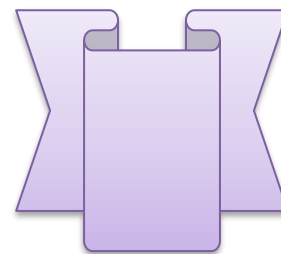
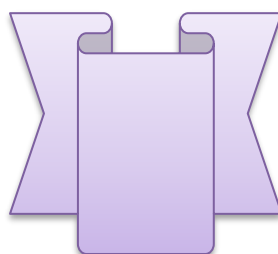
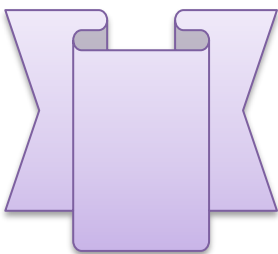
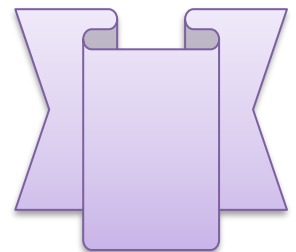
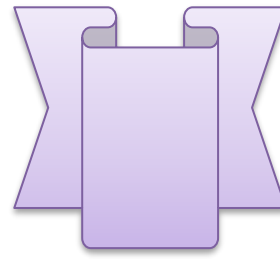
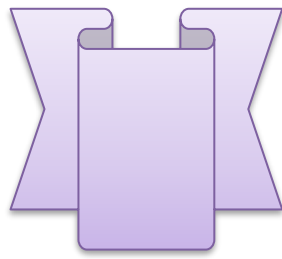
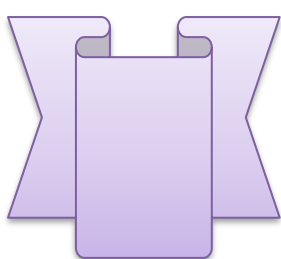
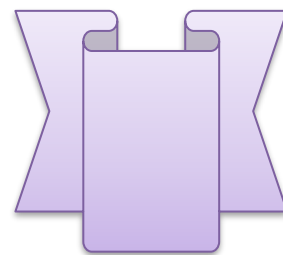
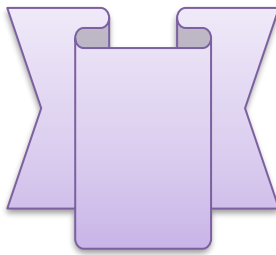
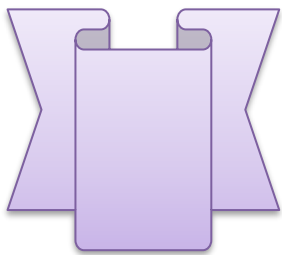


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Original Article

Diode 577-nm Laser Plus Tioconazole 28% Nail Solution versus Topical Tioconazole 28% Nail Solution Alone in Treatment of Onychomycosis

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ABSTRACT

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Background: Onychomycosis affecting 5.5% of the population worldwide which may be treated by medical antifungal therapy or laser therapy which is attractive to avoid side effects, prevent developing of microbial resistance and safe with no mutagenic or cytotoxic effect.

Aim of the Work: To evaluate the efficacy and safety of diode 577-nm laser in the treatment of onychomycosis.

Patients and Methods: This study involved 30 onychomycosis patients with 87 affected nails, everyone had two affected sites [finger nails/toe nails] then randomly allocated into two groups: group [A] in which one site was treated by diode laser [577-nm] plus Tioconazole 28% [Fungibacid 28% nail solution] nail solution while in group [B] the other site in the same patient was treated by Tioconazole 28% nail solution only. We assessed the improvement by Onychomycosis Severity Index [OSI], culture and patient satisfaction.

