A Study of Excimer Laser with Itraconazole versus Itraconazole Monotherapy in the Management of Onychomycosis: A Single-Center, Assessor-Blinded Randomized Control Trial

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ABSTRACT

Background: Onychomycosis, a prevalent and persistent fungal infection affecting nails, can be caused by dermatophytes, yeasts, and non-dermatophyte molds, impacting 5-10% of the global population. Oral medications like itraconazole are commonly used but have drawbacks such as extended treatment duration and side effects. Laser therapy is emerging as a promising alternative to mitigate systemic side effects and address nail abnormalities, and studies have shown its effectiveness in eradicating fungi.

Objectives: The study aimed to evaluate the effectiveness and safety of excimer laser treatment for onychomycosis and compare it with itraconazole alone by evaluating clinical improvement using the onychomycosis severity index (OSI).

Methods: Baseline onychomycosis severity was assessed using the OSI conducted by a third-party assessor. Nail scrapings were examined with potassium hydroxide and fungal culture. Oral antifungals were administered for 2-3 months. Group A received oral antifungals monotherapy, while Group B received oral antifungals and underwent excimer laser treatment weekly for 2-3 months with assessments conducted at seven timepoints: baseline, 2nd, 4th, 8th, and 12th weeks before each treatment, and at 16th, 20th, and 24th weeks from baseline.

Results: Fifteen patients (mean age 51.9 ± 15.6 years; 53.3% female) were enrolled, with a mean disease duration of 93 months and an average of five nails affected. Distolateral subungual onychomycosis was the predominant clinical type, most frequently caused by *Candida* and *Aspergillus species*. Both the excimer laser plus itraconazole group and itraconazole monotherapy group showed progressive clinical and mycological improvement during follow-up. By week 16, complete clinical clearance was achieved in 26.7% of patients in the combination group and 40.0% in the monotherapy group with similar results at weeks 20 and 24, while by week 12, 93.3% in both groups were KOH-negative and 100% had negative fungal cultures. No adverse effects were reported. Recurrence occurred in 6.7% in the combination group and two patients 13.3% in the monotherapy group. Dermoscopic features improved in both groups, with no statistically significant differences observed between treatment arms at any time point (all $p > 0.05$).

Conclusion: Excimer laser therapy is a safe and effective adjunct for onychomycosis, achieving outcomes comparable to oral antifungal monotherapy, with high clearance rates, low recurrence, and no adverse effects. The 308-nm excimer laser may be considered a valuable adjunct for patients unresponsive to or unsuitable for systemic therapy and immunocompromised patients.

Keywords: excimer laser, itraconazole, onychomycosis, fungal infection

INTRODUCTION

Onychomycosis, which constitutes roughly half of all nail disorders, is a prevalent, persistent fungal infection affecting either the nail plate or nail bed. It is brought about by dermatophytes, yeasts, and nondermatophyte molds[1] Onychomycosis is a widespread infection with a high global prevalence, impacting 5-10% of the global population. Dermatophytes are responsible for over 60% of onychomycosis cases, and mixed infections involving both dermatophytes and non-dermatophytes may occur in up to 40% of onychomycosis cases.[2]

The simplest method for detecting fungi is a 20% potassium hydroxide (KOH) preparation, though its sensitivity is limited to 40-60% while another option is culture on Sabouraud 2% dextrose agar with up to 70% false negatives, partly due to prior antifungal use.[1]

Disclosures: *The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

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Modern diagnostic methods such as conventional polymerase chain reaction (PCR), real-time PCR techniques, and matrix-assisted laser desorption ionization-time of flight mass spectrometry have become reliable for on-site identification of dermatophytes, yeasts, and non-dermatophyte molds in onychomycosis, assuming sufficient nail material is collected.[3]

Treatment options for fungal nail infections encompass both topical and oral agents. Nevertheless, creams and other topical treatments often prove ineffective in addressing nail fungus due to the formidable barrier posed by the hardness of the nail plate, making it challenging for topical medications to penetrate. The primary oral medications commonly employed for treating onychomycosis include griseofulvin, terbinafine, itraconazole, and ketoconazole. However, oral antifungal agents often require longer treatment durations and an increased likelihood of side effects. This necessitates daily intake for 8 weeks when addressing fungal infections of the fingernails and 12 weeks for toenails. Common adverse effects include headaches, gastrointestinal disturbances, skin rash, and elevated liver enzyme levels.[4] Itraconazole is frequently prescribed for one week per month over a span of 2 to 3 months. However, it can potentially interact with commonly used medications like the antibiotic erythromycin or asthma drug fluticasone.[49]

The utilization of lasers in addressing nail abnormalities presents itself as a promising choice to mitigate the systemic adverse effects associated with oral treatments. Additionally, it offers an alternative for patients who cannot undergo oral treatments due to preexisting organ dysfunction or potential drug interactions.[5] Laser systems are frequently employed to treat onychomycosis. They work by selectively photothermolysis, which inhibits fungal growth. However, the effectiveness of this treatment varies depending on the specific equipment utilized.[17]

This study aimed to assess the efficacy of the excimer laser in treating onychomycosis and intends to provide an adjunctive procedure to patients who have persistent lesions of onychomycosis and for individuals in which oral antifungals are contraindicated.

OBJECTIVES

General Objective

Evaluated the efficacy and safety of excimer laser in the treatment of onychomycosis

Specific Objectives:

1. Determined the baseline characteristics of patients undergoing excimer laser with itraconazole vs itraconazole monotherapy such as age, sex, duration of disease, severity, clinical type, location, number of diseased nail, type of fungi
2. Determined the significant difference in the percentage reduction of severity of onychomycosis using OSI at weeks 2, 4, 8, 12, 16, 20 and 24.
3. Assessed clinical improvement in terms of severity using OSI for onychomycosis at weeks 2, 4, 8, 12, 16, 20 and 24
4. Determined the mycologic cure of both groups on KOH or culture examination at baseline and week 12
5. Evaluated the tolerability, safety and adverse effects of excimer laser in treating onychomycosis
6. Monitored recurrence of lesions at weeks 16, 20 and 24 after the last treatment session
7. Compared the baseline and week 12 photographs and dermoscopy findings

Statement of the Hypothesis:

Null Hypothesis (HO):

There was no significant difference in the efficacy and safety between excimer laser with itraconazole and itraconazole monotherapy in the treatment of onychomycosis among Filipinos.

Alternative Hypothesis (Ha):

There was a significant difference in the efficacy and safety between excimer laser with itraconazole and itraconazole monotherapy in the treatment of onychomycosis among Filipinos.

