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A comparative study on efficacy of fractional carbondioxide laser assisted topical antifungal therapy with topical antifungal therapy alone for treatment of onychomycosis in adult north Indian population

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Abstract

Aim: The aim of the study is to compare the efficacy of fractional carbondioxide laser assisted topical antifungal therapy with topical antifungal therapy alone for treatment of onychomycosis in adult north Indian population.

Methods: We investigated 50 clinically suspected patient's nails of both gender and aged above 18 years for onychomycosis by KOH examination and Culture. The patients were then randomly divided in two groups, Group A and Group B with 25 patients in each group. Patients in group A received only topical antifungal drugs at 2 weeks of interval for 6 months. Patients in group B received fractional CO₂ laser treatment combined with topical antifungal drugs for 6 months. Nails of patients in each study group were analysed by clinical findings and Scoring Clinical Index for onychomycosis.

Results: Patients in group B who were treated with a combination of fractional CO₂ and topical antifungal showed a statistically significant improvement in SCIO scoring as compared to group A.

Conclusion: Fractional CO₂ laser assisted topical antifungal therapy is more effective treatment for onychomycosis as compared to topical antifungal therapy alone in adult north Indian population.

Keywords: Fractional carbondioxide laser, KOH, Indian population

Introduction

Onychomycosis is an infection of the nail unit caused by fungi (dermatophytes, non-dermatophyte molds and yeasts), presenting with discoloration of the nail, onycholysis and nail plate thickening [1, 2]. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected [3, 4].

Onychomycosis can be classified into distal lateral subungual onychomycosis (DLSO), superficial white 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 [5, 6].

Onychomycosis can be caused by dermatophytes (tinea unguium), non-dermatophyte molds and yeasts [7, 8]. Approximately 90% of toenail and 75% of fingernail onychomycosis are caused by dermatophytes notably *Trichophyton mentagrophytes* and *Trichophyton rubrum* 9-13. Non-dermatophytes molds that can cause onychomycosis include *Aspergillus* species, *Scopulariopsis* species, *Fusarium* species, *Acremonium* species, *Syncephalastrum* species, *Scytalidium* species, and *Paecilomyces* species 14-18. Non-dermatophyte molds account for approximately 10% of onychomycosis cases globally [19].

Typically, onychomycosis presents as a white or yellow brown discoloration of the nail. Violaceous, green, and black discoloration of the nail plate have also been

Observed [20]. Other clinical manifestations include subungual hyperkeratosis, detachment of the nail from the nail bed (onycholysis) and thickening of the nail plate (onychauxis) [21].

Treating onychomycosis is problematic for a variety of reasons. Oral therapy is more effective than topical therapy, but it is expensive, requires monitoring for toxicity, and can result in multiple drug interactions. Topical therapy is a long process that often requires nail debridement and multiple return visits and still delivers a relatively poor success rate. The

very nature of the hard, protective nail plate itself makes it difficult for topical drugs to reach the fungal pathogens beneath it [22]. Surgical nail avulsion for the treatment of onychomycosis should be avoided as potential side effects include postoperative pain, narrowing of the nail bed, distal paronychia and infection [23].

Lasers are potential therapeutic modalities for onychomycosis because they have very few contraindications, minimal adverse effects, short treatment regimens, and good patient compliance [24].

The carbon dioxide laser system is the oldest of the laser therapies for onychomycosis. It is an ablative laser and therefore can serve as a primary treatment for onychomycosis or as an adjunct to topical antifungals, providing a means of penetration through the nail plate to the nail bed [25].

Tissue heating from laser machines can produce direct damage or induce an immune reaction against pathogens [26, 27]. Furthermore, they have been studied as adjuvants to topical therapies for onychomycosis, as they can facilitate drug delivery through the nail plate by increasing permeability [28]. Ablative standard carbondioxide in combination with a topical antifungal drug, proved to be efficacious [29, 30] in various studies.

Aim: To compare the efficacy of fractional CO₂ laser along topical antifungal drugs with topical antifungal drugs alone in treatment of onychomycosis

Objectives

1. To study the efficacy of topical antifungal drugs in treatment of onychomycosis.
2. To study the efficacy of fractional CO₂ assisted topical antifungal therapy in treatment of onychomycosis.
3. To compare the efficacy of fractional CO₂ assisted topical antifungal therapy with topical antifungal therapy alone for treatment of onychomycosis.

Methods

Study Design

Hospital based prospective study.