Results: The OSI severity in Diode 577-nm + Tioconazole group decreased from 36.7% before treatment to 20% after 3 months and continue to decrease after 6 months to 3.3%. However, in Tioconazole only group, the severity still the same as before treatment 36.7% after 3 months while after 6 months decreased to 20%. There was a significant difference between patients with severe OSI score while no significant difference between patients with mild and moderate OSI score among both groups at the end of follow up. There were 2 [6.7%] patients after 3 months and 18 [60%] patients after 6 months have complete resolution in Diode 577-nm + Tioconazole group while in Tioconazole only group, no one has complete resolution after 3 months but after 6 months there were 11 [36.7%] patients have complete resolution with significant difference between both groups at 3 and 6 months [$p < 0.001$ & 0.046].

Conclusion: The 577-nm diode yellow laser is an effective and safe option for the treatment of onychomycosis.

Keywords: Onychomycosis; Diode 577-nm Laser; Tioconazole



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INTRODUCTION

Onychomycosis is fungal infection of the nail unit caused by [dermatophytes, non-dermatophyte molds, and yeasts], presenting with discoloration of the nail, onycholysis, and nail plate thickening, and may also affect the adjacent skin. It is a common condition affecting 5.5% of the population worldwide and represents 20-40% of all onychopathies and about 30% of cutaneous mycotic infections [1]. The diagnosis is generally suspected based on clinical features and confirmed by laboratory testing. The four main tests are: potassium hydroxide [KOH] smear, culture, histologically by periodic acid Schiff [PAS] stain, polymerase chain reaction [PCR] [2].

Onychomycosis may be treated by medical therapy as topical and systemic antifungal agents which associated with treatment failures, need for long-term therapy, high rates of recurrence, significant costs and side effect of systemic therapy, surgical treatment as nail debridement and nail avulsion or photodynamic therapy [PDT] [3].

Laser therapy are attractive to avoid side effects, prevent developing of microbial resistance, safe with no mutagenic or cytotoxic effect. Diode laser which is a special type of semiconductor device that converts electrical energy to laser light [4].

Antifungal mechanism of diode laser is based on the principles of photo modulation. Following exposure of tissue to light from diode laser, the target chromophore appears to be the cytochrome C oxidase in the mitochondrial respiratory chain. Consequently, there is an increase in the production of mitochondrial products, such as ATP, NADH, and RNA, and increased cellular respiration. When stimulated with this laser, production of reactive oxygen species, such as hydroxyl radicals [highly reactive molecule that easily damage tissue] and increased fungicidal capacity against fungi [5]. We aimed to evaluate the efficacy and safety of diode 577-nm laser in the treatment of onychomycosis.

PATIENTS AND METHODS

This is a prospective comparative study conducted at Dermatology department, Al-Azhar university hospital, Assiut during the period from August 2019 to December 2021. The study protocol was approved by the ethics committee of the Medical Faculty, Al-Azhar University, Assiut.

The study was carried out on patients who visited our clinic with nail lesions who were suspected as onychomycosis by clinical assessment. Onychomycosis is diagnosed by one or more of 4 main signs: nail thickening, discoloration [white, black, yellow or green] onycholysis and paronychia [6]. This study involved 30 onychomycosis patients with 87 affected nails, everyone had two affected sites [finger nails/toe nails] then randomly allocated into two groups: group [A] in which one site was treated by diode laser [577-nm] plus Tioconazole 28% [Fungibacid 28% nail solution, Mash, Permiere, Egypt] nail solution while in group [B] the other site in the same patient was treated by Tioconazole 28% nail solution only.

Patients with porphyria and hypersensitivity to porphyrin, coagulation disorder or current use of anti-coagulation medication, diabetic neuropathy or peripheral vascular, oral antifungal within 6 month or topicals within 1 month, using immunocompromising diseases, pregnancy, and breastfeeding were excluded. Diode laser [577-nm]: A 577-nanometer diode yellow laser [QuadroStar PRO YELLOW® Asclepion Laser Technologies, Germany] was applied. The spot mode of 1 mm was used. Application was started with a fluence of 18 J/cm², the fluence was increased by 2 J/cm² up to 22 J/cm², pulse duration ranged from 30 to 32 ms and frequency of 1sec. Six laser sessions with interval one month in between were applied.