REVIEW OF RELATED LITERATURE

Epidemiology

Onychomycosis has a worldwide prevalence estimated at approximately 10%, affecting up to 20% of individuals aged over 60, up to 50% of those over 70, and about one-third of people with diabetes.[41] In the United States, around 80% of cases of toenail onychomycosis are attributed to *Trichophyton rubrum*, while other infections are typically caused by *Trichophyton mentagrophytes* or *Epidermophyton floccosum*. Less frequently, toenail fungal infections may also involve *Candida parapsilosis* or *Fusarium species.*[29]

According to recent epidemiological studies that have been published, the worldwide prevalence of onychomycosis is approximately 5.5%.[9,10] Even when individuals receive appropriate oral antifungal therapy,

10% to 53% of patients still experience recurrence, which can manifest as either relapse or reinfection.[11]

In South America, the average prevalence was at its highest, reaching 18.8%. Meanwhile, in Europe, the mean prevalence stood at 8.9%, which was similar to North America at 9.0%. In Asia, the mean prevalence was 12.1%.[3]

In healthy adults in the United States, the typical nail growth rate is approximately 1.5 mm per month for toenails and 3-3.5 mm per month for fingernails.[28] Given this average growth rate, an effective treatment would ideally result in a completely replaced, clear fingernail in a healthy adult around 6 months after starting treatment. Similarly, it would lead to a fully replaced, clear great toenail approximately 12 months into the treatment.[27]

In the Philippines, findings revealed that fungal infections are the second most common reason for medical consultations, affecting approximately 12.98% of cases. Among these consultations, the most prevalent fungal conditions were pityriasis versicolor (25.34%), followed by tinea corporis (22.63%), tinea cruris (16.7%), and tinea pedis (16.38%).[43] Currently based from our research and knowledge, there is no data on the prevalence of onychomycosis in the Philippines.

Risk factors

Onychomycosis is a persistent fungal infection that affects the nail structure, encompassing the nail bed, nail plate, or matrix. Risk factors for onychomycosis include a weakened immune system, aging, diabetes, psoriasis, and nail issues. Other factors include past dermatological problems like excessive sweating and athlete's foot, and external factors such as tight-fitting shoes, injuries, and poor nail care. Additionally, the presence of certain medical conditions like cancer, vein problems, reduced blood circulation, obesity, and inflammatory bowel disease can also elevate the risk.[2,31]

The primary risk factor for onychomycosis is advancing age, likely attributed to factors such as diminished peripheral circulation, extended exposure to pathogenic fungi, recurrent nail injuries, less effective immune function, and a slower rate of nail growth.[34] Diabetes, which is another significant comorbidity in onychomycosis patients, affects around one-third of them. Additionally, individuals living with human immunodeficiency virus (HIV) are at an elevated infection risk, affecting one in four HIV-positive individuals. There is a suggestion that diabetes combined with onychomycosis may lead to reduced treatment effectiveness, possibly due to high blood sugar levels or inadequate foot hygiene. Cure rates for diabetic patients with onychomycosis reached 13.0%, compared to 18.8% in non-diabetic individuals, although these differences did not reach statistical significance.[33] While onychomycosis can manifest at any age, its occurrence becomes more prevalent as individuals age. It notably affects approximately 50% of individuals over the age of 70 and is relatively uncommon among pediatric populations.[32]

Recurrence rate and complications

Onychomycosis poses a challenge to effective treatment, and recurrences are frequent, often stemming from the challenges associated with maintaining long-term adherence to therapy.[8] It is a major health concern due to its potential to cause pain, discomfort, physical limitations, and negative psychological and social impacts on individuals' personal and professional lives. Research has shown that this condition significantly impairs the quality of life and overall well-being of those affected, leading to distress and reduced functionality and mental health.[39,40]

The use of ciclopirox 8% nail lacquer results in mycologic cure rates ranging between 29% and 36%. Studies have demonstrated that when itraconazole was administered, the combined clinical and mycologic cure rates reached 60.9%, while for the terbinafine group, it was 64.7%.[36] A new topical agent under imidazole, luliconazole, has received approval for treating tinea infections. Research findings indicate that the daily application of luliconazole 5% nail solution exhibited clinical effectiveness in treating onychomycosis, and it was found to be well-tolerated with no reports of severe adverse drug reactions.[44] In addition, a daily application of efinaconazole topical solution at a concentration of 10% could serve as a valuable topical choice for addressing mild to moderate onychomycosis.[46] Over 25% of patients achieved complete cures, while nearly two-thirds of those with mild onychomycosis were deemed successful in their treatment by the 52nd week.[45]

Typically, topical medications are often ineffective due to their inability to penetrate the nail plate effectively. Meanwhile, oral antifungal drugs carry a significant risk of causing liver and kidney toxicity, along with potential drug interactions. These limitations linked to oral antifungal treatment for onychomycosis underscore the demand for a safer yet equally efficient alternative.[4] The highest incidence of drug-induced liver injury caused by antifungal medications is associated with voriconazole (32.45%), followed by fluconazole (19.37%), and itraconazole (14.51%).[38]

Recurrence is a frequent occurrence in onychomycosis, affecting between 10% and 53% of patients.[37] It may manifest one year or longer after the initial infection has been successfully treated. Patients with a genetic inclination or those belonging to susceptible groups, such as the elderly or individuals with diabetes, have a higher likelihood of experiencing a recurrence. In the elderly, physical injury may trigger a relapse.[37]

Nails that have 100% dystrophy or affect the lunula can prove challenging to treat because they may have sustained permanent damage to the nail matrix. This permanent damage can potentially reduce the overall effectiveness of treatment when assessed across a group of individuals. Conversely, nails with minimal distal changes may not accurately represent the target population for this procedure. Therefore, it is advisable that the study population should encompass nails with a minimum of 25% involvement of the nail area and no more than 75% involvement of the nail area.[27]

Laser therapy

In contrast to topical and oral treatments, laser therapy presents a more hopeful approach for managing the condition in individuals with diabetes, elderly patients who cannot tolerate medications, and those dealing with liver or kidney issues.[35]

Subsequently, laser therapies like long-pulsed 1064-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) lasers, short-pulsed 1064-nm Nd:YAG lasers, CO2 lasers, pulsed dye laser and lasers operating at wavelengths of 870-nm, 930-nm, and 1320-nm have started to surface as novel treatments for addressing onychomycosis.[24,5]

The precise mechanism of action underlying laser treatment for fungal nail infections remains somewhat unclear, although various hypotheses have been proposed. It is suggested that antifungal effects may be triggered through local hyperthermia, as well as the photothermal impact of the laser beam's penetration through the nail plate and its interaction with the nail bed.[30] Specifically, the laser beam is believed to be absorbed by the melanin found on the cell walls of the fungi. This absorption potentially inhibits fungal growth through pigment photothermolysis, affecting the nail matrix and nail plate.[18,6] Another study reported that these methods were aimed at creating micro-channels in the nails to facilitate the enhanced absorption of topical antifungal agents.[5]In the previous year, an article discussing laser systems for the emerging field of onychomycosis treatment was published in the Journal of the American Podiatric Medical Association. By January 2012, the United States FDA had granted approval to four laser systems for the "temporary improvement of clear nail appearance in onychomycosis." These approvals were granted based on the concept of "substantial equivalence" to previously established devices with comparable technical features and uses. Laser therapy seems to hold promise as an alternative to conventional pharmacotherapy; however, it is essential that these systems have undergone limited clinical trials.[6]

