Research Paper

Comparative Efficacy of Fractional Carbon Dioxide Laser Combined with Topical 1% Luliconazole versus Oral Itraconazole Combined with Topical 1% Luliconazole in Onychomycosis: A Case Series Study

Dr Faraz Mohammed V.S[1], Dr Kandaswamy M[2]

[1]Junior Resident, Department of Dermatology, Venereology and Leprosy, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth Deemed to Be University, Puducherry, India
Email: farazmohammed59@yahoo.com | ORCID: https://orcid.org/0009-0006-3129-3469

[2]Professor and HOD, Department of Dermatology, Venereology and Leprosy, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth Deemed to Be University, Puducherry, India
Email: kandaswamy22@gmail.com | ORCID: https://orcid.org/0000-0002-9452-8011

ABSTRACT

Onychomycosis is a frequent nail fungus infection that can be hard to treat due to lack of drug penetration and recurrence and might need a long course. The aim of the study was to compare the effectiveness of fractional carbon dioxide (CO2) laser and a topical lotion of 1 percent luliconazole application versus oral itraconazole gels with topical lotion of 1 percent luliconazole application in treating onychomycosis. A potential comparative case series was carried out in 20 patients; 10 in each group. Group A was treated to fractional CO2 laser treatment along with topical 1% luliconazole lotion and Group B was treated to oral itraconazole with topical 1% luliconazole lotion. Clinical outcomes were determined on the basis of nail discoloring, nail thickening, nail subungival debris, normal nail growth, treatment tolerability and patient satisfaction. The outcomes indicated that 60% of Group A patients had excellent clinical improvement (>75%), with 30% having moderate improvement. Group B patients had 40% moderate in comparison with Group A patients. In the laser group, patient satisfaction was better than the itraconazole group as 70% expressed high patient satisfaction whereas 50% of patients expressed high patient satisfaction in the itraconazole group. Local transient temporary discomfort was reported in the laser group but systemic adverse effects were observed in the oral itraconazole group. The results indicate that the use of fractional CO2 laser, using topical 1% luliconazole, is a safe, potent and promising remedy to onychomycosis.

Keywords: Onychomycosis; Fractional CO_2 Laser; Luliconazole; Itraconazole; Combination Therapy.

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I. INTRODUCTION

Onychomycosis is a widespread fungal infection of the fingernails and toenails, with an incidence of almost 50% being in the nail world. It is mainly due to dermatophytes, yeasts and non-dermatophyte mould that causes nail discoloration, thickening, brittle and makes the nail plate peel off the nail bed [1]. Not life-threatening, onychomycosis may have a significant effect on the quality of life due to its discomfort, pain, cosmetic issues, and social humiliation. The illness in most cases is long-lasting, recurrent and it is hard to cure due to the slow growth of the nails and lack of penetration of antifungal medication through the nail plate. The standard therapy is likely to involve systemic antifungal therapy like itraconazole usually with topical antifungal agents like 1% luliconazole lotion [2]. Oral itraconazole can be used with a wide-range antifungal activity and positive clinical performance. But, long-lasting oral therapy can be related to adverse effects, drug interactions, hepatotoxicity, and non-compliance of patients. The topical luliconazole is a less toxic treatment with extensive antifungal agents, its application is probably met with limited success because of poor nail penetration [3].

Fractional carbon dioxide (CO_2) laser is a new technology that could be used to treat onychomycosis as an alternative or adjunctive therapy. The laser ablates microscopic channels in the nail plate enhancing absorption of topical antifungal agents and also has a direct antifungal effect by thermal destruction of fungal elements. The combination has the potential of enhancing treatment results and lessening the reliance on systemic medication. This research will endeavor to compare the effectiveness of

fractional carbon dioxide laser treatment in conjunction with topical 1% luliconazole lotion to oral itraconazole treatment in conjunction with topical 1% luliconazole lotion in the management of onychomycosis. Through comparing clinical response between two groups of patients, it is the aim of this case series that an effective and useful therapeutic way of dealing with onychomycosis can be achieved, with better patient outcomes and tolerability.

