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FRACTIONAL CARBON DIOXIDE LASER ASSISTED DELIVERY OF TOPICAL TAZAROTENE VERSUS TOPICAL TIOCONAZOLE IN THE TREATMENT OF ONYCHOMYCOSIS

By

Rania Ebrahim Mostafa, Hanan Mohamed Ali, Hoda Kamal Al-Sebaay and Ayman A. Farrag

Department of Dermatology and Venereology, Faculty of Medicine (Girls), Al-Azhar University, Cairo, Egypt

E-mail: raniaebrahim46@yahoo.com

ABSTRACT

Background: Onychomycosis treatment is still challenging as multiple treatment options are available but there is no fully curative or preventive treatment.

Objective: To evaluate the clinical and mycological efficacy of fractional carbon dioxide laser assisted delivery of topical tazarotene versus topical tioconazole in the treatment of onychomycosis.

Patients and methods: Forty patients with mycological confirmed onychomycosis. Patients were recruited From the Dermatology outpatient clinic at Al-Zahar, a University Hospital in the period from October 2019 to October 2020. Patients were randomly divided into two equal groups: First group was treated by fractional CO2 laser for 4 sessions at 3-weeks interval plus topical tazarotene 0.1% gel applied once a day on the affected nail plates and nail folds for 12 weeks, and second group was treated by both fractional CO2 laser for 4 sessions at 3-weeks interval plus topical tioconazole solution applied once a day on the affected nail plates and nail folds for 12 weeks. Patients were evaluated in terms of clinical improvement and mycological care. Treatment outcome was evaluated through physician's evaluation of improvement using physical examination in each follows up session, score clinical index of onychomycosis, and possible side effects.

Results: At the end of treatment, 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.

Conclusion: Fractional CO2 laser was expected to be an excellent choice for patients in whom systemic antifungals were contraindicated.

Keywords: Fractional Co2 laser, Onychomycosis, Tioconazole, Tazaroti.

INTRODUCTION

Onychomycosis is a chronic infection in nails. Many organisms could cause onychomycosis like dermatophytes, non-dermatophyte molds, and yeasts. It is a common disease in the population which affects about 2- 8%. There are multiple changes in nails occurs in onychomycosis as splitting of the nail, thickening of the nail plate and yellow brownish discoloration. Chronic diseases like Diabetes mellitus, immune deficient diseases may predispose to onychomycosis. Also, trauma of the nail, aging, nail psoriasis and genetic predisposition are considered as risk

factors for onychomycosis *(Elewski et al., 2015).*

Onychomycosis could be classified into different types which included:

1. Subungual onychomycosis which may be proximal (PSO) or distal lateral (DLSO).
2. Endonyx onychomycosis.
3. Total dystrophic onychomycosis (TDO).

This classification extend to include the mixed and secondary forms of infection *(Hay et al., 2011).*

There are multiple treatment choices for management of onychomycosis which include use of topical antifungal which needs long duration and of poor efficiency, use of oral antifungal with good efficiency but with potential serious side effects. So, there are other treatment modalities to use like nail avulsion with debridement, iontophoresis, and ultrasound and laser therapy *(Rosen et al., 2016).*

Laser therapy is considered as a new, effective and safe treatment for onychomycosis. It acts through disruption of fungi and spores by thermal effect of laser pulses which leads to eradication of fungal infection. There are many types of laser systems which could be used in the management of onychomycosis as NDYAG laser and CO2 laser. Also, photodynamic and ultra-violet light therapy could be as a therapy for onychomycosis *(Gupta et al., 2016).*

This study aimed to assess the clinical and mycological effect of the use of fractional co2 laser with topical tazarotenevs fractional co2 laser with topical ticonazole in the management of onychomycosis.

PATIENTS AND METHODS

The study was conducted on 40 patients, age from 20 to 65 years from outpatient's clinic at AL-Zahra, university Hospital during the period from October 2019 to October 2020.Clincal diagnosis of onychomycosis was based on results on microscopy and culture of nail specimens.

Forty adult patients [30 females (75%) and 10 males (25%)] with fingernail onychomycosis with a mean age of 34 years ± 10.2 (SD) were included, after exclusion of patients below 18 years old, patients who received topical anti-fungal therapy in the preceding one month or any systemic anti-fungal therapy during the previous 3 months, diabetic patients, pregnancy, lactation, those who took immunosuppressive drugs and presence of other diseases causing nail dystrophy such as psoriasis, eczema, and lichen planus and immunodeficiency e.g. HIV infected patients. Informed written consent was signed by every patient before beginning the study, and ethical committee of the Faculty of Medicine, Al -Azhar University approved the protocol of research.