Patients were included and excluded on basis of some inclusion and exclusion criteria which were as follows -

Inclusion criteria

1. Patients of both the sexes.
2. Patients aged between 18 years and 60 years.
3. Onychomycosis of toe and fingers of all types diagnosed with clinical nail morphology confirmed by positive fungal microscopy and culture growth.
4. Patients with minimum 1 nail involvement and maximum 5 nails including fingernail or toenail or both.
5. Patients with negative fungal culture are were excluded if fungal microscopy is positive.

Exclusion criteria

1. Patients below 18 years and above 60 years of age.
2. Patients with history of localized bacterial infections.
3. Patients with concomitant nail disease such as Psoriasis, lichen planus, hematomas or any other skin and nail disease that may interfere with diagnosis.
4. Patients having extensive infection of Tinea corporis, Tinea cruris and Tinea manum.
5. Patients having all fingernails or toenail involvement.

6. Patient having allergy to drugs used in treatment in study.
7. Patient with any Cardiac, hepatic, renal disorders, diabetes, HIV and mental illness.
8. Patient who had taken any oral antifungal medication with in last 3 months.
9. Patient who used topical antifungal medications in last 2 weeks.
10. Patients who had taken any form of immunosuppressants with in last 3 months.
11. Pregnant patients

Procedure that was followed during this study

A. Clinical assessment

1. A detailed history of every patient along with the complaints, duration of illness was taken. The socioeconomic factors like occupation, education and income was recorded. The hobbies of the patient, habits of nail cutting and footwear wearing, history of preceding trauma and history of treatment was taken. Family history of fungal infection in other members of the family was checked in every patient.
2. The general physical examination and systemic examination was conducted in all cases apart from mucocutaneous examination. The physical features of affected nails along with those of nail folds were noted. The presence of any associated superficial skin infections were looked. All the patients were examined for any other associated skin or systemic disease.

B. Collection of material

1. Suspected nails were cleaned with a spirit swab and nails were carefully scraped with a 15 number sterile blade till the junction of healthy and diseased portion reached. Minute scarping from this part of the nail plate and nail bed was collected taking as much as possible friable subungual debris. In cases where both finger and toe nails were involved, the samples were taken from both sides.

C. KOH examination and direct microscopy

1. Nail sample was treated with 20 percent KOH solution and slightly warmed, avoiding boiling. The sample was kept for 30 minutes and nail sample was examined under microscope.
2. Nail sample was placed on glass slide and covered with a coverslip and was examined under the low (10x) and high power (100x) of microscope for the presence of fungal elements.

D. Culture

1. The nail samples were inoculated in culture media of Sabouraud's dextrose agar with chlorophenicol and cyclohexamide. (Hi Media Laboratories)
2. Media was incubated at 37 degree Celsius and examined every day for 4 weeks. In cases where contamination occurred, subculture was done using same media mentioned above.
3. The identification of the isolates were done on basis of:
4. Colony morphology seen under microscope.
5. Colour of growth obtained on culture media.

E. Antifungal sensitivity

All samples which were KOH, direct microscopy and

culture growth positive were subjected to antifungal drug sensitivity using antifungal sensitivity kit (Hi media laboratories) which included the following drugs.

- i. Amphotericin B
- ii. Fluconazole
- iii. Terbinafine
- iv. Ketaconazole

Culture growth sensitive to any of drugs mentioned above that drug was used for treatment combined with fractional CO₂ laser (Sellas CIS F1) and alone also in treatment of onychomycosis.

F. Randomization and drug delivery

Patients were randomized into 2 groups:

1. **Group A:** Received topical antifungal drug on affected area once daily for duration of 6 months.
2. **Group B:** Received CO₂ laser treatment at 2 weeks intervals combined with topical antifungal drugs once daily for 6 months of duration.

All the patients of Group B were treated with Fractional carbon dioxide laser (Sellas CIS F1 Laser machine), combined with antifungal drugs at the energy of 10 to 15 mJ, pulse duration of 0.5 to 1 seconds and density of 10 percent over the affected area and spot size of 4 to 8mm. Total 12 sessions of CO₂ laser therapy were done on each patient group B.

All the patients of Group A were treated with topical antifungal drugs and advised to cover nail with a plastic wrap once every night for 8 to 12 hours and remove in next morning.

G. Evaluation of treatment in both study groups

1. Nails of patients of both study groups were analyzed by comparing clinical findings and Scoring Clinical Index for onychomycosis before and after the treatment.
2. The scoring clinical index for onychomycosis for superficial white onychomycosis, Proximal subungual onychomycosis and Distal subungual onychomycosis the values were calculated and compared before and after treatment in both study groups.
3. A higher SCIO index suggested that the onychomycosis was more severe and required more prolonged treatment. 31
4. Evaluation of treatment response in treatment group B was done through photography using camera, comparing the clinical findings of nails involved in onychomycosis and by calculating the scoring clinical index for onychomycosis after fractional CO₂ laser session every 2 weekly and after 3 months of last treatment.
5. Evaluation of treatment response in group A was done with photography with digital camera, comparing the clinical features of nails involved in onychomycosis and by calculating the scoring clinical index for onychomycosis in every 2 week and after 3 months of last treatment.

