3.43	22.7 ± 4.99	21.7 ± 7.07	ANOVA; 0.63	0.73
Percentage of improvement in OSI score at the end of treatment[a], range (mean ± SD)	5–100% (61.73 ± 38.11)	0–80% (26.68 ± 25.55)	0–100% (64.88 ± 34.49)	Kruskal-Wallis test; 6.3	0.042
Significance between group	$P1$ = 0.036, $P2$ = 0.879, $P3$ = 0.024				
Percentage of improvement in OSI score after 3 months of follow-up[b], range (mean ± SD)	0–100% (67.55 ± 38.89)	0–50% (25.15 ± 20.52)	0–100% (74.9 ± 36.49)	Kruskal-Wallis test; 8.85	0.012
Significance between groups	$P1$ = 0.018, $P2$ = 0.699, $P3$ = 0.006				
Degree of improvement at the end of treatment, n (%)				Chi-squared test; 11.5	0.043
No (0–25%)	2 (20)	6 (60)	2 (20)		
Mild (26–50%)	1 (10)	3 (30)	1 (10)		
Moderate (51–75%)	1 (10)	1 (10)	2 (20)		
Marked (76–100%)	6 (60)	0	5 (50)		
Significance between groups	P 1 = 0.014, P 2 = 1.000, $P3$ = 0.034				
Degree of improvement after 3 months of follow-up, n (%)				Chi-squared test;17.5	0.001
No (0–25%)	2 (20)	4 (40)	2 (20)		
Mild (26–50%)	1 (10)	6 (60)	0		
Moderate (51–75%)	1 (10)	0	1 (10)		
Marked (76–100%)	6 (60)	0	7 (70)		
Significance between groups	$P1$ = 0.007, $P2$ = 1, $P3$ < 0.001				
Degree of patients' satisfaction[a], n (%)				Chi-squared test; 13.46	0.014
Not satisfied	1 (10)	2 (20)	0.		
Mildly satisfied	1 (10)	5 (50)	1 (10)		
Moderately satisfied	3 (30)	3 (30)	2 (20)		
Very satisfied	5 (50)	0	7 (70)		
Significance between groups	$P1$ = 0.046, $P2$ = 0.79, $P3$ = 0.003				
Fungal cultures after the end of treatment[a], n (%)				Chi-squared test; 7.3	0.037
Negative	6 (60)	2 (20)	8 (80)		
Positive	4 (40)	8 (80)	2 (20)		
Significance between groups	$P1$ = 0.17, $P2$ = 0.628, $P3$ = 0.007				

P: significance between the three groups, $P1$: comparing between laser and topical groups, $P2$: comparing between laser and combined groups, $P3$: comparing between topical and combined groups

OSI onychomycosis severity index score

[a] Assessment 1 month after the six months of treatment

[b] Assessment after 9 months from study initiation for follow-up

Table 2 Onychomycosis severity index score of the three groups before treatment, at the end of treatment, and at follow-up

Onychomycosis severity index score	Before treatment	At the end of treatment (assessment 1 month after the 6 months of treatment)	Assessments after 9 months of study initiation for follow-up	*P*
Laser group (n = 10)				
Min.–max.	18–25	0–19	0–20	< 0.001
Median	20	5	3.5	
Significance between periods	$P1$ = 0.007, $P2$ < 0.001, $P3$ = 0.314			
Topical group (n = 10)				
Min.–max.	16–35	10–28	10–35	0.014
Median	21.5	18.88	17.5	
Combined group (n = 10)				
Min.–max.	17–25	0–25	0–25	< 0.001
Median	25	5.25	3.2	
Significance between periods	$P1$ = 0.01, $P2$ = 0.001, $P3$ = 0.371			

P: P value for Friedman test; significance between different times of evaluation in each group was done using post hoc test (Dunn's multiple comparisons test), *P*1: comparing between OSI score before and at the end of treatment, *P*2: comparing between OSI score before treatment and after 3 months of follow-up, *P*3: comparing between OSI score at the end of treatment and after 3 months of follow-up

