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Fractional CO_2 Laser Plus Topical Tioconazole 28% versus Topical Tioconazole 28% Alone in the Treatment of Onychomycosis

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ABSTRACT

Background: Onychomycosis is a chronic fungal infection of the nail unit. The therapeutic options include oral antifungals as terbinafine, pulse itraconazole, fluconazole and voriconazole. Various laser systems have been tried for resistant cases to improve the results of treatment as carbon dioxide (CO_2) and Nd:YAG lasers.

Objective: Compare between two treatment methods; combined therapy of fractional CO_2 laser (FCO_2L) plus topical tioconazole 28% nail solution versus topical tioconazole 28% nail solution alone in the same patient with fingernails onychomycosis. **Methods:** This was prospective comparative interventional study conducted on 20 patients with two or more affected fingernails. The degree of affection of the studied nails was assessed clinically by onychomycosis severity index (OSI) and was confirmed by KOH and mycological culture. The studied nails were categorized into two corresponding groups; group (A), fingernails were treated with combined therapy in the form of 4-6 fractional CO_2 laser sessions four weeks apart plus topical tioconazole 28% twice daily for six months, group (B), fingernails were treated with topical tioconazole 28% alone twice daily for six months. **Results:** A high statistically significant improvement was reported among patients treated with combined therapy than those who treated with antifungal only. The CO_2 laser plus topical tioconazole solution yielded significantly higher percentage of improvement for onychomycosis.

Conclusion: Both combined therapy and local therapy reported safe and promising outcomes. However combined therapy was associated with better improvement and local therapy was associated with minimal adverse events.

Keywords: Onychomycosis, Distal lateral subungual onychomycosis, Superficial onychomycosis, Proximal subungual onychomycosis, FCO_2L, Topical tioconazole 28%.

INTRODUCTION

Onychomycosis is a chronic fungal infection of the nails [(1)]. Numerous predisposing factors such as traumas, psoriasis, old age, immunodeficiency disorders, and genetic constitution may predispose to such condition [(2)]. It could be classified into distal lateral subungual onychomycosis (DLSO), white superficial onychomycosis (WSO) proximal subungual onychomycosis (PSO), endonyx onychomycosis, and total dystrophic onychomycosis (TDO). In addition, mixed and secondary forms of infection are included to this classification [(3)]. The currently used treatment modalities for onychomycosis comprise; oral antifungal agents with comparatively good efficiency, but serious adverse events; topical antifungals that needs long duration with nail avulsion, debridement and iontophoresis; ultrasound, and finally laser therapy [(3)].

Laser-assisted drug delivery (LADD) treatment has been considered as novel safe and efficient modality in the context of onychomycosis management where fungal eradication may be mediated via disturbance of fungi and spores by the thermal action of laser therapy[(4)]. Different laser approaches are tried for cases of resistant onychomycosis with variable results including CO_2 and Nd:YAG lasers[(5,6)]. This study was conducted to compare between two methods of treatment in the same patient with fingernails onychomycosis; the first was the fractional CO_2 laser (FCO_2L) plus topical tioconazole 28% nail solution and the second was only topical tioconazole 28% solution.

PATIENT AND METHODS

This was a prospective comparative interventional study conducted on 20 cases attending Mansoura University Hospital Outpatient Clinic of Dermatology at the period between March 2021 to March 2022.

Patients were of either sex, aged between 18-65 years with two or more affected fingernails onychomycosis of any type, which was diagnosed clinically. Excluded individuals were pregnant, lactating, having any other nail diseases, receiving immunosuppressive; systemic or topical antifungals during previous three months, systemic diseases, chemotherapy, radiotherapy and organ transplantation.

Entire cases were subjected to history taking; clinical examination to determine the extent and clinical type of onychomycosis (DLSO, PSO, WSO and TDO). Severity and degree of affection of nails were assessed by onychomycosis severity index and score clinical index of onychomycosis.