A study showed that the effectiveness of laser therapy for onychomycosis was approximately 63%. In comparison, the mycological effectiveness of itraconazole pulse therapy and continuous terbinafine therapy for onychomycosis were 79.6% and 84.8%, respectively. Therefore, the overall efficacy of laser treatment was moderately lower than that of traditional oral antifungal treatments. However, laser therapy had the advantage of fewer reported side effects, such as liver and kidney damage or gastrointestinal reactions.17

In practice, 1064-nm Nd:YAG lasers and CO2 lasers are more commonly utilized than 1320-nm Nd:YAG lasers. Numerous studies found that the combination of laser treatment with topical drugs yielded significantly higher mycological and clinical efficacy compared to laser treatment monotherapy.17 Another study illustrated that fungal nail infections can be efficiently and securely managed using the Q-Switched Nd:YAG 1064-nm/532-nm laser. Moreover, it can be employed in conjunction with systemic oral antifungal medications, resulting in a more concise treatment duration.[18]

In the case of fungal cells, particularly the mycelium enclosed by the chitin wall, heat dissipates slowly between laser pulses, leading to a gradual temperature increase within the mycelium, unlike the surrounding tissue, which efficiently disperses heat through tissue and water. Furthermore, lasers can disrupt the proteins essential for fungi to break down keratin. Additionally, changes in keratin, such as reduced disulfide bond intensity (at 490-590 cm) and modifications in β-sheet-dominant structures, have been observed following laser treatments.[26]

Notably, recent research has revealed a light absorption peak at 415 nm for *Trichophyton rubrum*, a pathogen responsible for onychomycosis. A similar absorption peak is observed in onychomycotic nails but is absent in healthy nails. This absorption peak is likely associated with mitochondrial cytochrome c found in fungi. Utilizing a wavelength in this range enables the laser to selectively target the fungi.[26]

Excimer laser

The 308-nm xenon-chloride excimer laser, a novel form of phototherapy, utilizes ultraviolet B (UVB) radiation and consists of a combination of a noble gas and a halide. Currently, the 308-nm excimer laser has been proven effective in the treatment of various skin conditions, including vitiligo, psoriasis, atopic dermatitis, alopecia areata, allergic rhinitis, folliculitis, granuloma annulare, lichen planus, mycosis fungoides, palmoplantar pustulosis, pityriasis alba, CD30+ lymphoproliferative disorder, leukoderma, prurigo nodularis, localized scleroderma and genital lichen sclerosus.[14] The 308-nm wavelength, which closely resembles the 311-nm used in nb-UVB phototherapy, is believed to operate through a similar mechanism. Ultraviolet B spectrum radiations are known to have immunosuppressive effects, including the induction of apoptosis in T-lymphocytes and immunomodulatory effects.[20]

Radiation with a wavelength less than 300-nm is highly efficient at eradicating microorganisms. Ultraviolet C radiation at a wavelength of 253.7-nm is especially potent in this regard. This particular range is referred to as the germicidal zone. Ultraviolet C radiation has limited penetration capabilities and does not reach beyond the layer of dead skin cells. It does not directly kill the cells but rather inflicts damage to their DNA, rendering the cells non-functional.[19] A study confirmed through testing that fungi can be effectively eradicated using minimal parameters, specifically with an energy pulse of 144 mJ and an energy density of 0.74 J/cm2, without any subsequent regrowth. With these parameters, it becomes feasible to administer 200 pulses at a repetition frequency of 10 Hz.19 Ultraviolet C radiation eliminates fungi by damaging their DNA. The research findings indicate that ultraviolet C radiation does not penetrate the fingernail deeply enough to harm the underlying soft tissue significantly. Fungi can be effectively eradicated by exposing them to low doses of radiation generated by an excimer laser.[19]

The benefits of monochromatic excimer laser therapy, when compared to other types of phototherapies, are highlighted as follows: reduced exposure to ultraviolet doses, shorter treatment duration, and, most importantly, the ability to precisely target specific areas of the skin without affecting the surrounding normal skin. Excimer lasers have limited tissue absorption depth, enabling the removal of microscopic tissue layers with minimal damage to the neighboring areas.[19]

Among patients undergoing this treatment, there have been reports of mild pain during irradiation. Fortunately, this discomfort is generally well-tolerated and typically resolves within a day.[7]

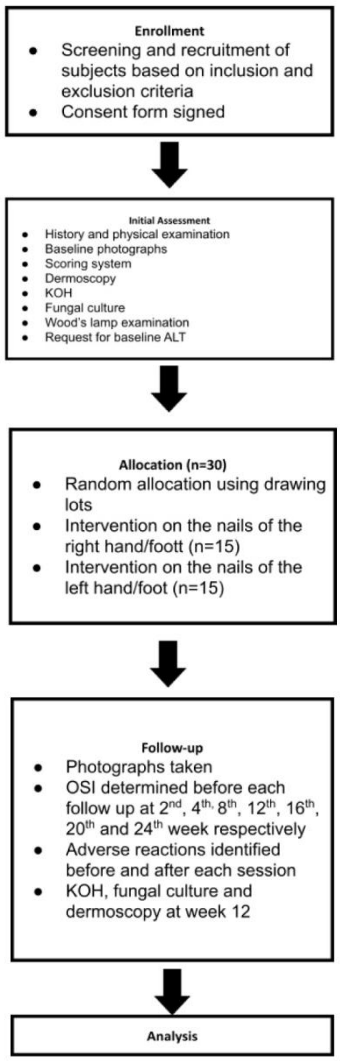
Regarding potential complications arising from laser therapy for onychomycosis, it documented the incidence of such complications is relatively low, which reaffirms its effectiveness as a treatment option for this condition. Nevertheless, it is essential to acknowledge potential side effects, which can include sensations of pain, heat, or tingling, as well as temporary darkening of the nail.[7]

RESEARCH DESIGN

The study was a single-center, assessor-blinded, randomized control trial study among eligible participants at the Jose R. Reyes Memorial Medical Center, Department of Dermatology from January 2024 to June 2025.

METHODOLOGY

Conceptual Framework



The approval of the Institutional Review Board (IRB) and the Chair of the Department of Dermatology was obtained before conducting this experimental study.