II. RELATED WORKS

Onychomycosis is a chronic nail infection caused by the fungus, which is difficult to treat due to slow nail growth, lack of drug penetration into the nail plate, length of treatment and high rate of recurrence. The past few years have seen the growing interest in streamlining treatment methods due to systemic antifungal treatment, topical preparations, laser-based therapy and combination therapy. The efficacy and safety of itraconazole oral use in dermatophyte onychomycosis was evaluated by Elewski, Tosti and Tavakkol [10], and revealed that itraconazole is an effective systemic therapy, whose success rates are satisfactory in most patients. Both have shown improvements in their clinical condition after the oral therapy was given to them; they have also pointed out their problems on the length of treatment period, systemic adverse effects, drug interactions, and monitoring at the time of therapy. Wide-ranging study by Gupta, Stec and Summerbell [11] revolved around epidemiology, diagnosis and treatment of onychomycosis and reasoned that the ailment remains one of the most prevalent nail diseases in the world. Their review highlighted that oral antifungal agents are still used as the standard treatment but recurrence and incomplete cure are still seemingly challenging issues.

A study of Ranjan et al. [12] examined how fractional CO_2 laser in single-session works after using urea occlusion in the management of onychomycosis. The pilot study had proven an enabling improvement in the appearance of nails and detection of the fungus indicating that laser therapy can enhance the infiltration of antifungal treatment agents and improve the treatment. Their results validated the increasing role of laser-assisted treatment as an adjunctive modality. The new problem targeted by Gupta and Foley [13] is the issue of antifungal resistance in onychomycosis where there has been an increasing resistance to dermatophytes and vulnerability of traditional systemic therapy. This has necessitated finding an alternative or a combination of treatment measures as an alternative to oral antifungal monotherapy. Iozumi et al. [14] analyzed long-term treatment response with topical antifungal solution in severe onychomycosis, and found that a persistent use of topical therapy could give clinical response particularly in mild-moderate disease. Treatment failure is however very common and usually occurs in cases of long-term and patient noncompliance. Abdelrahman, Hassan and Eid [15] compared the use of fractional CO_2 laser with topical tioconazole versus using Q-switched Nd:YAG laser and they found better clinical response with the use of fractional CO_2 laser. Their random comparative trial reinforced the evidence in favor of interventions using lasers in nail infections.

Gupta, Foley and Versteeg [16] updated on emerging treatments on recalcitrant onychomycosis and noted improvements in combination therapy using a topical agent, systemic antifungal and energy-based devices. Through their results, they point out that multimodal therapy could lead to better outcomes in cases, which are hard to treat.

Tosti, Piraccini and Scher [17] looked at the recent developments in laser-assisted therapy and they found that the use of the fractional laser technology offers high potential rate of effectiveness because of their ability to deliver drugs deeper into the ungual region, and direct destruction of fungi. Not very recently, Xiong et al. [18] carried a systematic review and a meta-analysis of fractional CO 2 laser therapy to treat onychomycosis and provided positive results of its efficacy and safety, underlining its applicability as an adjunct type of treatment.

Versteeg and Gupta [19] also examined the uses of combination treatment in the management of onychomycosis and found out that using antifungal treatments with laser treatment has been shown to enhance treatment outcome compared to their monotherapies. Lastly, Lipner [20] presented the recent progress in new antifungal and laser-targeted methods and reiterates that more recent combination methods can be deployed to form the future of treatment of onychomycosis.

According to the literature at hand, both oral itraconazole and topical therapy is still essential but there is an increasing body of evidence that has identified the use of fractional CO_2 laser as an adjunctive modality. Nevertheless, no previous research studies directly compares or contrasts fractional CO_2 laser use, with topical 1 per cent luconazole, with oral itraconazole use, with topical 1 per cent fluconazole, on which the current study is based.

III. METHODOLOGY

Study Design

This study will be done as a prospective comparative case series study to test the effectiveness of fractional carbon dioxide (CO2) laser as compared with oral itraconazole coupled with topical 1% luliconazole lotion to determine its effectiveness in the treatment of onychomycosis [4]. The research will involve the two groups of intervention in comparison of clinical improvement and response to the treatment in a specified follow up.