We assessed improvement of clinical appearance of the nails using the Onychomycosis Severity Index [OSI] [7]. Also, we evaluated the mycological cure by culture samples which taken from all patients at the last session. Patient satisfaction according to treatment satisfaction scale of OnyCOE-t [Questionnaire] patient classified as very satisfied, satisfied, poorly] and adverse effects also recorded. The collected data was analyzed by Statistical package for Social Science [IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.]. The Mean and standard deviation [mean ± SD] were used to describe the parametric numerical data. P value < 0.05 was considered significant.

RESULTS

This study involved 30 patients with onychomycosis. Their age ranged from 18 to 45 years with mean ±SD of 29.67± 9.09 years. The majority of cases were females [90%]. The most

causative fungi were non-dermatophyte molds [NDMs] representing 66.7% of studied cases followed by *Candida albicans* [13.3%], *Trichophyton rubrum* in 6.7% cases and mixed [*Candida albicans*+ NDMs] in 13.3% cases. Distal lateral subungual onychomycosis was observed in most patients [73.3%], total dystrophic onychomycosis was found in 6.7% cases, Proximal subungual onychomycosis in 16.7% and black superficial onychomycosis in 3.3% of cases. Finger nails was the most frequent site affected [66.7%] followed by Toe nails in 33.3%. Mean of duration of the disease was 15.76 ± 5.75 month [Table 1].

Regarding mean of OSI, Tioconazole only group has a nonsignificant higher index [12.53 ± 11.57] than Diode 577-nm + Tioconazole group [9.13 ± 8.90] after 3 months of treatment. However, after 6 months of treatment, Tioconazole only group has a significant higher index [6.70 ± 6.35] than Diode 577-nm + Tioconazole group [4.0 ± 4.58] [$p=0.012$]. There was a significant difference between mean of OSI score among both groups at the end of follow up [$p=0.021$] [Table 2].

The OSI severity in Diode 577-nm + Tioconazole group decreased from 36.7% before treatment to 20% after 3 months and continue to decrease after 6 months to 3.3%. However, in

Tioconazole only group, the severity still the same as before treatment 36.7% while after 6 months decreased to 20%. There was a significant difference between patients with severe OSI score while no significant difference between patients with mild and moderate OSI score among both groups at the end of follow up [Table 3].

Regarding resolution in Diode 577-nm + Tioconazole group, there were 2 [6.7%] patients after 3 months and 18 [60%] patients after 6 months have complete resolution while in Tioconazole only group, no one has complete resolution after 3 months but after 6 months there were 11 [36.7%] patients have complete resolution with significant difference between both groups at 3 and 6 months [$p < 0.001$ & 0.046] [Figure 1].

Regarding culture after end of all sessions, Tioconazole only group has higher significant positive results [$p=0.039$] with a significant difference in both groups between pre and posttreatment cultures [$p < 0.001$] [Table 4].

According to satisfaction score, the double therapy of Diode 577-nm + tioconazole had significant improvement results and subsequently more patient satisfaction compared to using tioconazole only [$p < 0.001$] [Figure 2].

Table [1]: Mycological and clinical characteristics of Onychomycosis patients

Parameters		Studied patients [n= 30]	
Culture [n, %]	NDMs	20	66.7%
	<i>Candida albicans</i>	4	13.3%
	<i>Trichophyton rubrum</i>	2	6.7%
	Mixed	4	13.3%
Lesion [n, %]	DLSO	22	73.3%
	TDO	2	6.7%
	PSO	5	16.7%
	PSO & BSO	1	3.3%
Site [n, %]	Toe nails	10	33.3%
	Finger nails	20	66.7%
Duration of the disease [month] [n, %]	Mean± SD	15.76 ±5.75	
	Range	6 – 24	