Onychomycosis severity index (OSI):

- **Area of affection (A)**:(0-5); +1 for < 10%, +2 for 11–25% + 3 for 26–50%, +4 for 51–75%, and +5 for > 75% involvement.
- **Proximity of disease to the nail matrix (P):** where nail is divided in a transverse manner into five equal partsand a numeric value of one to five with one given to the quadrant involving the free edge .
- **Subungual hyperkeratosis (SAH):** thickness of > 2 mm or dermatophytomas (10 points).

Nail assessement was equal to (A×P) +10 (SAH) and reported **mild** if ≤5**, moderate** 6–15, and **severe** if ≥16[(7)].

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Score Clinical Index of Onychomycosis (SCIO): dependeds on growth component that include age and location of infection, and clinical component of affected nails, which include clinical form of onychomycosis (f), depth of nail involvement (d) and degree of hyperkeratosis (h). Such values are after that substituted into the equation $[(d/3)3\text{-}f\ (f + h\ (3 - f))]^{1-[(2-f)(3-f)/2]}$. **(8)**. By utilizing the previous equaltion in WSO, PSO and DLSO the values are one, three, and between one and five, correspondingly. It was calculated for all patients individually by SCIO available at http://www.onychoindex.com

Samples collection and processing:

Fifty nail samples were collected from twenty patients with fingernails onychomycosis after cleaning the infected nails with 70% ethyl alcohol to remove any debris, bacteria or ointments. Standard mycological tests were conducted using potassium hydroxide preparation (KOH 20%), and after that all samples were cultured on 2 plates of Sabouraud's dextrose agar (SDA), with and without cyclohexamide.

The studied nails were categorized into two corresponding groups; group A:25 nails; treated with topical tioconazole 28% twice daily for six months combined with a 4-6 monthly fractional CO_2 laser sessions; group B:25 nails; received topical tioconazole 28% nail solution alone every 12 hours for six months (Trade name: Fungibacide nail solution, DBK Pharma, Mash premiere, Egypt).

Laser sessions:

Performed using fractional CO_2 laser (DEKA SmartXide DOT, Italy) with the following parameters: Power10–15 W (based on nail thickness), H-Pulse shape, duration500 µs, spacing 700–800 µm, stack three. The laser beam was applied to the whole nail plate and adjacentnail fold 30 minutes after topical application of lidocaine 2% gel.

Clinical evaluation:

Done monthly by two independent observers, digital photographing for six months of treatment and three months of follow up, assessed by OSI and mycological assesment, graded into; **complete** response (normal-appearing nail > 90%, smooth and shiny nail plate), **excellent** (75-90% normal appearing nail), **good** (40-75% normal-appearing nail), **mild** (normal-appearing nail < 40%) and **no** response. Satisfaction assessment were reported as very satisfied, satisfied, slightly satisfied, or unsatisfied and any associated side effects were reported**(9)**.

Ethical approval: The study was accepted by the Institutional Review Board, Mansoura Faculty of Medicine, Code number: MS.20.02.1050. A detailed description of the study's objectives was given to each participant before they completed an informed written consent form. The Helsinki Declaration was adhered to at every stage of the investigation.

Statistical analysis

Data analysis was conducted by SPSS software (Inc., PASW statistics for windows version 25. Chicago, USA). Qualitative data were defined using number and percent and were compared by Chi-Square test. Quantitative data were defined using median and range for non-normally distributed data, which were comapred by Mann Whitney U test and Wilcoxon signed rank test, and using mean±SD for normally distributed data following assessing normality using Shapiro Wilk test. In the context of all the previously ustilized test, p was considred significant when its values was less than 0.05.

RESULTS

The study included twenty patients with finger nail onychomycosis [18 females (90%) and 2 males (10%)] with ages ranged from 18-65 years (mean 33.3± 10.8). The housewives represented the most common group (85%). The socio-demographic characters of the studied cases in the enrolled patients are shown in table 1.