The comparative design of a case series would be suitable since it allows conducting direct clinical observation of clinical outcomes in two groups of patients who have undergone two treatment modalities in the usual clinical conditions. The design enables the evaluation of the effect, tolerability, and practicability of the newer laser-based therapy in comparison with the conventional systemic therapy.

Study Setting

The research will be conducted in the Department of Dermatology, the part of the clinical institution/hospital where the study will be conducted. In the outpatient department of the hospital, patients admitted with clinically suspected onychomycosis will be vetted against qualification and recruited following an informed consent. The renewal of the diagnoses and treatment will be conducted on a dermatological basis.

Study Population

The study population will consist of adult patients with the diagnosis of onychomycosis with one or more of their nails (fingernails and toenails) who come to dermatology outpatient clinics throughout the study period [5].

A total of 20 patients will be enrolled in the study. The number of eligible participants will be broken down into two groups of 10 patients each.

Sampling Method

The convenience method of sampling will be employed. The sample size of the patients to be recruited will be attained through a series of consecutive recruitment of patients to the study until it has reached the required population size.

Study protocol will dispense participants into two treatment groups.

Inclusion Criteria

The following criteria will be used to select the patients:

- Age above 18 years
- Clinical diagnosis of onychomycosis of the nail of fingers or toes.
- Positive potassium hydroxide, (KOH) microscopy and/or fungal confirmation where needed.
- Informed consent was agreed to by patients who were voluntary and had a written consent.
- Patients who can be followed up in the course of treatment.

Exclusion Criteria

Patients who will be excluded will be those with the following conditions:

- Women who are pregnant or lactating.
- Severely ill patients (systemically)
- History of hypersensitivity of itraconazole or luliconazole.
- Patients who have had systemic antifungal therapy in the last 3 months.
- Psoriasis, lichen planus, trauma, and other non-fungal nail dystrophy patients.
- Liver disease or cannot take oral itraconazole.
- Patients who refuse to be involved or cannot follow-up.

Group Allocation and Intervention

The patients that are registered will be split into 10 equal groups.

Group A

Group A patients will be provided with:

- **Fractional Carbon Dioxide (CO_2) Laser Therapy**
- **Topical 1% Luliconazole lotion**

Fractional CO_2 laser treatments will be taken periodically (under the supervision of a dermatologist). The laser parameters such as fluence, density, duration of pulse and passes will be standardized on the basis of the protocol at the institution. After laser therapy, patients will use the topical 1% luliconazole lotion on the affected nail once in a day during the time of the treatment [6].

Group B

Patients in Group B will receive:

- **Oral Itraconazole**
- **Topical 1% Luliconazole lotion**

The itraconazole will be given in line with the routine pulse or continuous dosage by the treating dermatologist. During this study, topical 1% luliconazole lotion will be applied daily on the affected nails.

Table 1: Treatment Groups and Interventions

Group	Number of Patients	Intervention	Duration

Group A	10	Fractional CO_2 laser + topical 1% luliconazole lotion	As per follow-up schedule
Group B	10	Oral itraconazole + topical 1% luliconazole lotion	As per follow-up schedule
Total	20	Comparative case series	Entire study duration

Study Procedure

Baseline Neo-natal, demographic and clinical data will be noted on each participant including:

- Age
- Gender
- Duration of disease
- Site involved (fingernail/toenail)
- Number of nails affected
- Clinical type of onychomycosis
- Previous treatment history
- Relevant medical history

A cautious examination of nails will be carried out prior to treatment. The affected nails will be documented by taking baseline clinical photographs which will then be compared with the completed clinical photographs on follow up.

It will then start with the patients being on their treatment.

Regular follow up visits will be established to monitor the treatment response and compliance and adverse effects. The improvement of nail appearance, the reduction of discoloration, the decrease of thickening and a planting of the healthy nail will be measured by clinical analysis.

Serial clinical photographs can be captured every time the patient is receiving a visit to monitor improvement.

Outcome Measures

Primary Outcome

The key objective will be:

- **Clinical improvement of onychomycosis lesions after treatment**

Clinical improvement will be measured in terms of:

- Lessening of nail stains.
- Weakening of nail plate
- Reduction of the subungual debris.
- Normal growth of the proximal nails.
- percent clearance of nails in general.