Recruitment and initial evaluation

Recruitment and screening was done via face-to-face consultation at the outpatient complex of the Department of Dermatology, Jose R. Reyes Memorial Medical Center after gaining approval from the IRB.

An in-vitro pilot study with 5 onychomycotic nail specimens was done. The agar plates were inoculated with the 5 specimens circularly at 1, 3, 5, 7, 9, and 11 o'clock. The culture media was marked to distinguish the right and left sides for a comparison of sides. Afterward, the cultures were incubated for a maximum of 30 days at 30° C.[47]

Each fungal culture was treated with a different setting. The fungal culture was divided into equal quadrangles. The upper left part was treated with a 150 mj/cm2 single dose. The lower left part was treated with a 300 mj/cm^2 single dose. The upper right part was treated with a 150 mj/cm^2 thrice a week for one week. The lower right part was treated with a 300 mj/cm2 thrice a week for one week. Laser treatment was done without covering the fungal cultures and without cooling. The distance between the hand piece and culture was equal. For protection, the investigator wore latex gloves and goggles to cover the eyes. After treatment, the cultures were incubated at 30° C and the temperature remained constant throughout the study. The specimens were checked right after if the fungal species survived or not via KOH examination.

The initial phase involved screening to determine eligibility. The study was introduced with outlining the procedure, potential outcomes, and any adverse reactions. The primary investigator provided information on conventional treatment alternatives. Patients signed an informed consent form to enroll in the study, followed by a comprehensive history and physical examination.

Onychomycosis severity index is a scoring system used to categorize the severity of onychomycosis into mild, moderate, or severe cases. This classification was determined by multiplying the score for the extent of nail involvement (ranging from 0 to 5) by the score for the proximity of the infection to the nail matrix (ranging from 1 to 5). Baseline scoring was done by a third-party assessor (board certified dermatologist) on the nails of both hands. Baseline photographs were taken using a 12-megapixel camera (*iPhone 11, Apple*) in a single, well-lit room.

A Wood's lamp was placed above the nails under a dark room. It was used to observe any specific fluorescent pattern on the nails.[15]

Dermoscopy photos were evaluated by another third-party assessor (board certified dermatologist) on the nails of both hands or feet.

Nail scrapings were gathered from the proximal border of the onycholytic area using a surgical blade 15 (scalpel number 3, Secheron Germany). Before collecting the samples, the affected area was cleaned with 70% ethyl alcohol to eliminate bacteria and debris. For the purpose of isolating yeasts and non-dermatophyte molds, sabouraud dextrose agar was utilized. The cultures were incubated at a temperature of 25ºC for a maximum period of 30 days, with daily monitoring to assess fungal growth.[16] The identification of fungal species involved the examination of both the macroscopic (macromorphology) and micromorphological characteristics of isolated colonies. Two licensed medical technologists independently assessed both the KOH preparations and fungal culture results. One assessor is a licensed medical technologist and certified medical laboratory scientist with over six years of experience in clinical laboratory science, nuclear medicine, and dermatopathology. This assessor holds certifications from the Professional Regulation Commission (PRC), the American Society for Clinical Pathology, and the American Society for Clinical Pathology and Commission on Graduates of Foreign Nursing Schools International. The second assessor is a graduate of the Medical Colleges of Northern Philippines and a licensed medical technologist certified by the PRC, with two years of experience as a generalist in a secondary laboratory and four years of experience in a primary laboratory. He was mentored by a highly experienced medical technologist with over 20 years of expertise in the field.

Randomization, treatment allocation and blinding

All participants received the interventional treatment on the nails of one side of the hand or feet. Randomization whether the treatment was done on the right or left determined using simple allocation by drawing lots. Paper slips numbered from one to thirty were placed into a box. A patient randomly selected one slip, and if the number was even, the treatment was administered on the right side; otherwise, it was on the left. This way, the number of patients who were treated on the right side was equal to patients treated on their left. The primary investigator and all participants were aware of the treated side. A blinded third-party assessor not involved in the study did the assessment for the nails of both hands.

Technical Information

An excimer laser device (*Exciplex® Excimer Light Machine*) was used in this study. It is a portable, handheld monochromatic excimer light device with a wavelength of 308 nm.

Figure 1. Excimer laser device

Study Intervention

All patients received the intervention on the same side on each subsequent visit. Before each session, patients were asked to thoroughly wash and dry their hands, and to remove nail polish, if present.

All patients were given oral antifungals (itraconazole 100mg capsule 2 capsules twice daily 7 days) for 2-3 months after having their alanine aminotransferase (ALT) levels were determined. Group A hand received oral antifungal for 2-3 months. Group B hand received oral antifungal for 2-3 months and excimer laser weekly for 2-3 months.

Treatment with excimer laser repeated every week, starting after initial assessment at baseline for a total of 12 sessions. Assessment of each participant was done at 7 timepoints: at baseline, 2nd, 4th, 8th, and 12th week before each treatment session as well as after the last treatment at 16th, 20th and 24th from the baseline. The total study duration was 6 months.

Clinical Assessment

During the follow-up appointments, photographs were taken both before and right after each treatment session using a 12-megapixel camera (*iPhone 11, Apple*). These photographs served for documentation and evaluation purposes and maintained the consistent settings, patient positioning, and lighting conditions for all images. Evaluation of clinical outcomes will be conducted separately for the nails of both hands.

A third-party assessor (board certified dermatologist) who was not part of the study performed a manual evaluation of the nails. He used the OSI scoring system for this assessment. Any adverse effects noted during previous sessions, including but not limited to pigmentation issues, erythema, edema and pruritus, were documented before each subsequent treatment. Furthermore, immediate assessment of any adverse reactions was conducted after each treatment session.

Primary and Secondary Endpoints

The primary endpoint of this study was reduction of mean percentage difference in the OSI on the treated and untreated side between the baseline and each follow-up.

The secondary endpoints of this study was the change in OSI on the treated and untreated side between the baseline and each follow-up.

Stopping guidelines

The intervention was discontinued for any participant who experiences moderate to severe adverse reactions, such as burns or increase in liver enzymes 3x, even if it occurs just once. Additionally, any participant who chooses to no longer take part in the study was free to withdraw at any time.

STUDY SUBJECTS

Patients assessed with onychomycosis via KOH examination and fungal culture at the outpatient department of Dermatology, Jose R. Reyes Memorial Medical Center were enrolled in this study.