Patients were randomly divided into two equal groups: Group A: All the affected nails were treated with a fractional CO2 laser for 4 sessions at 3-weeks interval plus topical tazarotene 0.1% gel applied once a day on the affected nail plates and nail folds for 12 weeks. **Group B:** The affected nails were treated with both fractional CO2 laser for 4 sessions at 3-weeks interval plus topical tioconazole solution applied once a day on the affected nail plates and nail folds for

12 weeks. All patients were treated with fractional ablative CO2 laser 10600 nm (Smart Xide, DOT, DEKA, Italy) using power of 10 Watt, Pulse duration of 500 µs , spacing of 700 and stack 3.

Onychomycosis was diagnosed clinically, and Mycological assessment:

Clinically assessment: Photographs were taken using the same camera settings, lighting, and nail position by the digital camera (NikonJapan) and were obtained of affected nails before treatment, during the follow up visits and the end of treatment. Treatment efficiency wear determined by comparing infected area at baseline and 12 weak. It was analyzed into 4 grades as follows: complete response (fully normal-appearing nail), significant response (75% normal-Appearing nail compared with the area of the initially infected nail), moderate response (50%-75% normal-appearing nail), and no response (25% normal-appearing nail).

Mycological assessment: In all patients, specimens were obtained from the appropriate site (e.g., subungual debris) of the involved nail (s) by using scalpel No.15 then scrapings were examined by:

Specimens were placed on a clean glass slide, and a drop of 20 % KOH / 40% dimethyl sulfoxide (DMSO) mixture was added. The sample then examined thoroughly for the presence of fungal elements including filamentous, septate or aseptate, branched hyphae with or without arthrospores and yeast cells.

Scrapings were inoculated on (SDA+C) and (DTM) to identify the pathogenic fungi and to confirm the fungal infection.

Treatment evaluation:

1. Physician's evaluation of treatment: Photographs were taken using the same camera settings, lighting, and nail position and were obtained at baseline and at 4, 8, and 12 weeks after the start of therapy. Treatment efficacy were determined by comparing the infected area at baseline and 12 weeks.
2. OSI score was one of the measurements describing changes in the affected nails during the period of the treatment. We calculated OSI score before receiving any treatment after 6 months from the beginning of the therapy to assess the efficacy of the therapy. We also used the difference in OSI score between the beginning of the treatment and after 9 months from the start of the therapy to assess the effect of the therapy in follow up.
3. The patients were considered as responder when there were complete disappearance of onychomycosis. However, if there was no change, the patients were considered as non-responder, if there is a decrease in nail dystrophy the patients were considered as partial responder.
4. Side effects and complications during period of treatment were evaluated.

Statistical analysis:

Data were analyzed using IBM SPSS software package version 23 (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), median, and inter quartile range (IQR). Chi-squared test was used to compare the two groups according to categorical variables and Mann Whitney test to compare the two groupsin non-parametric data. The confidence interval was set to 95%.So, the p-value was considered significant at the level of <0.05.

RESULTS

Onychomycosis duration ranged from 6 -120 months and 3 - 60 months in Group A and B respectively. The study included a total of 40 onychomycotic toes and fingers. Of patients, three types of onychomychosis were included in our study, Distolateral which represented [50% and 70%], followed by total dystrophic (TDO) which represented [50% and 20%], and proximalsubungualonychomycosis which represented [10% in the 2nd group] among the 2 studied groups respectively. The OSI score before treatment ranged from 4 to 26. KOH done at baseline were all positive for Hyphae in [50% and 40%] of studied cases in both groups , Spores presented in 20% of Fr CO2 + Ticonazol group, hypha and spores presented in 30% of studied cases in both groups, and Yeast cells presented in[20% and 20%] ofstudiedcasesofFrCO2+Tazarotingroupand Fr CO2 + Ticonazol group respectively. The baseline clinical and demographic data of included patients **(Table 1)**.