Secondary Outcomes

Secondary outcomes will consist of:

- Satisfaction of the patient with the treatment.
- Tolerability of treatment
- Side effects identified in treatment.
- Treatment compliance
- Follow-up recurrence in case of recurrence.

Table 2: Data Variables Collected from Participants

Variable	Method of Assessment
Age	Patient history
Gender	Patient record
Duration of onychomycosis	Patient history
Nail involved	Clinical examination
Number of nails affected	Clinical examination
Clinical subtype of onychomycosis	Dermatological assessment
Baseline severity	Clinical observation and photography
Treatment response	Follow-up clinical assessment
Adverse effects	Patient reporting and examination
Patient satisfaction	Follow-up interview

Data Collection Method

The structured case record form which will be used to collect data will be prepared specifically to do the study. The investigator will be recording all the observations that will occur whenever a patient is visited.

Photos will be kept with consent to be used in comparison of pre and post treatment outcomes.

All patient data would be stored under confidence and anonymized to analyze.

Statistical Analysis

The data obtained will be put into Microsoft Excel and the statistical software will be used to analyze the data. The summary will be provided using descriptive statistics and they will include:

- Mean age
- Gender distribution
- Duration of disease
- Number of nails affected
- Treatment outcomes

Continuous variables will be expressed as mean ± standard deviation, while categorical variables will be expressed as frequency and percentage.

The two groups will be compared and differences in response to treatment analyzed. Depending on the type of data, appropriate statistical tests, like Chi-square test or Student t-test might be employed. A p-value <0.05 will be considered statistically significant.

Ethical Considerations

The study will start with ethical approval by the Institutional Ethics Committee.

All the participants will be asked to sign an informed consent written before enrolment. Each participant should be informed about the objectives of the study, its procedures, the benefits it is going to have, and its potential risks.

Subjects will be free to pull out of the study at their own will, without compromising their healthcare services.

During the study, confidentiality of patient identity and medical records will be taken seriously. All data taken will be utilized academically and research-wise.

IV. RESULTS AND ANALYSIS

The number of patients included in the study was 20, clinically diagnosed with onychomycosis. All clients adhered to the scheduled therapy and post-therapy. The patients were segregated in the two groups of 10 each.

- **Group A:** Fractional Carbon Dioxide (CO_2) Laser + Topical 1% Luliconazole Lotion
- **Group B:** Oral Itraconazole + Topical 1% Luliconazole Lotion

The results were evaluated according to the clinical improvements of the nail appearance, decrease of discoloration, nail plate thickening, subungual debris, healthy nail regrowth, treatment adherence and satisfaction of patients.

The results of the comparative analysis are given below.

4.1 Demographic Profile of Patients

The study took into account 20 patients. The participants were between the ages of 22 and 61. Most of the patients were aged 31-50 years which is often known to have increased prevalence of onychomycosis since they were likely to have trauma recurrently, occupational as well as long-term exposure to the fungi [7].

Out of the 20 patients, males were affected slightly more as compared to females.

Table 1: Age and Gender Distribution of Patients

Variable	Group A (n=10)	Group B (n=10)	Total
Male	6	5	11
Female	4	5	9
Mean age (years)	39.8	41.2	40.5
Age range	24–58	22–61	22–61

Analysis

Both groups were similar in terms of the average age. There was a slight male predominance with 55-percent of all participants. The result is consistent with the established epidemiology of onychomycosis whereby increased workplace exposure and trauma to nails might be contributing to the development of the fungus.

Figure 1: "Pathophysiology and Clinical Features of Onychomycosis"

4.2 Clinical Characteristics of Onychomycosis

All the patients were examined thoroughly with nails at the baseline. Toenail involvement was observed in most of the patients whereas fewer patients were affected with the fingernail involvement.
The most widespread clinical type that was witnessed was distal lateral subungual onychomycosis.