Inclusion Criteria

- Filipino
- Male or female
- At least 18 years old
- Signed informed consent
- Have a clinical diagnosis of distal subungual onychomycosis in the nail of at least two digits, with 20% to 50% clinical involvement of the target nail, without dermatophytomas or lunula (matrix) involvement, without lunular or proximal involvement
- Exhibit positive mycology results (KOH or fungal culture)
- Willing to refrain from using polish or other medication
- Have undergone a washout period of topical steroids, topical antifungals and systemic antifungals for nails of 6 months before study enrollment
- Able to complete the study and comply with follow up period

Exclusion Criteria

- Less than 18 years old
- Females who are pregnant, plan to become pregnant during the study, or are nursing a child
- Persons who are hypersensitive to antifungal medications
- Persons who have received systemic antifungal therapy for any reason within 3 months, or topical antifungal therapy on the toenails or skin immediately adjacent to the toenails within 3 weeks prior to the start of the study
- Persons who have received an investigational drug within 4 weeks of the first dose of study product, or who are scheduled to receive an investigational drug other than the study product during the study
- Persons who have participated in a clinical trial for the systemic treatment of onychomycosis of the toenails within 6 months prior to the first dose of study product
- Persons who are not prepared to give up use of any nail cosmetic products for the duration of the study
- Persons who have any known immunodeficiency or history of malignancy in the last 4 years, excluding nonmelanoma skin cancer
- Persons currently suffering from any disease or condition, that could include abnormal laboratory tests, and/or who are currently using medication which in the opinion of the investigator may affect the evaluation of the study product or place the subject at undue risk
- Persons with psoriasis, lichen planus, or other medical conditions known to induce nail changes, other abnormalities or can cause nail breakdown that can predispose to secondary fungal infection
- Persons with a history of any condition that could possibly affect absorption of drug (e.g., gastrectomy), uncontrolled diabetes, clinically significant peripheral vascular disease or peripheral circulatory impairment, or has had any major illness within 30 days prior to the screening examination
- Persons with a history of drug or alcohol abuse within the past 2 years

ASSESSMENT INSTRUMENTS

Photographs at baseline and on subsequent follow-up were taken using a 12-megapixel camera (*iPhone 11, Apple*).

Onychomycosis severity index was employed to assess the severity of onychomycosis, with the following grading system: 0 indicating the absence of onychomycosis, 1-5 representing mild onychomycosis, 6-15 denoting moderate onychomycosis, and 16-35 signifying severe onychomycosis (See Table 1).[21]

Table 1. Onychomycosis severity index (OSI) of onychomycosis

Area of involvement		Proximity of disease to matrix		Presence of dermatophytoma or subungal hyperkeratosis >2mm	
Affected nail %	Points	Amount of involvement from distal edge	Points	Present	Points
0		<1/4	1	No	0
1-10		¼-½	2	Yes	10
11-25	2	>½-¾	3		
26-50	3	>¾	4		
51-75	4	Matrix involvement	5		
76-100	5				

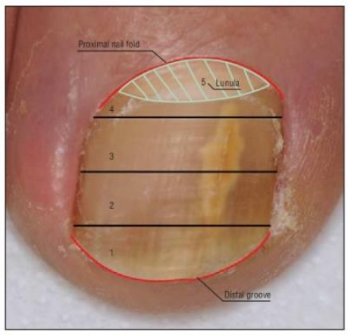


Figure 2. Onychomycosis severity index (OSI)[21]

Fungal culture was conducted both at the beginning of the treatment (baseline) to confirm the presence of the fungi.

Potassium hydroxide examination was conducted both at the beginning of the treatment (baseline) and 12 weeks after the treatment to determine mycological cure, defined as negative results in microscopy and culture. Potassium hydroxide test was graded using the semi-quantification of fungal hyphae in the KOH mount using hyphal index for this assessment.

Table 2. Semi-quantification of fungal hyphae in the potassium hydroxide (KOH) mount using hyphal index[48]

KOH mount finding (per 100 fields)	Grading according to the Hyphal Index
Absence of fungal hyphae	0
Presence of up to 4 hyphae	1+
Number of hyphae present between Hyphal Index 1+ and 3+	2+
Presence of multiple hyphae	3+

The occurrence of any adverse reactions was recorded and documented during each of the follow-up assessments. This comprehensive approach ensured that any potential adverse effects were carefully monitored and recorded for a more in-depth understanding of the treatment's safety profile.

The recurrence of lesions was documented and carefully recorded. If any signs or symptoms resurface, they underwent evaluation using the KOH examination. A positive result from the KOH examination served as confirmation of the recurrence.

STATISTICAL/ DATA ANALYSIS PLAN

Sample Size Calculation

This paper used the following formula to calculate the required sample size for the study.

$$n = 2\frac{\left\{Z_{\alpha/2}\sqrt{2(P)(1-P)} + Z_{1-\beta}\sqrt{(P_1)(1-P_1)+(P_2)(1-P_2)}\right\}^2}{(P_1-P_2)^2}$$

Where:

P_1 is the prevalence of outcome in unexposed group

P_2 is the prevalence of outcome in the exposed group

P is $((P_1+P_2)/2$

α is level of significance

β is 1 – Power of test

Following the paper of Weber et al. (2018), this paper used a 95% significance level, 80% power, 40.00% for P1 (expected clinical improvement for itraconazole alone) and 90.00% for P2 (expected clinical improvement for excimer laser with itraconazole). The parameters yielded a required sample size of 30.

$$n = 2\frac{\left\{1.96\sqrt{2(0.65)(1-0.65)} + 0.84\sqrt{(0.4)(1-0.4)+(0.9)(1-0.9)}\right\}^2}{(0.4-0.9)^2} \approx 30$$

Given that the trials were conducted intrabody, 15 individuals were recruited for the study.

Data Analysis Plan

Categorical variables were summarized as frequencies and percentages, and continuous variables were presented as means with standard deviations. Comparisons of categorical outcomes, including OSI, mycologic results, adverse effects, and dermoscopic findings, were performed using Pearson's chi-squared test or Fisher's exact test, as appropriate. A significance level of 5% was applied for all statistical analyses. Analyses were conducted using STATA version 16.1 and Microsoft Excel.

Table 3. Baseline Demographic and Clinical Characteristics of the Patients

Variables	Values
Age, mean ± SD (years)	51.9 ± 15.6
Sex, n (%)	
Female	8 (53.3%)
Male	7 (46.7%)
Body part treated, n (%)	
Foot	8 (53.3%)
Hand	7 (46.7%)
Laterality of Excimer Laser with Itraconazole, n (%)	
Left	7 (46.7%)
Right	8 (53.3%)
Duration of disease, mean ± SD (months)	93.1 ± 94.1
Number of nails affected, mean ± SD	5.1 ± 3.5
Severity, n (%)	
Mild	5 (33.3%)
Moderate	3 (20.0%)
Severe	7 (46.7%)
Clinical type, n (%)	
Distolateral subungual onychomycosis	12 (80.0%)
Total dystrophic onychomycosis	2 (13.3%)
Mixed onychomycosis	1 (6.7%)
Fungi, n (%)	
Candida	6 (40.0%)
Aspergillus	5 (33.3%)
Trichophyton	2 (13.3%)
None	2 (13.3%)
Wood's lamp, n (%)	
Negative	15 (100.0%)

Table 3 presents the baseline demographic and clinical characteristics of the 15 patients included in the study. The mean age of the participants was 51.9 ± 15.6 years, comprising 8 females (53.3%) and 7 males (46.7%). Lesions were located on the foot in 8 patients (53.3%) and on the hand in 7 patients (46.7%). The excimer laser combined with itraconazole was applied to the left side in 7 patients (46.7%) and the right side in 8 patients

(53.3%). The mean duration of disease was 93.1 ± 94.1 months, and the mean number of nails affected was 5.1 ± 3.5.