NDMs: Non-dermatophyte molds, DLSO: Distal lateral subungual onychomycosis, TDO: Total dystrophic onychomycosis, PSO: Proximal subungual onychomycosis, BSO: black superficial onychomycosis

Table [2]: Difference in mean of OSI between Group and Group B before and after end of all sessions in onychomycosis patients

OSI	Group A			P value	Group B			P value
	Pre ttt.	3 Months	6 Months		Pre ttt.	3 Months	6 Months	
Mean±SD	14.70 ±12.46	9.13± 8.90	4.0± 4.58	P1=0.051 P2<0.001*	13.78 ±12.22	12.53± 11.57	7.70± 6.35	P1=0.686 P2=0.019*
Median	15.0	2.0	1.0	P3=0.007*	12.0	4.0	3.5	P3=0.048*
Range	3 -35	1 – 30	1– 16		2 -35	2 – 35	1– 18	
P4 value	0.012*							

P1: Comparison between OSI score before ttt. and after 3 months posttreatment, P2: comparison between OSI score before ttt. and after 6 months posttreatment, P3: comparison between OSI score after 3 months and 6 months posttreatment, P4: comparison between both groups after 6 months posttreatment, SD= standard deviation, *p value was significant

Table [3]: Difference in OSI between group A and group B before and after end of all sessions in onychomycosis patients

OSI	Group A				Group B			P value
	Pre	3 M. Post	6 M. Post		Pre	3 M. Post	6 M. Post	
Mild	14 [46.7%]	14 [46.7%]	2 [6.7%]	P1=1.000 P2< 0.001 * P3< 0.001 *	15 [50%]	15 [50%]	6 [20%]	P1=1.000 P2= 0.016 * P3= 0.016 *
Moderate	5 [16.7%]	8 [26.7%]	9 [30%]	P1=0.3518 P2=0.227 P3=0.779	4 [13.3%]	4 [13.3%]	7 [23.3%]	P1=1.000 P2=0.321 P3=0.321
Severe	11 [36.7%]	6 [20%]	1 [3.3%]	P1=0.155 P2= 0.001 * P3= 0.045 *	11 [36.7%]	11 [36.7%]	6 [20%]	P1=1.000 P2=0.156 P3=0.156
P value	P4=0.133 [Mild]; P5=0.561 [Moderate]; P6= 0.046 * [Severe]							

Table [4]: Comparison between group A and group B according to culture before and after end of all sessions in onychomycosis patients

Culture	Group A		Group B		p- value*
	Negative	Positive	Negative	Positive	
Pre	0 [0%]	30 [100%]	0 [0%]	30 [100%]	0.039 *
Post	18 [60%]	12 [40%]	11 [33.3%]	19 [66.7%]	
P1 value	< 0.001 *		< 0.001 *		