Table 2: Baseline Clinical Characteristics

Clinical Characteristic	Group A	Group B	Total
Toenail involvement	8	7	15
Fingernail involvement	2	3	5
Single nail affected	4	3	7
Multiple nails affected	6	7	13
Distal lateral subungual onychomycosis	7	6	13
Total dystrophic type	2	3	5
Superficial white type	1	1	2

Analysis
The presence of toenail in 75% of the patients confirmed the fact that toenails are more commonly affected as compared to fingernails. There was also a more prevalence of multiple nail involvement as compared to isolated nail disease [8].
The most common subtype was distal lateral subungual onychomycosis which comprised most of the cases in the treatment groups.

4.3 Treatment Response
Follow-up visits were used in measuring clinical response which occurred through reduction in discoloration, reduction of thickening, reduction of subungual debris and healthy regrowth of the nail.

Figure 2: "Pathophysiology and Clinical Features of Onychomycosis"

Fractional CO 2 laser, when used with topical luliconazole patients improved nail clarity and proximal healthy nail growth faster than patients undergoing oral itraconazole used with topical luliconazole.

Table 3: Comparison of Clinical Improvement after Treatment

Treatment Outcome	Group A (Laser + Luliconazole)	Group B (Itraconazole + Luliconazole)
Excellent improvement (>75%)	6	4
Moderate improvement (50–75%)	3	4
Mild improvement (<50%)	1	2
No response	0	0

Analysis
An excellent clinical improvement was seen in 60% of patients in Group A as opposed to 40% in Group B.
Both groups had a moderate improvement but slightly higher in Group B and one patient in Group A had a mild response with two patients in Group B having mild improvement.

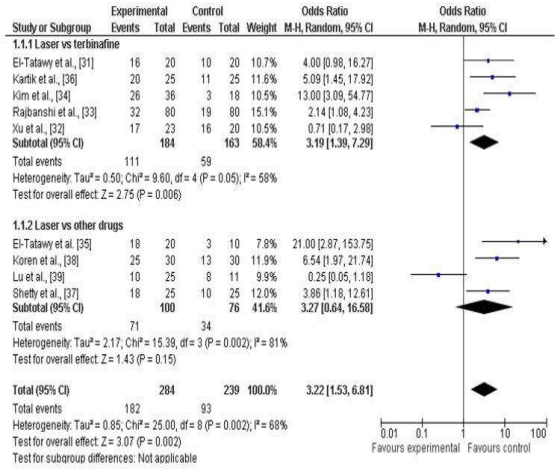

Figure 3: "Comparative Treatment Outcomes in Onychomycosis"

There was no case of treatment failure in either group. Generally, Group A had improved more visibility and faster nail clearance than Group B.

4.4 Adverse Effects and Treatment Tolerability

Evaluation of adverse effects was done each time of follow up visit.

Most patients who underwent laser treatments noted slight procedure pains or a temporary burning pain right after the surgery. These symptoms spontaneously improved.

Systemic side effects were more frequent in patients who were given oral itraconazole.

Table 4: Adverse Effects Observed in Both Groups

Adverse Effect	Group A	Group B
Mild pain/burning during procedure	3	0
Temporary redness	2	0
Gastric discomfort	0	2
Nausea	0	1
Elevated liver enzymes	0	1
No adverse effects	5	6

Analysis

Group A had slight local side effects, which were well tolerated, and temporary.

Group B was associated with having itraconazole therapy-related systemic adverse effects (gastrointestinal symptoms and mild laboratory abnormality).

There had been no serious complications nor had laser therapy been considered unsafe or distasteful.

4.5 Patient Satisfaction and Overall Outcome

Satisfaction regarding the patient was measured according to the visible improvement level, ease of treatment, convenience and readiness to proceed with the treatment [9].

Patients receiving fractional CO_2 laser also were more satisfied as the improvement was quicker and oral medication no longer required.

Table 5: Patient Satisfaction Score

Satisfaction Level	Group A	Group B
Highly satisfied	7	5
Satisfied	2	3
Moderately satisfied	1	2
Unsatisfied	0	0

Analysis

Most patients in the two categories were happy about the outcomes of treatment. But a greater level of satisfaction was noted in Group A.

Seventy percent of the patients undergoing laser treatment were highly satisfied as compared to 50 percent in the itraconazole group.

This implies that laser-assisted therapy could be associated with enhanced patient acceptance based on observable results, decreased exposure of medication systemically with more convenient treatment timing.