Table (1): Comparison between Fr CO2+ Tazarotin group and FR CO2+Ticonazol group regarding demographic data and characteristics of the studied patients

Parameters \ Groups		Fr CO2 + Tazarotin No. = 20	Fr CO2 + Ticonazol No. = 20	P-value
Age	Median(IQR)	31.5 (27 – 43)	31 (27 – 42)	1.000‡
	Range	21 – 55	20 – 65	
Sex	Female	18 (90.0%)	12 (60.0%)	0.028*
	Male	2 (10.0%)	8 (40.0%)	
Duration (months)	Median(IQR)	11 (8 - 24)	6 (5 - 12)	0.019‡
	Range	6 – 120	3 – 60	
Finger or Toe nail	Toe	12 (60.0%)	14 (70.0%)	0.507*
	Finger	8 (40.0%)	6 (30.0%)	
Type of onychomycosis	Distro lateral	10 (50.0%)	14 (70.0%)	0.073*
	Proximal subungual	0 (0.0%)	2 (10.0%)	
	Total dystrophic	10 (50.0%)	4 (20.0%)	
%of affected area	Median(IQR)	52.5 (30 – 60)	35 (25 – 40)	0.032‡
	Range	25 – 60	25 – 55	

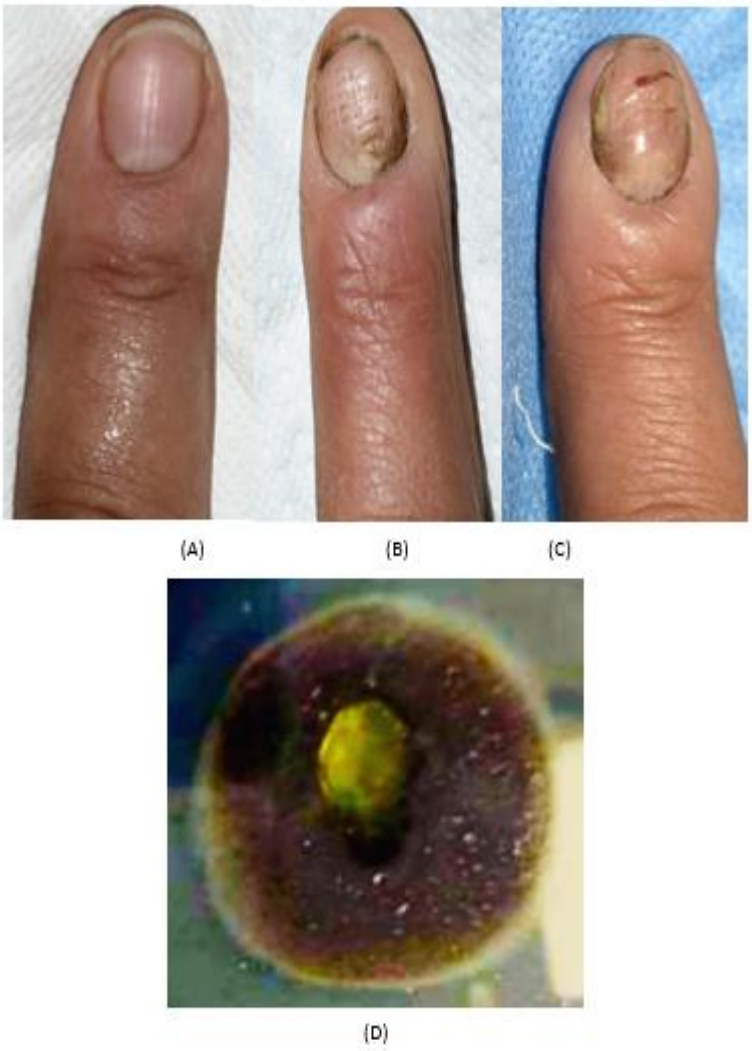
*:Chi-square test; ‡: Mann Whitney test

The median values of OSI scores of patients of the two studied groups at begging and after treatment. There was a statistically significant difference between 2 study groups regarding to Onychomycosis severity index (OSI) (mild, moderate, severe) after treatment and significant difference regarding Onychomycosisindex (OSI) by number after treatment (P = 0.008). No statistically significant difference found between Fr CO2 + Tazarotin group before and after treatment regarding to OSI by mild, moderate and severe **(Table 2)**.