OSI onychomycosis severity index score

Combined group showed significantly higher clinical efficacy rate (69.6% vs 50.9%) and mycological clearance rate defined as negative fungal microscopy (57.4% vs 38.9) compared with laser group. Shi et al. [14] treated 30 patients with 12 sessions of fractional CO_2 laser at 2-week intervals combined with terbinafine cream once daily for 6 months. They assessed the clinical efficacy rate from the percentage of fully normal-appearing nails or nails with ≤ 5% abnormal appearance, while the mycological clearance rate was assessed from the percentage of nails with negative fungal microscopy. The clinical efficacy rate was 58.9% at the end of treatment, 63.5% after 1 month of the last treatment, and 68.5% after 3 months from the last treatment. The mycological clearance rate was 77.4% at 1 month and 74.2% at 3 months after the last treatment. In the current study, the combined therapy was given for a period of 6 months, which was equal to Zhou et al. [20] and Shi et al. [14] and twice longer than those in the study of Lim et al. [9] and Bhatta et al. [19]. Similar to their studies, the current study found that fractional CO_2 laser combined with topical tioconazole 28% nail lacquer was effective for treating onychomycosis; with a significant decrease in the mean OSI score at the end of treatment and at the third month of follow-up than before treatment. Marked clinical improvement was achieved in 50% of the patients at the end of treatment, and the efficacy increased to 70% at follow-up. Negative results in fungal cultures were found in 80% of patients at the end of treatment. Abd El-Aal et al. [21] randomly assigned 102 onychomycosis patients into groups A and B, and both groups were treated with four sessions of fractional CO_2 laser and followed by topical tazarotene 0.1% in group A and topical tioconazole 28% in group B. One month after the last session, 35.3% showed complete improvement in group A versus 33.3% in group B without significant difference. The longer treatment period in our study (six sessions at monthly interval fractional CO_2 sessions) might explain the better results we obtained and might recommend longer treatment protocols with laser therapy in hope to achieve cure.

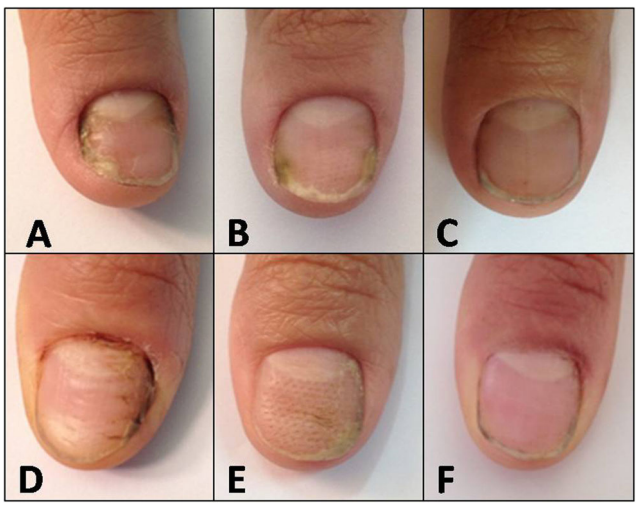

Fig. 1 Clinical results of onychomycosis patients treated by six sessions of fractional carbon dioxide laser at monthly intervals. **A, D** Before treatment. **B, E** One month after the last session. **C, F** At follow-up (3 months after the sixth laser session) with marked improvement (> 75%)

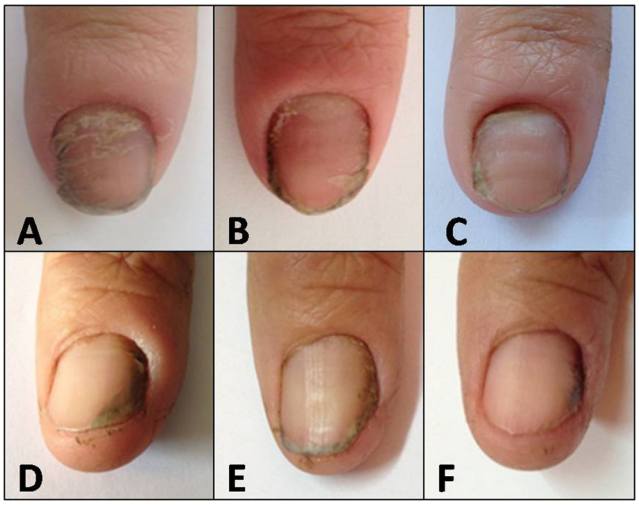

Fig. 2 Clinical results of onychomycosis patients treated by topical tioconazole 28% lacquer twice daily for 6 months. **A, D** Before treatment. **B, E** At the end of the sixth month of treatment. **C, F** At follow-up—after 3 months of the end of treatment with mild improvement (26–50%)

In the current study, laser group also showed a significant decrease in the mean OSI score at the end of treatment and after 3 months of follow-up than before treatment ($P < 0.001$). Marked clinical improvement was detected in 60% of patients both at the end of treatment and after 3 months of follow-up. Mycological clearance in fungal cultures was found in 60% of patients at the end of treatment. The results of the current study were consistent with those found by Yang et al. [22] who used eight sessions of fractional CO_2 laser monotherapy within 3 months. OSI score was 21.11 ± 11.94, 13.63 ± 12.1, and 13.7 ± 13.93 at baseline, at the end of treatment, and 3 months after completion of treatment, respectively. They showed a clinical efficacy of 52.11% and mycological clearance rate according to direct microscopy and fungal culture of 57.75% at the end of treatment and 61.97% at 3 months after completion of treatment, suggesting that fractional CO_2 laser treatment alone is effective to treat onychomycosis. It should be noted that laser monotherapy has an advantage of avoiding the exhausting topical application of nail treatment at home for long months and therefore improving the patient's compliance to therapy.