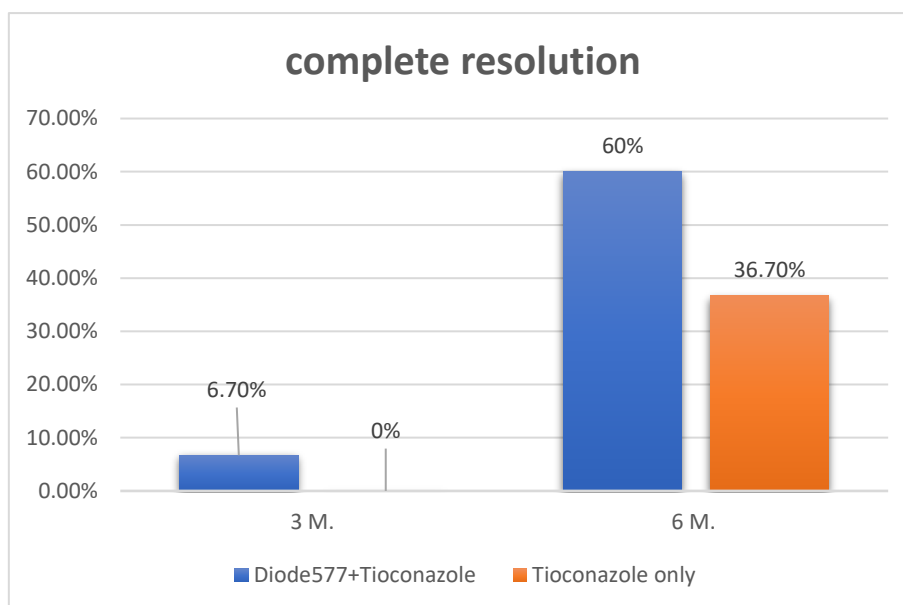


Figure [1]: Comparison between groups regarding complete resolution at end of all sessions

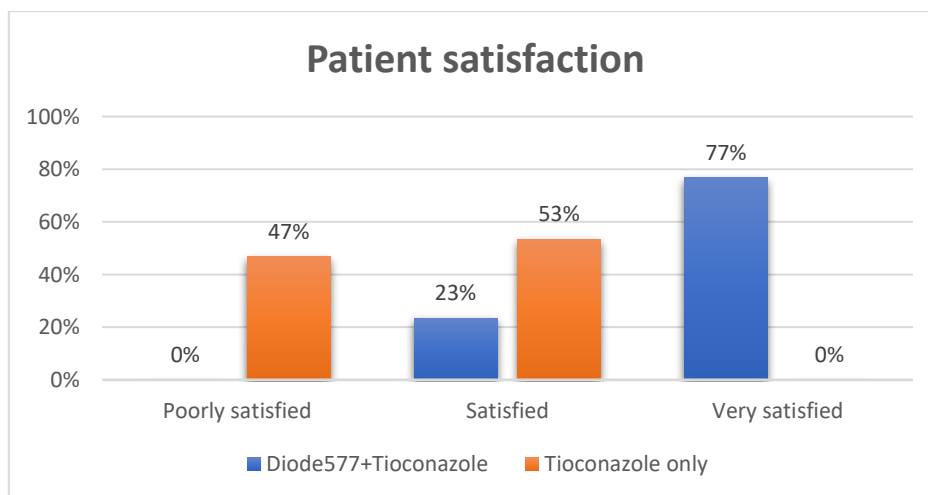


Figure [2]: Comparison between groups regarding satisfaction



Figure [3]: Female patient 20 years old presenting with Distal and Lateral Superficial onychomycosis in both big toes. The right big toe was treated by yellow laser 577-nm + tioconazole 28% nail solution, the left big toe was treated by tioconazole 28% nail solution only, with excellent improvement in both fingers. A: Pretreatment; B: After 3 session; C: After 6 session of treatment



Figure [4]: Female patients 43 years old presented with onychomycosis in two finger nails. The left one was treated by yellow laser 577-nm + tioconazole 28% nail solution [with excellent improvement], the right one was treated by tioconazole 28% only [with vs. good improvement]. A: Pretreatment; B: After 3 session; C: After 6 session of treatment

DISCUSSION

Lasers can be an alternative option for onychomycosis patients. Lasers can elicit fungicidal effects by photothermally heating fungal mycelium through selective photo thermolysis^[8].

To the best of our knowledge, this is the first study to use the pro yellow 577-nm laser in treating onychomycosis, there were several studies in literature utilized the 1064-nm-Nd: YAG laser and CO2 lasers in the treatment, however the diode yellow 577-nm has higher energy, so the present study aimed to evaluate efficacy and safety of Diode laser 577-nm in treatment of onychomycosis.