Table (2): Comparison between Fr CO2 + Tazarotin group and Fr CO2 + Ticonazol group regarding to onychomycosis severity index (OSI) before treatment

Parameters \ Groups		Fr CO2 + Tazarotin	Fr CO2 + Ticonazol	P-value
		No. = 20	No. = 20	
Onychomycosis index(OSI)	Median(IQR)	12.5 (9 - 25)	9 (5 - 12)	0.058‡
	Range	4 – 26	5 – 24	
Onychomycosis severity index(OSI)	Mild	2 (10.0%)	6 (30.0%)	0.017*
	Moderate	8 (40.0%)	12 (60.0%)	
	Severe	10 (50.0%)	2 (10.0%)	

*:Chi-square test; ‡: Mann Whitney test



Figure(1): Female patient 33 years old with distal lateral subungual type of onychomycosis (DLSO) in right 2nd finger treated with both topical tazarotin and fraction carbon dioxide laser: (a) Clinical picture before treatment, (b) Clinical picture after 2 months of treatment, (c) Complete clinical response 3 months after treatment due to reduction of OSI score from 6 to zero score (marked improvement),and (d) Culture showing green brownish colonies of trichophyton.

Figure(2): Female patient 43 years old with in distal lateral subungualonychomycosis (DLSO) in left thump treated with both topical ticonazol and fraction carbon dioxide laser: (a) Clinical picture before treatment, (b) Clinical picture after 2 months of treatment, (c) Complete clinical response 3 months after treatment due to reduction of OSI score from 10 to zero score (marked improvement) ,and (d) Culture showing powdery tan/sandy colonies of scopulariopsis spp.

DISCUSSION

Onychomycosis treated by laser device still under discussion, and the studies about efficacy of fractional Co2 laser in the treatment of nail fungus diseases are not adequate. Fr CO2 + Ticonazol group showed mild improvement of Nail discoloration in 10%, good response in 50%, while Onycholysis mildly improved in 10%, good response in 50%, Sub fungal hyperkeratosis mildly improved in 10%, good response in 40% and culture improved in 10% after treatment. There was a statistically significant decrease in the incidence of candida tropicals, aspergillusniger and aspergillusflavus after treatment than before treatment.Also, there was a statistically significant increase in the incidence of negative cases after treatment (80%) than before treatment (0%), while no statistically significant changes found in the incidence of candidaalbicans, aspergillusnidlans and scopuloriopsisbervicularis.

In the current study, 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.There was a statistically significant difference between Fr CO2 + Tazarotin group before and after treatment regarding to OSI by number, while there was no statistically significant difference found between Fr CO2 + Tazarotin group before and after treatment regarding to OSI by (mild, moderate, sever), while there was a statistically significant difference between Fr CO2 + Ticonazole group before and after treatment regarding to OSI. There was a statistically significant decrease in the incidence of aspergillusniger after treatment than before treatment. Also, there was a statistically significant increase in the incidence of negative cases after treatment (30%) than before treatment (0%), while no statistically significant changes found in the incidence of candida albicans, Candida tropical, Aspergillusnidlans, Clascosporam species and Trichophytonrubrum.

Zhou et al. (2016) studied patients which divided into two groups: first group is treated by fractional CO2 laser without any topical medication over the course of 12 sessions at 14 day intervals ,while second group is treated by fractional CO2 laser received 12 sessions at 14 day intervals with topical anti-fungal treatment (luliconazole 1% cream once daily).

Abd El-Aal et al. (2018) treated onychomycosis by both Fr CO2 + Tazarotin (group A) and Fr CO2 + Ticonazol (group B), regarding clinical improvement. There was no statistically significant difference between the two studied groups, whereas group A was 35.3% in versus group B was 33.3% showed full improvement, and group A was 33.3% versus group B was 21.6% showed significant improvement.

Shi et al. (2017) treated by fractional CO2 laser on 12 sessions at 14 day intervals mixed with topical medication (terbinafine cream for 6 months once daily). They evaluated the clinical improvement rate from abnormal part of nail, if fully normal appearance or ≤ 5% abnormal appearance, whoever the mycological improvement rate was measured from the percentage of nails with -ve fungal microscopy. At the end of treatment .The clinical efficacy rate was 58.9%, with follow up one month after last session was 63.5%, and follow up 3 months was 68.5%. The mycological improvement rates in follow up 1 month after last session was 77.4%, and 74.2% in follow up after 3 months after the last session.