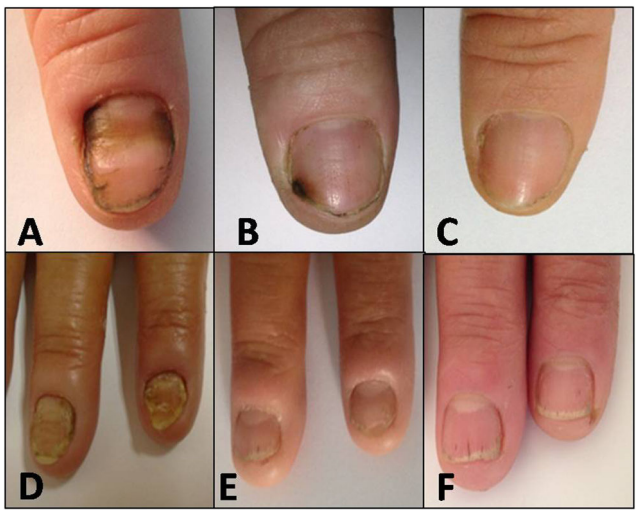

Fig. 3 Clinical results of onychomycosis patients treated by six sessions of fractional carbon dioxide laser sessions at monthly intervals plus topical tioconazole 28% lacquer twice daily for 6 months. **A, D** Before treatment. **B, E** One month after the last session. **C, F** At follow-up (3 months after the sixth laser session) with marked improvement (> 75%)

Comparing between laser and combined groups in the current study regarding clinical improvement and mycological cure revealed no significant difference between both groups. This suggests that fractional CO_2 alone may be effective in the treatment of onychomycosis. On the contrary, Zhou et al. [20] found that fractional CO_2 laser treatment combined with topical treatment had a significantly better efficacy than fractional CO_2 laser treatment alone.

In the current study, laser therapy was well tolerated by the patients. Severe pain was only reported by 10% of patients, 55% reported moderate pain, and 35% reported mild pain. Other studies involving fractional CO_2 for treatment of onychomycosis reported that only some patients experienced mild pain during laser treatment [9, 14, 19, 20]. This discrepancy may be related to the difference in parameters used.

It is generally believed that the mechanism by which fractional CO_2 laser treats onychomycosis is mainly through its photothermal effect which increases the temperature of local tissue, thus killing the fungi in the laser-treated affected nail [23]. Additionally, fractional CO_2 laser makes the local tissue of affected nail vaporize and exfoliate, causing diffuse remodeling and at the same time destroys the fungal growth environment, thus contributing in fungal growth inhibition [24]. Furthermore, fractional CO_2 laser can enhance the absorption of topical antifungal agents through the hard densely keratinized nail plate, thereby improving their penetration and efficacy [25]. These facts could explain the significantly better mycological cure results of the combined group in the present study in comparison with the topical group.

Further prospective studies on larger population of onychomycosis patients and with longer periods of follow-up are recommended. Comparing the effectiveness of fractional CO_2 laser with other types of lasers in the treatment of onychomycosis and testing the effectiveness of fractional CO_2 laser in combination with other more potent topical antifungals is also recommended. In addition, further research is needed to evaluate the ideal parameters of laser sessions, the number of sessions needed, and the adequate interval between sessions.

Table 3 Side effects reported by onychomycosis patients of the three studied groups

Side effects	Laser group ($n = 10$)	Topical group ($n = 10$)	Combined group ($n = 10$)
Pain, *n* (%)			
Severe	1 (1%)		1 (1%)
Moderate	5 (50%)	–	6 (60%)
Mild	4 (40%)		3 (30%)
Bleeding	–	–	–
Oozing	–	–	–
Bacterial infection	1 (10%)	–	1 (10%)
Contact dermatitis	–	3 (30%)	2 (20%)
Itching	–	1 (10%)	1 (10%)
Erythema	–	–	–
Nail fold swelling	1 (10%)	3 (30%)	2 (20%)

Conclusion

In conclusion, the current study revealed that fractional CO_2 laser is safe and effective for treatment of onychomycosis. Its efficacy approximates that of fractional CO_2 laser combined with tioconazole 28% nail lacquer and surpasses that of topical tioconazole 28% monotherapy. Fractional CO_2 laser is expected to be an excellent choice for patients in whom systemic antifungals are contraindicated.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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