Regarding clinical severity, 5 patients (33.3%) had mild, 3 (20.0%) had moderate, and 7 (46.7%) had severe onychomycosis. The most common clinical type was distolateral subungual onychomycosis (12 patients; 80.0%), followed by total dystrophic onychomycosis (2 patients; 13.3%) and mixed onychomycosis (1 patient; 6.7%). Culture results identified *Candida species* in 6 patients (40.0%), *Aspergillus species* in 5 (33.3%), and *Trichophyton species* in 2 (13.3%), while 2 patients (13.3%) had no fungal growth. All patients tested negative under Wood's lamp examination.

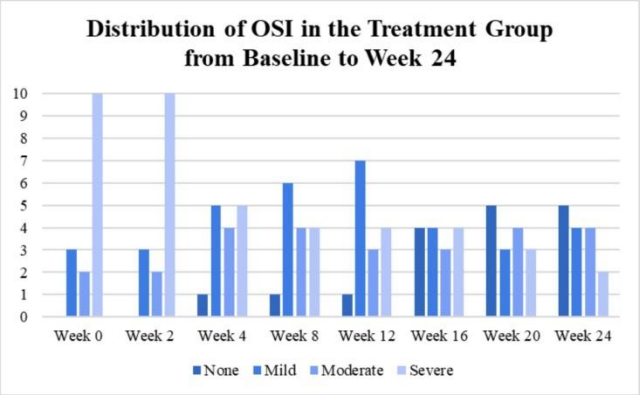


Figure 3. Distribution of OSI in the treatment group from baseline to week 24

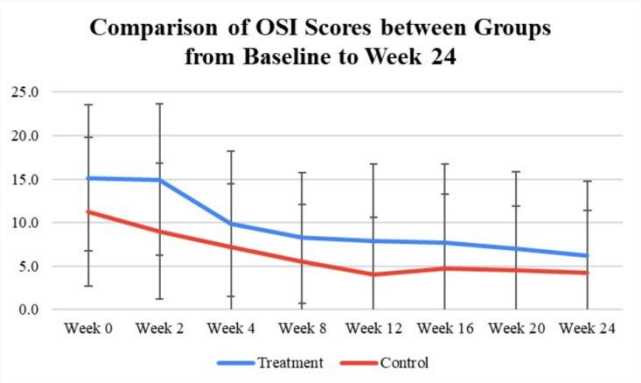


Figure 4. Comparison of OSI scores between groups from baseline to week 24

Table 4. Comparison of OSI between treatment groups at baseline and follow-up visits

Variables	Excimer Laser with Itraconazole (n 15)	Itraconazole Monotherapy (n 15)	p-values[1]
Baseline, n (%)			
Absent	-	-	.868
Mild	3 (20.0%)	5 (33.3%)	
Moderate	2 (13.3%)	2 (13.3%)	
Severe	10 (66.7%)	8 (53.3%)	
Week 2, n (%)			
Absent	-	1 (6.7%)	.401
Mild	3 (20.0%)	6 (40.0%)	
Moderate	2 (13.3%)	2 (13.3%)	
Severe	10 (66.7%)	6 (40.0%)	
Week 4, n (%)			
Absent	1 (6.7%)	1 (6.7%)	.895
Mild	5 (33.3%)	6 (40.0%)	
Moderate	4 (26.7%)	5 (33.3%)	
Severe	5 (33.3%)	3 (20.0%)	
Week 8, n (%)			
Absent	1 (6.7%)	2 (13.3%)	.631
Mild	6 (40.0%)	7 (46.7%)	
Moderate	4 (26.7%)	5 (33.3%)	
Severe	4 (26.7%)	1 (6.7%)	
Week 12, n (%)			
Absent	1 (6.7%)	3 (20.0%)	.369
Mild	7 (46.7%)	9 (60.0%)	
Moderate	3 (20.0%)	2 (13.3%)	
Severe	4 (26.7%)	1 (6.7%)	
Week 16, n (%)			
Absent	4 (26.7%)	6 (40.0%)	.602
Mild	4 (26.7%)	6 (40.0%)	
Moderate	3 (20.0%)	1 (6.7%)	
Severe	4 (26.7%)	2 (13.3%)	
Week 20, n (%)			
Absent	5 (33.3%)	5 (33.3%)	.641
Mild	3 (20.0%)	6 (40.0%)	
Moderate	4 (26.7%)	2 (13.3%)	
Severe	3 (20.0%)	2 (13.3%)	
Week 24, n (%)			
Absent	5 (33.3%)	5 (33.3%)	.505
Mild	4 (26.7%)	7 (46.7%)	
Moderate	4 (26.7%)	1 (6.7%)	
Severe	2 (13.3%)	2 (13.3%)	

[1]** - significant at the 1% level; * - significant at the 5% level.

Table 4 summarizes the OSI classifications for patients in the excimer laser with itraconazole combination group and the itraconazole monotherapy group at baseline and during follow-up visits through week 24.

At baseline, most patients in both groups presented with severe onychomycosis (66.7% in the combination group and 53.3% in the monotherapy group), with no significant difference in OSI classifications between groups (p 0.868).

Over time, both groups demonstrated a progressive improvement toward milder disease categories. By week 16, 26.7% of patients in the combination group and 40.0% in the monotherapy group showed no signs of onychomycosis. Similar patterns were observed at weeks 20 and 24, where the proportion of patients with absent or mild disease continued to increase in both groups.

Despite these favorable trends, no statistically significant differences were observed between the two treatment groups at any time point (all p > 0.05), indicating comparable efficacy of excimer laser plus itraconazole combination therapy and itraconazole monotherapy in reducing disease severity over the 24-week follow-up period.