Table (1): Socio-demographic Characters of the Studied Cases

Variables		**Studied patients (N = 20)**	
Sex	**Male**	2	10%
	Female	18	90%
Occupation	**Housewife**	17	85%
	Carpenter	1	5%
	Secretory	1	5%
	Driver	1	5%
Exposure	**Water**	7	35%
	Water and detergents	13	65%
Residence	**Rural**	15	75%
	Urban	5	25%
Family history	**Absent**	14	70%
	Present	6	30%
Smoking	**Absent**	18	90%
	Present	2	10%

The most ferquently affected finger were the thumbs followed by middle and ring fingernails. Also, the most prevelant clinical type was DLSO, followed by PSO , and the least common was TDO (Table 2).

Table (2): Distribution of The Affected Fingernailand Clinical Type of Onchomycosis among Both Groups:

Variables		**Studied patients (N = 20)**	
Affected finger (N = 50)	Little finger	6	12%
	Ring finger	11	22%
	Middle finger	11	22%
	Index finger	6	12%
	Thumb	16	32%
Clinical type (N = 50)	PSO	10	20%
	TDO	5	10%
	DLSO	35	70%

DLSO: Distolateral Subungual Onychomycosis, **PSO**: Proximal Subungual Onychomycosis, **TDO:** Total Dystrophic Onychomycosis

There was highly statistically significant decrease in OSI and SCIO in group A and in group B three months following the course of treatment. Group A showed more decrease in both OSI and SCIO than group B (Table 3).

Table (3): Comparison of Degree of Severity among Studied Groups

	Group A before ttt (N=25)	**Group A after ttt (N=25)**	**GroupB before ttt (N=25)**	**Group B After ttt (N=25)**	**P1**	**P2**	**P3**	**P4**
OSI Severity								
No	0	15(60%)	0	6 (24%)				
Mild	0	8 (32%)	0	15 (60%)	0.088	<0.001*	<0.001*	0.036 *
Moderate	17 (68%)	2 (8%)	22 (88%)	4 (16%)				
Severe	8 (32%)	0 (0%)	3 (12%)	0 (0%)				
Median	10 (8-18)	0 (0-3.5)	10 (8-15)	3 (1-4)	0.188	<0.001*	<0.001*	0.032 *
SCIO Severity								
No	0 (0%)	15(60%)	0 (0%)	6 (23%)				
Mild	3 (12%)	8(32%)	4(36%)	15 (60%)	0.788	<0.001*	<0.001*	0.036*
Moderate	20 (80%)	2(8%)	20 (70%)	4 (16%)				
Severe	2 (8%)	0(0%)	1(0%)	0 (0%)				
Median	6.7 (6.7-11.6)	0 (0-3.3)	6.7 (6.7-10.8	1.3 (0.65-5.1)	0.476	<0.001*	<0.001*	0.030*

*: Statistically significant, SCIO: Score Clinical Index of Onychomycosis, **OSI**: onychomycosis severity index

P1: test of significance before treatment between group A and B/ **P2**:test of significance before and after treatment in group A, **P3**:test of significance before and after treatment in group B, **P4**:test of significance after treatment between group A and B

Group A was associated with a significant increase in improvement compared to group B (Table 4).

Table (4): Comparison of Clinical Improvement among the Studied Groups

Improvement	**Group A N=25(%)**	**Group B N=25(%)**	**p value**
Complete	11 (44%)	3 (12%)	
Excellent	9 (36%)	6 (24%)	
Good	4 (16%)	10 (40%)	0.022 *
Mild	1 (4%)	5 (20%)	
No	0 (0%)	1 (4%)	

*: Statistically significant

The mycological cultures were positive in 100% of both groups before treatment. Regarding the type of the fungus, non-dermatophyte molds (NDMs) were the commonest and accounted for 56%, in which the Aspergillus niger was 36%, Aspergillus fumigatus 16% and Alternaria 4%, followed by Candida species (36%) and finally the dermatophytes were accounted for 8% (Table 5). After three monthes of treatment, the cultures turned negative in 92% in group A (23/25) and 68% in group B (17/25) with significant differences in both groups. Group A shows more decrease in the fungal infection than group B after treatment (Table 5).