At the start of our study, we assessed the severity of onychomycosis for each group [according to OSI] as the following: [Group A, sides treated by double therapy]: 11 [36.7%] cases had severe score, 14 [47.7%] cases had mild scores and 5 [16.6%] cases had moderate

scores, the mean was 14.70 ± 12.46 , and in [Group B, sides treated by topical only]: 11 [36.7%] cases had severe score, 15 [50%] cases had mild score and 4 [13.3] cases had moderate score, the mean was 13.78 ± 12.22 .

After treatment, severity of OSI in group A decreased from 36.7% before treatment to 20% after 3 months and continue to decrease after 6 months to 3.3%. However, in group B, the severity still the same as before treatment 36.7% while after 6 months decreased to 20%. There were 2 [6.7%] after 3 months and 18 [60%] patients after 6 months in group A have complete resolution while in group B, no one has complete resolution after 3 months but after 6 months there were 11 [36.7%] patients have complete resolution with significant difference between both groups at 3 and 6 months [$p < 0.001$ & 0.046]. Also, there was a significant difference between mean of OSI score among both groups at the end of follow up [$p=0.021$]. These findings can demonstrate the antifungal

capacity of our diode pro yellow 577-nm laser, depending into photochemical reaction.

A study done by **Mosbeh et al.** ^[9] which involved 102 mycotic toe nails and randomly allocated into two groups where 64 nails treated by 808-nm Diode laser plus local antimycotic agent and 38 nails by local antimycotic only as a control. At the end of treatment, complete remission was observed in 15 [23%] in the laser group, while in the control group, the complete remission was observed in 10 [27.7%] nails without significant difference between the two group. **Abd El-Aal et al.** ^[10] reported that clinical response after one month of last session showed that 35.3% of patients have complete improvement in FrCO₂ + Tazarotene 1% gel group versus 33.3% in FrCO₂ + Tioconazole 28% solution group without significant difference.

Another comparative study of **Ebrahim Mostafa et al.** ^[11] revealed that in Fr CO₂ + Tazarotin group, OSI became mild in 10%, moderate in 30% and severe in 40% after treatment, while in Fr CO₂ + Ticonazol group, it became mild in 40%, moderate in 10% and severe in 10% after treatment] which differed significantly.

According to culture after end of all sessions to our patients, group B has higher significant positive results [p=0.039] and there was a significant difference in both groups regarding pre and post treatment results [p < 0.001]. After all sessions, 18 [60%] patients of group A had negative mycologic culture, however in group B, 11 [33.3%] patients only had negative culture [p<0.001].

Also, **Cao et al.** ^[12] revealed that patients treated by YAG laser plus topical ketoconazole cream, the clinical and fungal cure rate of them were [both 74.67%] which were higher than those of laser only group [63.22%, 68.97%], but they were not significantly different [p = 0.081, 0.266; p > 0.05].

Double therapy of Diode 577-nm + tioconazole had significant improvement results and subsequently more patient satisfaction compared to using Tioconazole only [p<0.001]. Also, our patients of group A experienced tolerable pain during laser treatment, but there were no other adverse reactions reported.

In the same line, **El-Tatawy et al.** ^[13] study showed that in laser only group, 50% were very

satisfied, 30% Moderately satisfied, 10% mildly satisfied and 10 % were not satisfied. the topical only group 10% Moderately satisfied, 30% mildly satisfied and 60 % were not satisfied. While in the combined group the majority were very satisfied [70%], 20% Moderately satisfied and 10% mildly satisfied which differed significantly with the superiority to combined group.

Our study has shown that laser-assisted topical therapy could be as effective as combination therapy. Moreover, laser-assisted topical therapy has many advantages over combination therapy, such as no serious adverse effects, comparatively short treatment course, use in patients with comorbid conditions, and no risk of development of resistance.

Conclusion: The 577-nm diode yellow laser is an effective and safe option for the treatment of onychomycosis. Of note, the combination with topical antifungals will increase overall treatment efficacy, Particularly, patients with contraindications against systemic antifungals may benefit from this multimodal therapeutic approach.

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