Table 5. Comparison of Mycological Outcomes Between Treatment Groups at Baseline and Follow-Up Visits

Measure	Time Point	Variables	Excimer Laser with Itraconazole (n 15)	Itraconazole Monotherapy (n 15)	p-values1
KOH, n (%)	Baseline	3+	5 (33.3%)	5 (33.3%)	1.000
		Spores	3 (20.0%)	3 (20.0%)	
		Yeast Cells	1 (6.7%)	1 (6.7%)	
		None	6 (40.0%)	6 (40.0%)	
	Week 12	Spores	1 (6.7%)	1 (6.7%)	1.000
		None	14 (93.3%)	14 (93.3%)	
Fungal Culture, n (%)	Baseline	Positive	13 (86.7%)	13 (86.7%)	1.000
		Negative	2 (13.3%)	2 (13.3%)	
	Week 12	Negative	15 (100.0%)	15 (100.0%)	1.000

Table 5 compares the mycological outcomes between the combination therapy group (excimer laser with itraconazole) and the itraconazole monotherapy group at baseline and week 12 follow-up. At baseline, both groups demonstrated comparable distributions of KOH findings (p 1.000). By week 12, the majority of patients in both groups were KOH-negative (93.3%), with only one patient in each group remaining positive for spores, and no significant difference was observed between groups (p 1.000).

For fungal culture, baseline positivity was equally high in both groups (86.7%), while all patients achieved negative cultures by week 12 (100%). Again, no statistically significant differences were observed between the two treatment arms (p1.000).

Table 6. Comparison of adverse effects and recurrence between treatment groups at follow-up visits

Variables	Excimer Laser with Itraconazole (n 15)	Itraconazole Monotherapy (n 15)	p-values1
Adverse Effects, n (%)			
Absent	15 (100.0%)	15 (100.0%)	1.000
Recurrence, n (%)			
Present	1 (6.7%)	2 (13.3%)	.500
Absent	14 (93.3%)	13 (86.7%)	

[1]** - significant at the 1% level; * - significant at the 5% level.

Table 6 summarizes the adverse effects and recurrence rates in both groups. No adverse effects were reported in either the combination therapy or monotherapy group. Recurrence was observed in one patient (6.7%) in the combination therapy group with *Trichophyton species* and in two patients (13.3%) in the monotherapy group with *Trichophyton species* and *Aspergillus species*, with no statistically significant difference between groups (p 0.543).

Table 7. Comparison of dermoscopy findings between treatment groups at baseline and follow-up visits

Measure	Time Point	Variables	Excimer Laser with Itraconazole (n 15)	Itraconazole Monotherapy (n 15)	p-values[1]
Longitudinal White Striae, n (%)	Baseline	Positive	10 (66.7%)	11 (73.3%)	.500
		Negative	5 (33.3%)	4 (26.7%)	
	Week 12	Positive	6 (40.0%)	6 (40.0%)	1.000
		Negative	9 (60.0%)	9 (60.0%)	
Jagged Proximal Edge, n (%)	Baseline	Positive	8 (53.3%)	8 (53.3%)	1.000
		Negative	7 (46.7%)	7 (46.7%)	
	Week 12	Positive	7 (46.7%)	7 (46.7%)	1.000
		Negative	8 (53.3%)	8 (53.3%)	
Intermittent Spiked Pattern, n (%)	Baseline	Positive	13 (86.7%)	14 (93.3%)	.500
		Negative	2 (13.3%)	1 (6.7%)	
	Week 12	Positive	11 (73.3%)	12 (80.0%)	.500
		Negative	4 (26.7%)	3 (20.0%)	
Chromonychia	Baseline	Positive	15 (100.0%)	14 (93.3%)	.500
		Negative	-	1 (6.7%)	
	Week 12	Positive	12 (80.0%)	11 (73.3%)	.500
		Negative	3 (20.0%)	4 (2.67%)	
Distal Irregular Termination, n (%)	Baseline	Positive	13 (86.7%)	12 (80.0%)	.500
		Negative	2 (13.3%)	3 (20.0%)	
	Week 12	Positive	10 (66.7%)	10 (66.7%)	.650
		Negative	5 (33.3%)	5 (33.3%)	
Trachyonychia, n (%)	Baseline	Positive	7 (46.7%)	6 (40.0%)	.500
		Negative	8 (53.3%)	9 (60.0%)	
	Week 12	Positive	4 (26.7%)	5 (33.3%)	.500
		Negative	11 (73.3%)	10 (66.7%)	
Linear Edge, n (%)	Baseline	Positive	10 (66.7%)	9 (60.0%)	.500
		Negative	5 (33.3%)	6 (40.0%)	
	Week 12	Positive	6 (40.0%)	7 (46.7%)	.500
		Negative	9 (60.0%)	8 (53.3%)	

[1] ** - significant at the 1% level; * - significant at the 5% level.

Table 7 presents the dermoscopic findings at baseline and Week 12. At baseline, both treatment groups demonstrated comparable proportions of longitudinal white striae, jagged proximal edge, intermittent spiked pattern, chromonychia, distal irregular termination, trachyonychia, and linear edge, with no significant differences across any parameter (all $p > 0.05$). At week 12, reductions were observed in positive dermoscopic signs in both groups, although the differences between combination therapy and monotherapy remained statistically non-significant for all features

DISCUSSION

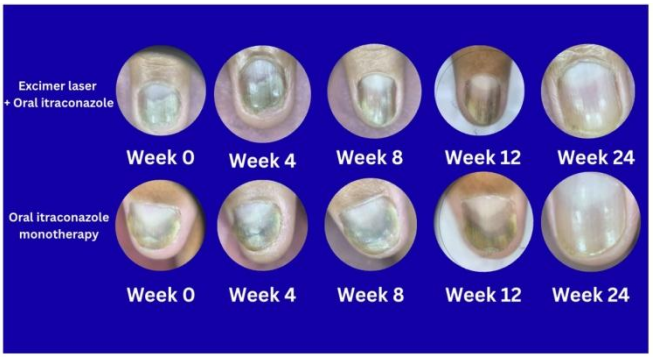


Figure 5. Representative clinical photographs at baseline, week 4, week 8, week, 12 and week 24 for both excimer laser with itraconazole and itraconazole monotherapy groups

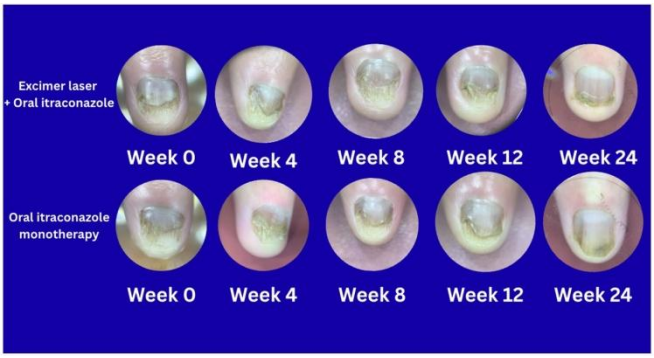


Figure 6. Representative clinical photographs at baseline, week 4, week 8, week 12 and week 24 for both excimer laser with itraconazole and itraconazole monotherapy groups