Table (5): Comparison of Mycological Culture Results before and after Treatment among Both Groups

	Group A before ttt	**Group A after ttt**	**GroupB before ttt**	**Group B After ttt**	**P1**	**P2**	**P3**
NDM							
Asp fumigatus	4 (16%)	0 (0%)	4 (16%)	2 (8%)			
Asp Niger	9 (36%)	1 (4%)	9 (36%)	4 (16%)			
Alternaria	1 (4%)	0 (0%)	1 (4%)	0 (0%)	< 0.001*	< 0.001*	0.034*
Yeasts							
C. albicans	6 (24%)	1 (4%)	6 (24%)	2 (8%)			
C. krusei	3 (12%)	0 (0%)	3 (12%)	0 (0%)			
Dermatophytes							
Trichophyton	2 (8%)	0 (0%)	2 (8%)	0 (0%)			

P1: test of significance before and after treatment in group A/ **P2:** test of significance before and after treatment in group B/ **P3**: test of significance after treatment between group A and B

Clinical and mycology cultures result photos before and after treatment in both groups:

CASE (1)

Group A: Combined Group

(A1) (A2) (A3)

Figure (1): A1: Affected fingernail before treatment; DLSO, **A2**: Complete improvement for the affected fingernail after treatment, **A3**: Mycology culture was positive from the affected fingernail before treatment for *Aspergillus fumigatus* isolate and no growth observed after treatment.

Group B: Topical Group

(B1) (B2) (B3) (B4)

Figure (2): B1: Affected fingernail before treatment; PSO, B**2**: Good response for the affected fingernail after treatment, **B3**: Mycology culture was positive from the affected fingernail before treatment mainly for *Aspergillus fumigatus* isolate, **B4:** Mycology culture was positive from the affected fingernail after treatment for mainly *Aspergillus niger*.

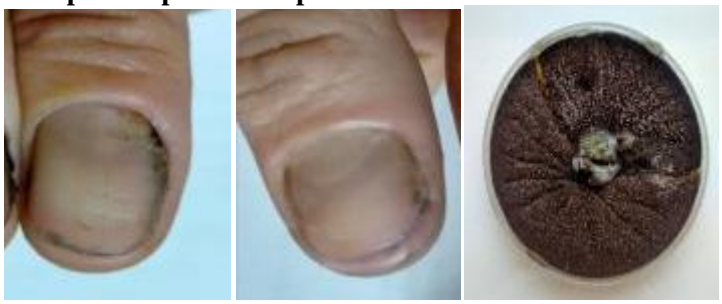
CASE (2)

Group A: Combined Group

(A1) (A2) (A3)

Figure (3): A1: Affected fingernail before treatment; DLSO, **A2**: Excellent response for the affected fingernail after treatment, **A3**: Mycology culture was positive from the affected fingernail before treatment for *Aspergillus Niger* isolate and no growth observed after treatment.

Group B: Topical Group

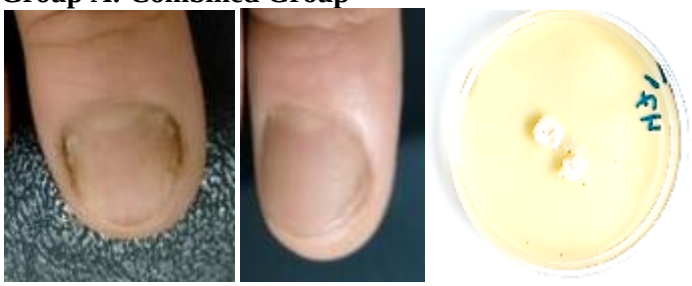


(B1) (B2) (B3)

Figure (4): B1: Affected fingernail before treatment; DLSO, B**2**: Good response for the affected fingernail after treatment, **B3**: Mycology culture was positive from the affected fingernail before treatment for *Aspergillus Niger* isolate and no growth observed after treatment.