Post laser care

- 1 No wound care or dressings were necessary after treatment.
- 2 Patients were encouraged to keep feet dry and to rotate shoes and socks in case of toenail involvement.

- 3 Patients were made aware of temporary darkening under nail that might occur after laser treatment.
- 4 Patients were examined after each session of fractional CO₂ laser to evaluate post procedure pain and rating of pain intensity was done as number from 0 to 10 using numerical rating scale. Here 0 means no pain, 1 to 4 means mild pain and 5 to 7 means moderate pain and 8 to 10 means severe pain.
- 5 Mild analgesics were used in patients that were complaining of pain after laser treatment.
- 6 Patients were evaluated for other complications after laser treatment such as nail dystrophy and onycholysis.

Data was collected and subjected to statistical analysis.

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test and the level of significance was set at $p < 0.05$.

Results

The present study compared the efficacy of topical antifungal drugs versus fractional CO₂ laser combined with topical antifungal drugs. In this study total 50 patients were included and randomly divided into two groups i.e. group A (topical antifungal drugs) and group B (fractional CO₂ laser with topical antifungal drugs). In both group A and B, majority of cases belong to a age group between 20 to 30 years.

The gender distribution among the study groups is 80% and 72% of the subjects in group A and B were males respectively. Hence there was male dominance in this study. In this study major type of onychomycosis found in both the groups was Distal Lateral Subungual Onychomycosis which was followed by Proximal Subungual onychomycosis in group A and Superficial white onychomycosis in group B. It also shows more number of cases of Distal lateral subungual onychomycosis in group B as compared to group A as showed in graph I.

SCIO (Scoring clinical index for onychomycosis) was calculated before starting and also after completion of 6 months of the topical antifungal therapy in group A by using parameters such depth of involvement of nail plate and Degree of hyperkeratosis and difference between the scoring was calculated.

SCIO scoring was calculated by using formula – $[(d/3)^3 - f(f+h(3-f))]1 - [(2-f)(3-f)/2]$ where f stands for clinical form, d stand for depth of involvement and h stand for degree of hyperkeratosis.

Comparison of SCIO scoring before starting the therapy and after completion of 6 months of topical antifungal drugs therapy was done and mean SCIO score at baseline was 4.06 ± 1.92 which after intervention reduced to 3.79 ± 1.90 with statistically significant difference when compared using paired t test as shown in table I.

Comparison of SCIO scoring before starting the fractional CO₂ assisted topical antifungal drugs therapy and after completion of 6 months of fractional CO₂ laser assisted topical antifungal drugs therapy was done and mean SCIO score at baseline was 5.74 ± 1.95 which after intervention

reduced to 4.59 ± 2.08 with statistically significant difference when compared using paired t test as shown in table II. Comparing the result before and after the therapy in group A and B, mean difference in SCOI (Baseline-6 Months) was 0.27 ± 0.13 and 1.16 ± 0.87 respectively. Hence mean reduction in SCOI score was more in group B as compared to group A with statistically significant difference as shown in table III.

Discussion

Onychomycosis is known as fungal infection of nail. It is becoming resistant to many available treatment options therefore new treatment modalities are required for effective treatment. New oral and topical antifungal agents (used alone or in combination) are considered the mainstay of therapy against onychomycosis. Even in the most experienced hands, these approved and widely used drugs may offer only disappointing results with high rates of relapse. Laser treatments are the most rapidly expanding area of onychomycosis therapy. Laser devices can be used to enhance drug delivery, activate topically applied drugs, or photothermally kill fungi. Laser treatments have a number of advantages over traditional therapy as they are primarily conducted in the clinic by trained professionals, reducing the need for patient compliance. They also have the potential to reduce adverse events and systemic interactions. The carbon dioxide laser system is the oldest of the laser therapies for onychomycosis. It is an ablative laser and therefore can serve as a primary treatment for onychomycosis or as an adjunct to topical antifungals, providing a means of penetration through the nail plate to the nail bed [32, 33].

Site

Maximum site of involvement in Group A as well as B was hand as compared to the feet in this study, which might be because hands (fingernails) are more prone to trauma. Moreover, fingernail infection can harm the patient's life and disfigurement in nails can affect their self-esteem, thereby compelling them to report to a doctor early. Similarly Amr Mohamed Zaki *et al.* [33] in their study found that fingernails were more affected than toenails.