In the treatment of onychomycosis, fractional ablative of FCO2 laser therapy alone was an efficient therapy as it believed that FCO2 laser treats onychomycosis by thermal effect with ablation the target's tissue fungi which were extremely sensitive to temperature above 55°C.It also destroyed the fungal growth environment by the photo thermal effect of fractional CO2 laser which leads to fungal growth inhibition *(Abd El-Aal et al., 2018).*

Although the mechanism of laser treatment of nails infected by fungi is not well known, several hypotheses have been proposed: First, the laser beam may

penetrate the nail plate to the nail bed, creating local hyperthermia. Protein denaturation also triggers fungal apoptosis. Second, laser energy may be absorbed by melanin in fungal cell walls; the resulting pigment- associated photothermolysis inhibits fungal growth in the nail matrix and plate *(Kim et al., 2016).*

Adverse effects of laser therapy for onychomycosis reported in the literature ranged from pain up to tissue necrosis, but the current study did not comment on like these side effects *(Karsai S et al., 2017).*

CONCLUSION

Treatment with laser devices in generally and the FCO2 especially helped in the delivery of topical medications in the treatment of nail fungus, which made the treatment results better compared to not using the laser and only with topical treatment. Tazarotene (0.1%) gel and ticonazol (28%) solutions were one of the most effective topical treatments in the treatment of nail fungus. Treatment using laser devices was the appropriate solution for patients who suffer from diseases that prevented them from using topical and systemic treatments for nail diseases.

Conflict of interest:

This study was not met with any conflict of interest.

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استخدام الليزر المتجزئ ثاني أكسيد الكربون للمساعدة على توصيل التازاروتين الموضعي مقابل التيكونازول الموضعي في علاج فطريات الأظافر

رانيا إبراهيم مصطفى، حنان محمد علي، هدى كمال السباعي، أيمن عبد الرحمن فراج

قسم الأمراض الجلدية والتناسلية، كلية الطب (بنات)، جامعة الأزهر، القاهرة، مصر

E-mail address: raniaebrahim46@yahoo.com

خلفية البحث: لا يزال علاج مرض فطرالأظافر يمثل تحديًا حيث تتوفر خيارات العلاج المتعددة ولكن لا يوجد علاج علاجي أو وقائي بالكامل.

الهدف من البحث: تقييم فعالية ليزر ثاني أكسيد الكربون المتجزئ بمساعدة التازاروتين الموضعي مقاب لتيكونازول الموضعي في علاج فطريات الأظافر.

المرضى وطرق البحث: تم تضمين أربعين مريضًا مصابًا بمرض فطر الأظافر وتم تقسيمهم عشوائيًا إلى مجموعتين متساويتين.وقد تم علاج المجموعة الأولى باستخدام ليزر ثاني أكسيد الكربون المتجزئ لمدة 4 جلسات بفاصل 3 أسابيع بالإضافة إلى تازاروتين موضعي 0.1٪ جل تم وضعه مرة واحدة يوميًا على لوح الظفر المصاب وطيات الظفر لمدة 12 أسبوعًا،و تم علاج المجموعة الثانية باستخدام ليزر ثاني أكسيد الكربون المتجزئ لمدة 4 جلسات بفاصل 3 أسابيع بالإضافة إلى محلول تيوكونازول الموضعي الذي تم وضعه مرة واحدة يوميًا على لوح الظفر المصاب وطيات الظفر لمدة 12 أسبوعًا. كما تم تقييم المرضى من حيث التحسن السريري والرعاية الفطرية، تم تقييم نتائج العلاج من

خلال تقييم الطبيب للتحسن باستخدام الفحص البدني في كل جلسة متابعة ، وسجل المؤشر السريري لداء الفطريات والآثار الجانبية المحتملة.

نتائج البحث: في نهاية العلاج أصبح المؤشر السريري لمرض فطر الأظافر في المجموعه الأولى التي تستخدمليزر ثاني أكسيد الكربون المتجزئبالإضافة إلى تازاروتين موضعي 0.1٪ جل: استجابه بسيطه في 10% ،و استجابه متوسطه في 30%، و استجابه قويه في 40% بعد العلاج. بينما في المجموعه الثانيه التي تستخدم ليزر ثاني أكسيد الكربون المتجزئ بالإضافة إلى محلول تيوكونازول الموضعي حدثت استجابه بسيطه في40%، و استجابه متوسطه في10%، و استجابه قويه في10 % بعد العلاج.

الاستنتاج: ليزر ثاني أكسيد الكربون المتجزئ خيار ممتازللمرضى المحظورين من مضادات الفطريات الجهازيه.