CASE (3)

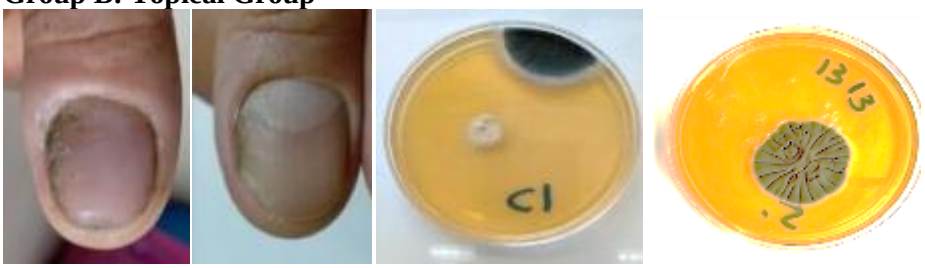
Group A: Combined Group



(A1) (A2) (A3)

Figure (5): A1: Affected fingernail before treatment; DLSO, **A2**: Complete improvement for the affected fingernail after treatment, **A3**: Mycology culture was positive from the affected fingernail before treatment for Trichophyton isolate and no growth observed after treatment.

Group B: Topical Group



(B1) (B2) (B3) (B4)

Figure (6): B1: Affected fingernail before treatment; DLSO, B**2**: Good response for the affected fingernail after treatment, **B3**: Mycology culture was positive from the affected fingernail before treatment for Trichophyton isolate, **B4:** Mycology culture was positive from the affected fingernail after treatment for *Aspergillus fumigatus*.

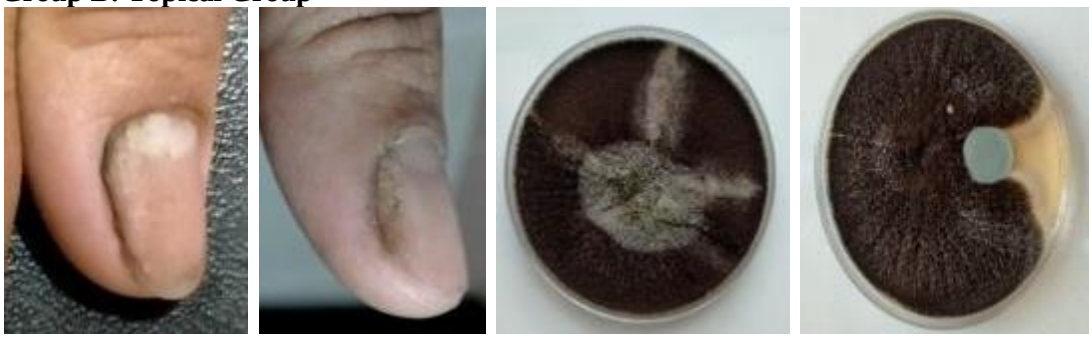
CASE (4)

Group A: Combined Group

(A1) (A2) (A3)

Figure (7): A1: Affected fingernail before treatment; DLSO, **A2**: Good response for the affected fingernail after treatment, **A3**: Mycology culture was positive from the affected fingernail before treatment for *Aspergillus niger* isolate and no growth observed after treatment.

Group B: Topical Group



(B1) (B2) (B3) (B4)

Figure (8): B1: Affected fingernail before treatment; DLSO, B**2**: Good response for the affected fingernail after treatment, **B3**: Mycology culture was positive from the affected fingernail before treatment for *Aspergillus niger* isolate, **B4**: Mycology culture was positive from the affected fingernail after treatment for *Aspergillus niger*.

DISCUSSION

Onychomycosis is a common nail disorder that has social, psychological and cosmetic effects [10]. This study included 20 patients with two or more affected fingernails onychomycosis diagnosed clinically and confirmed by KOH examination and mycological culture. They were enrolled to compare the efficacy and safety of FCO_2L plus topical tioconazole 28% nail solution vs topical tioconazole 28% nail solution alone in the same patient.