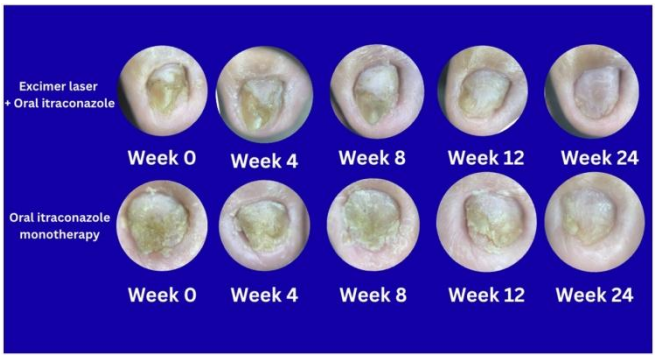


Figure 7. Representative clinical photographs at baseline, week 4, week 8, week 12 and week 24 for both excimer laser with itraconazole and itraconazole monotherapy groups

This study evaluated the efficacy and safety of excimer laser in the treatment of onychomycosis. There was no significant difference observed between both treatment groups for OSI, KOH, fungal culture, dermoscope, adverse effects and recurrence in 24 weeks. Both groups demonstrated progressive improvement toward milder classifications, with no statistically significant differences between them. By week 12, the majority of patients in both groups were KOH-negative, with only one patient per group remaining positive for spores, and all fungal cultures had converted to negative. No adverse effects were reported in either the combination therapy or the monotherapy group.

Given that ultraviolet c radiation has fungicidal properties, both the oral antifungal medication and the excimer laser were effective in eradicating the fungus.[6] Itraconazole inhibits the fungal cytochrome P450-dependent enzyme lanosterol 14-α-demethylase, thereby blocking the conversion of lanosterol to ergosterol and disrupting fungal cell membrane synthesis. It demonstrates fungistatic activity against yeast-like fungi and fungicidal activity against *Aspergillus species*.[51] As demonstrated in previous studies, fungi are highly sensitive to ultraviolet radiation, with even relatively low-power wavelengths in the ultraviolet spectrum capable of consistently destroying them.[6]

Excimer lasers exhibit minimal tissue absorption depth, enabling the precise removal of microscopic tissue layers while minimizing collateral damage to surrounding areas. Studies have shown that only a small radiation dose is required to eradicate fungi, an advantage in preventing injury to the soft tissue beneath the nail.[19]

The results indicate that nails do not transmit radiation at wavelengths below 400-nm. Importantly, when irradiating the nail with a laser in the ultraviolet c spectrum, there is no concern of ultraviolet penetration into the underlying skin, thereby avoiding potential adverse thermal, biochemical, or photophysical effects.[19]

Recurrence occurred in one patient from the combination therapy group and in two patients from the monotherapy group. Notably, even with appropriate oral antifungal treatment, recurrence remains common, affecting 10% to 53% of patients, and may present either as relapse or reinfection.[11]

Reductions in dermoscopic features such as longitudinal white striae, jagged proximal edge, intermittent spiked pattern, chromonychia, distal irregular termination, trachyonychia, and linear edge were observed in both groups by week 12, with no statistically significant differences between combination therapy and monotherapy. A previous study similarly reported clearance of white opalescent areas and the appearance of whitish-yellowish zones progressing toward the distal nail unit following three sessions of laser therapy. Simple dermoscopy thus serves as a practical tool for evaluating treatment outcomes.[52]

Excimer laser is also cost-effective, with an estimated cost ranging from (350-(800 per session for a total of 8-12 sessions amounting (2,800-(9,600, making it a practical alternative to prolonged systemic or topical therapy. Compared to itraconazole 100mg capsule 2 capsules twice daily 7 days for 2-3 months from (5,000-(10,000 with (90-120 per capsule.

CONCLUSION

In conclusion, excimer laser therapy proved to be a safe and effective adjunct in the management of onychomycosis, demonstrating comparable outcomes to oral antifungal monotherapy in terms of clinical, mycological, and dermoscopic parameters, with no reported adverse effects. Both treatment approaches achieved high rates of fungal clearance and progressive

improvement, with low recurrence observed over 24 weeks. The 308-nm excimer laser can be considered a new and effective tool in the treatment of onychomycosis, particularly for patients who do not respond to standard medications or are unsuitable for systemic antifungal therapy. This method may serve as an efficient alternative for managing chronic nail fungal infections, particularly in patients with diabetes, those for whom traditional treatments are inappropriate, immunocompromised individuals, and those who are refractory to therapy. Furthermore, both modalities may be used in combination to optimize therapeutic outcomes.

LIMITATIONS OF THE STUDY

The study was an operator-dependent procedure. As of this writing, there is still no standardized treatment protocol for the treatment of onychomycosis using this device and further standardization and certification is needed for its application on onychomycosis. The duration of relapse from the last session of treatment was unknown beyond three months after the last session and further studies are needed to support its efficacy on long term control of onychomycosis.

The primary investigator and study subjects cannot be blinded because all participants will receive the treatment on the nails of each hand and foot.

The treatment groups included both hands and feet, which may have influenced the study results due to several factors.

RECOMMENDATION

Long-term follow-up studies spanning 3 to 5 years are recommended to evaluate the sustained efficacy, recurrence rates, and overall clinical outcomes of excimer laser therapy for onychomycosis. Continuous monitoring will help determine its lasting impact, safety profile, and potential role as a standard alternative treatment in chronic or refractory cases.

DISCLOSURES

The primary investigator personally funded this study and neither the primary nor co-investigators received any sponsorship from any manufacturer, distributor or company.

ETHICAL CONSIDERATIONS

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. The research protocol was submitted for approval to the IRB of Jose R. Reyes Memorial Medical Center, and to the Chair of the Department of Dermatology before commencing the study.

Only the primary investigator, co-authors and residents-in-charge of the patient have access to subjects' medical charts. Subjects who met the inclusion criteria was required to sign an informed consent form, stating their permission to have their clinical data and photographs be taken. The procedure was properly explained and possible side effects were discussed with the patient. The investigator only included the patient's age, sex and necessary information such as diagnosis and treatment outcomes. The patient's name, contact number and address were taken during enrollment for follow-up purposes. Code names were assigned to each participant and their names as well as their other personal information did not appear on any of the data collection tools.

After the study period, the participant had the option to receive the same treatment on the untreated side of the face free of charge care of the primary investigator or to receive conventional treatment options for onychomycosis.

DATA PROTECTION PLAN

All data obtained from this study were stored in the primary investigator's database with projected storage duration of 10 years in case the investigators need to review the source data should there be questions about the results. These data were used solely for the study and the principal investigator and co-authors can access these data. We will destroy the data after the said duration. Data collection commenced after approval of the IRB and lasted for twelve months duration of the study.

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