TABLE 5

Onychomycosis Treatment Options and Clinical Cure Rates

Medication	Location	Dosage	Clinical cure rate	Cost*
Oral				
Fluconazole (Diflucan)	Fingernails	150 mg weekly until the entire nail grows out	76%	$50 ($2,000)
	Toenails	150 mg weekly until the entire nail grows out	31.2%	$100 ($4,500)
Itraconazole (Sporanox)	Fingernails	Two treatment pulses of 200 mg twice daily for one week separated by three weeks without treatment	78%	$37 ($1,540)
	Toenails	200 mg daily for 12 weeks	14% to 62.6%	$115 ($4,500)
Terbinafine	Fingernails	250 mg daily for six weeks	75%	$12 (—)
	Toenails	250 mg daily for 12 weeks	38% to 76%	$20 (—)
Topical				
Ciclopirox 8%	Fingernails	Applied once daily for 24 weeks	5.5%	$20 (—) for one bottle
	Toenails	Applied once daily for 48 weeks	6% to 9%	$20 (—) for one bottle
Efinaconazole 10% (Jublia)	Toenails	Applied once daily for 48 weeks	15.2% to 17.8%	— ($650 for one bottle)
Tavaborole 5% (Kerydin)	Toenails	Applied once daily for 48 weeks	6.5% to 9.1%	$430 ($1,500) for one bottle

*—Estimated lowest GoodRx price. Actual cost will vary with insurance and by region. Generic price listed first; brand name price in parentheses. Information obtained at https://www.goodrx.com (accessed July 29, 2021; zip code: 66211).

Information from references 19 and 22–31.

Figure 4: "Comparative Treatment Outcomes in Onychomycosis"

Overall Comparative Analysis

The current research was a comparison of two treatment management options in the management of onychomycosis:

- Fractional CO_2 laser + topical 1% luliconazole lotion

  versus
- Oral itraconazole + topical 1% luliconazole lotion

The combination of oral itraconazole with topical 1 per cent luliconazole lotion.

The two modalities of treatment were clinically beneficial in treating nail fungal disease. Nevertheless, some significant differences were identified.

The CO_2 laser fractional group showed to have a better overall clinical response, faster mendability as well as patient satisfaction. The topical delivery of luliconazole was probably improved by penetrating the nail plate by the use of a laser which resulted in better therapeutic results. Good results were also achieved in the oral itraconazole group and it continues to be a useful standard treatment. Nevertheless, systemic side effects and limitations due to medication were more common. Results indicate that fractional CO_2 laser with topical 1% luliconazole is a potential safe and effective alternative to oral itraconazole prophylaxis, especially in patients, in which systemic antifungal prophylaxis is contraindicated or poorly tolerated. Since the study involved a rather weak sample of only 20 patients, the recommendation would be to apply bigger studies with a longer follow-up to ascertain its long-term effectiveness, recurrence, and continuous nail clearance.

V. CONCLUSION

This research was able to compare the effectiveness of fractional carbon dioxide (CO_2) laser and topical 1% luliconazole lotion vs oral itraconazole and topical 1% luliconazole lotion in managing onychomycosis in 20 patients. Both of the treatment modalities showed clinical improvement and were able to decrease nail discoloration, thickening and other appearances of fungal infection. But, the one that was treated with fractional CO_2 laser using topical luliconazole reported a relatively improved situation, a more swiftness in the nail of the patient in terms of clearance and a patient that was quite satisfied. The laser-assisted method also emerged to be tolerated well with few temporary local discomfort, with the oral itraconazole group exhibiting some systemic side effects, like gastric discomfort and nausea. These results imply that fractional CO_2 lasers can increase the penetration of topical antifungal therapy and its efficacy as well as decrease the usage of systemic medication. This can be of particular help in patients, who are unable to take oral antifungals, or contraindicated to systemic treatment. The limited sample size used therefore limits the results, but they suggest that fractional CO_2 laser with topical 1% luliconazole is a safe, effective and promising treatment of onychomycosis. It should be provided in bigger studies with extended follow-up to better uphold these results and determine long-term outcomes and recurrence rates.

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