In the current study there was predominance in female (90%), housewives (85%); rural areas (75%), and prolonged exposure to water and detergent was found in (65%) patients. Likewise, **Zaki *et al.*[11]** have reported that the prevalence of onychomycosis was observed to be higher in females (71.7%) compared to males (28.3%); other researches also revealed comparable findings[9,12].

Increase the physical activities, traumas, maceration, carbohydrate-rich diet, the habit of working, and exposure to soil saprophytes could probably be the explanation for the increased prevalence of housewives in rural areas.

The current study demonstrated that DLSO (70%) was the most frequent type followed by PSO (20%) and finally TDO (10%). Nearly, Brazilian study done by **Raujo *et al.*[13]** showed that DLSO (62.5%) was the most prevalent clinical type followed by 20.8% with PSO infection and 12.5% with TDO. Similarly, **El-Tatawy *et al.*[14],** found that DLSO (70%) was the most prevalent type then PSO (20%) and TDO (10%). The studies of **Bhatta *et al.*[15] and Zhou *et al.*[16]** revealed that DLSO was reported in 36 cases (48%) followed by TDO in 27 (36%). **Zaki *et al.*[11]**, in Cairo, found that DLSO was the most frequent form in their studied cases (75%), followed by TDO (18.3%), then PSO (3.3%), and lastly WSO**.**

In the present study, OSI was calculated before treatment and the median value was 10 (8-18) and 10 (8-15) in group A and B respectively without significant difference. After the end of treatment by three months, median value of OSI score in group A was 0 (0-3.5) versus 3 (1-4) in group B. There was a highly statistically significant improvement (P <0.001) and decreased OSI in both groups, that was more in group A than group B. In the same line, **Zhou *et al.*[16]** found a baseline OSI of (18.0 ± 11.5) in fractional CO_2 group and (16.6 ± 10.6) in itraconazole group. After six months of treatment, significant decrease in the OSI score was demonstrated in the two groups; higher in the FCO_2L group (8.65±7.09) in comparison with the itraconazole group (7.36±6.65). Likewise, **El-Tatawy *et al.*[14]** found after the course of therapy, laser and combined laser with topical tioconazole groups revealed a significant improvement in OSI score (P=0.036, 0.024, correspondingly) in comparison with the topical tioconazole group (P= 0.879). **Abdelhamid *et al.*[17]** compared OSI score in his study of topical tazarotene 0.1% gel vs topical tioconazole 28% solution and found that median range was 8 (4-14) and decreased to 6 (2-10) in tazarotene group with statistically difference between before and after treatment, while in tioconazole group, the median range was 12 (8-20) base line and 12(0-12) after treatment with statistically difference in between. After treatment, there was no statistically significant difference between the two groups.

In the present study the SCIO was also measured at the beginning of the study with median 6.7 (6.7-11.6) in group A and 6.7 (6.7-10.8) in group B. Three months after the end of treatment, SCIO median range decreased to 0 (0-3.3) in group A and 1.3 (0.65-5.15) in group B. There was highly significant decrease of SCIO measurements in both groups (P<0.001) more in group A than group B.

Similarly, **Al-Meligi *et al.*[18]** calculated base line SCIO with median range 8.0, which decreased to 6.1 after 3 months of treatment with CO_2 laser combined with topical tioconazole sessions. SCIO measurements were significantly different before and after treatment (P=0.001*). **Chau *et al.*[19]** reported baseline mean SCIO of 7.5 that decreased to 2.4 at the end of combined CO_2 laser and topical clotrimazole treatment. For itraconazole plus topical clotrimazole treated patients, the initial mean SCIO value was 5.9 and decreased to 3.9 at the last visit. They have demonstrated that such reductions in the FCO_2L-treated group was significantly increased compared to the itraconazole-treated group (p<0.001*). **Kartik *et al.* [20]** compared SCIO scoring base line after completion of 6 months of FCO_2L assisted topical antifungal drugs therapy and topical antifungal alone in onychomycosis treatment. The mean SCOI score in combined group at baseline was 5.74±1.95, which diminished to 4.59±2.08 with statistically significant difference, while in topical antifungal group was 4.06±1.92 at baseline, which after intervention decreased to 3.79±1.90 with statistically significant difference. Comparing the result before and after therapy, the mean difference in SCOI was 1.16±0.87 and 0.27±0.13 respectively. Hence mean reduction in SCOI score was more in combined group as compared to topical group with statistically significant difference.