This finding is in agreement with many studies that showed that fingernail onychomycosis is more common than toenail onychomycosis [33, 34].

In contrast, other studies show that toenail onychomycosis is more common than fingernail onychomycosis [35]. The low incidence of toenail onychomycosis in this study may be attributed to the use of open footwear and lesser concern for the appearance of the feet and toenails [35].

Types of onychomycosis

In this study; most common type of onychomycosis found in both the groups was Distal Lateral Subungual Onychomycosis which was followed by Proximal Subungual onychomycosis in group A and Superficial white onychomycosis in group B.

Tro V. Chau *et al.* [3] in their study found that distal and lateral subungual onychomycosis was the most common pattern of onychomycosis in their study, followed by total dystrophic onychomycosis. A similar result was found in the studies of Gupta *et al.*, the largest epidemiology survey reported [36].

Similarly Amr Mohamed Zaki *et al.* [34] in their study

revealed that yeast (31%) was the commonest fungal species causing onychomycosis in all studied groups followed by Nondermatophytes (28.5%), dermatophytes were detected in (22%) and trichosporon species infection detected in 18.5% of cases.

A similar result had been reported in India by Wajid, Khaleel, Begum Amirunnisa *et al.* (2016) who reported that Candida species was the most common isolates in 65 patients (43.3%) followed by NDM 33.

Similar results were reported in a study from Egypt by Abd El-Aal, Abdo *et al.* (2019) [66] who revealed that the commonest isolated fungi were yeast infection by 37% followed by NDMs infection by 22.5% and trichosporon species infection by 18% and dermatophyte infection was only detected in 10% [38].

In contrast, other studies showed that the most common fungal isolate was dermatophyte (mainly *Trichophyton rubrum*) followed by yeast (mainly *Candida albicans*) [33, 34]. Overall, the predominance of causative agents varies depending on ethnicity and different environmental factors such as climate, humidity, occupation, and different lifestyles and upon geographical location and temporal distribution [33].

It is generally believed that the mechanism by which fractional CO₂ 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. Additionally, fractional CO₂ 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. Furthermore, fractional Carbon dioxide laser can enhance the absorption of topical antifungal agents through the hard densely keratinized nail plate, thereby improving their penetration and efficacy. These facts could explain the significantly better mycological cure results of the combined group in the present study in comparison with the topical group [6].

Similar results were found by Zhou *et al.* (2016) [38] who reported that fractional CO₂ laser combined with luliconazole 1% cream was effective to treat infected nails and had a higher efficacy than fractional CO₂ laser treatment alone [33].

Zhang *et al.* (2016) reported that the combination therapy with the fractional 2,940-nm Er:YAG laser and amorolfine showed a much better effect than the use of amorolfine alone [39].

Lim *et al.* [25] studied the efficacy of fractional CO₂ 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.* [40] using a total of three sessions of fractional CO₂ 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.

In a study by Zaki Am *et al.* [33], a total of 120 patients with onychomycosis were randomly assigned to three groups. Group A patients were treated with fractional CO₂ laser

followed by topical tioconazole 28% for five sessions with 3 weeks interval. Group B patients were treated with only fractional CO₂ laser for five sessions with 3 weeks interval. Group C patients were treated with only topical tioconazole 28% for 16 weeks. The clinical effect, KOH examination, and culture for the affected nails in the three groups were analyzed. One month after the last session, regarding clinical response, 55% showed complete clinical improvement in Group A versus 30% in Group B versus 25% in Group C with a significant difference in between.

Naomi Nakano *et al.* (2006) studied efficacy of topical terbinafine 1% cream in onychomycosis. They reported complete cure in 77.3% patients, marked improvement in 7.6% of patients and slight improvement in 1.5% of patients. 41

Lecha *et al.* (2002) used 1% ketoconazole cream once a week for 24 weeks and they observed 69% cure Rate. 42 These findings are similar to present study.

Further prospective studies on larger population of onychomycosis patients and with longer periods of follow-up are recommended. Comparing the effectiveness of fractional CO₂ laser with other types of lasers in the treatment of onychomycosis and testing the effectiveness of fractional CO₂ laser in combination with other more potent topical antifungals is also recommended.

Limitations

The limitations of the present study are:

- Limited sample size
- Short term follow up
- Multiple scars of pits that were created for delivery of topical antifungal drugs on nail plate.

Conclusion

Fractional CO₂ laser combined with topical antifungal is a safe and effective treatment for onychomycosis, and its efficacy is superior to topical antifungal alone. Fractional CO₂ laser is expected to be an excellent choice for patients in whom systemic antifungals are contraindicated

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