Concerning clinical improvement, the current study displayed that; group A was associated with statistically significant improvement compared to group B (p-value =0.02). Group A showed complete response in 44% and 12% in group B, excellent response was 36%, 24%, good response was 16%, 40%, mild response was 4%, 20% and no response was 0%, 4% in group A and B, correspondingly. In addition to disrupting the fungal development environment and vaporizing and exfoliating the local nail tissue, the FCO_2L also contributes to the suppression of fungal growth. Moreover, FCO_2L may increase the penetration and effectiveness of topical antifungal medications by facilitating their absorption through the tough, highly keratinized nail plate [21,22].

This agreed with **Lim *et al.*[5]** who evaluated the efficiency of FCO_2L (three sessions at 4-week interval) combined with a topical amorolfine once daily as a treatment for 24 cases with onychomycosis. They recorded that 92% of cases got normal-appearing nails. Similarly **Zhang *et al.*[12]** recorded that the combined therapy with the fractional 2,940-nm Er: YAG laser and amorolfine revealed a significant improvement compared to amorolfine only. Also, **Bhatta *et al.*[15]**, in their study of FCO_2L at 4-week interval combined with a topical terbinafine cream, 73.32% of cases had fully or more than 60% normal-appearing nails following three months from the last treatment. In the same line, **Zhou *et al.*[16]** recorded that FCO_2L combined with luliconazole 1% cream was effective to treat infected nails and had a higher efficacy than FCO_2L treatment alone.

Also, **Shi *et al.*[9]** have displayed that the clinical efficacy rate of FCO_2L at 2-week intervals combined with terbinafine cream once daily for six months was 58.9% at the end of therapy, 63.5% after four weeks of the last treatment, and 68.5% after three months from the last therapy. In the same line, **Šveikauskaitė *et al.*[23]** used FCO_2L therapy in association with a topical amorolfine cream to efficiently treat onychomycosis of nails, with 50% of cases demonstrating a full response. **Abd El-Aal *et al.*[24]** conducted their study on two groups; group A treated with four sessions of FCO_2L and followed by topical tazarotene 0.1% and group B treated with topical tioconazole 28% alone. They have demonstrated that one month after the last session, in the context of clinical response, 35.3% revealed complete improvement in Group A vs 33.3% in Group B with no significant difference (P>0.05). Similarly, **El-Tatawy *et al.*[14]** in their study showed that marked improvement was 70% and moderate improvement was 10% in combined CO_2 laser plus topical tioconazole 28% group while in topical tioconazole group, moderate improvement was detected in 10% and no improvement in 20% of the patients. In parallel, **Zaki *et al.*[11]** displayed that; one month after the last FCO_2L sitting, as regards clinical response, 55% revealed complete improvement in combined CO_2 laser and topical tioconazole group versus 25% in topical tioconazole alone with a significant difference in between.

All the enrolled fingernails in this study were selected after confirmation by positive mycological culture before treatment in both groups. Non-dermatophyte molds (NDMs) were the commonest and accounted for 56%, in which the Aspergillus niger was36%, Aspergillus fumigatus 16% and Alternaria 4%, followed by Candida species (36%) and finally the dermatophytes were accounted for 8%.

These results coincide with **Borah *et al.*[25]**, who found NDMs, yeasts, and dermatophytes accounted for 47.5%, 33.8%, and 18.8%, respectively. Similarly, **Thomas *et al.*[26]** reported that 45.4% of fungal isolates were NDMS, followed by yeast-like fungi (34.6%) and dermatophytes (20%), and mentioned that Aspergillus species were the commonest NDMS isolates. In Cairo, **Abdelhamid *et al.*[17]**, reported that Aspergillus niger represented 51.4% of cases, followed by Candida albicans in 15.7%, Aspergillus flavus in 4.7% and **Ahmed *et al.*[27]** found that the most common fungal isolates were NDMs (30%), especially Aspergillus species, followed by dermatophytes (18%) and yeasts (10%).

On the other hand, in India, **Wajid *et al.*[28]** recorded that Candida spp has been considered the most frequent isolates followed by NDM. In Egypt, **Abd El-Aal *et al.*[24]** displayed that the most frequent isolated fungi were yeast infection (37%) then NDMs (22.5%) and dermatophyte infection was only detected in 10%. Also, **Zaki *et al.*[11]**, found that the most frequent isolated fungi were yeasts by 31%, followed by non-dermatophytes molds 28.5%, and dermatophyte infection by 22%.

The discrepancy between reports and increasing the NDMs isolation from onychomycosis, may be due to increasing life expectancy from chronic sickness, a rise in the number of immunocompromised individuals, and humidity that disrupts the balance of normal flora and compromises physical barriers to infection, making hosts more vulnerable to saprophytes as well as pathogenic fungi [29].

In the current study, mycological cultures after treatment by three months were negative in 92% and 68% in group A and group B, correspondingly. There was a statistically significant decrease in fungal infection among both groups, which was more in group A than group B (P< 0.03).

In accordance to some extent, **Bhatta *et al.*[15]** found that 95% had negative fungal microscopic results, and 92% had negative culture three months after the end of FCO_2L sessions combined with topical terbinafine cream. **Shi *et al.*[9]** found that mycological clearance rate was 77.4% at one month and 74.2% at three months after the end of FCO_2L combined with topical terbinafine. In the same line, **Abd El-Aal *et al.*[24]** have recorded a significant difference between both studied groups in terms of KOH film and the culture results before and after treatment, they become negative in 92% and 100% of patients in fractional CO_2 laser plus tazarotene group and 78% and 96% of patients in topical tioconazole group, respectively (p value<0.001).

Likewise, **El-Tatawy*et al.*[14]** demonstrated that; a significant incidence of mycological culture result was determined in the combined CO_2 laser with topical tioconazole group than the topical tioconazole group. **Šveikauskaitė *et al.*[23]** reported negative mycological examinations within three months after fractional CO_2 laser combined with topical amorolfine group. In accordance, **Zaki *et al.*[11]** have demonstrated that; there was a statistically significant differences as regard culture results before and after treatment by combined CO_2 laser plus topical tioconazole group, and patients in topical tioconazole group (p-value <0.001). In contrast, **Chau *et al.*[19],** reported that direct microscopy was

negative in (79.1%) in itraconazole plus topical clotrimazole group compared to (73.3%) in the CO_2 laser with topical clotrimazole laser group at the end of the treatment period without statistically significant difference. The discrepancy in results may be attributed to antiseptic techniques in sample collection, discrepancy in the antifungal drug used, patient compliance to the treatment or the strict avoidance of excessive water exposure.

Regarding adverse effects, the current study demonstrated that group A was associated with pain found in 16% while erythema was observed in 8% in group B. Additional studies comprising fractional CO_2 in the context of onychomycosis treatment recorded that fewer cases developed mild pain during laser therapy[15,16]. Likewise, **El-Tatawy *et al.*[14]** have displayed that combined therapy was associated with pain of various degrees (one case was severe, 6 moderate and 3 mild), while topical agent only was associated with no pain at all.

Regarding patient satisfaction in this study, 90% of group A were very satisfied vs 50% in group B. Low percentages were reported by **Zaki *et al.*[11]**, in combined group versus topical group 60%, and 30%, respectively.

CONCLUSION

Both combined therapy and local therapy reported safe and promising outcomes. However combined therapy was associated with better improvement and local therapy was associated with minimal adverse events. On the other hand, further large-scale and well-designed RCTs have to be conducted.

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