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Is Laser Therapy an Effective Alternative Treatment for Onychomycosis in Patients where the Hepatotoxity of Oral Antifungals is of Concern?

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Is Laser Therapy an Effective Alternative Treatment for Onychomycosis in Patients where the Hepatotoxity of Oral Antifungals is of Concern?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not, "Is laser therapy an effective alternative treatment for onychomycosis in patients where the hepatotoxicity of oral antifungals is of concern?"

STUDY DESIGN: Review of three English language primary studies, published between 2010 and 2012.

DATA SOURCES: Two randomized controlled trials (RCTs) and one prospective cohort study were found using Cochrane Systematic Reviews and PubMed. These studies analyzed the effectiveness of laser therapy in patients with onychomycosis.

OUTCOMES MEASURED: Main outcomes measured were nail clearance and mycological assessment. Nail clearance was determined clinically using photographs taken at different intervals and mycological assessment was determined by microscopic exam. Adverse effects were tracked in all studies and patient satisfaction was considered in one study. The tools used to assess significance of outcomes measured were p-values, percentage of nail clearance, and negative mycological assessment.

RESULTS: All three studies showed a significant nail clearance and fungal culture after laser therapy intervention. In the Ladsman et al study, it was shown using an 870 and 930-nm laser improved nail clearance by at least 3mm ($p<0.0073$) and negative fungal cultures in 42% of the toes after one treatment and 75% on day 60 with an (ABI of 40%).[1] In the Zhang et al study, the Long-Pulse 1064-nm laser showed no significant difference in treatment duration, but did show positive improvement in nail clearance and fungal cultures regardless the duration of treatment.[2] In the Kimura et al prospective cohort study, it was shown using the Sub-Millisecond 1064-nm laser showed complete clearance in 51% and significant clearance in 81% of patients. Of the 51% with complete clearance, they also were 100% negative on fungal culture.[3]

CONCLUSSION: The results of one RCT and one cohort study which compared before and after treatment groups demonstrated that laser therapy may be an effective treatment for onychomycosis in patients that may not be able to take oral antifungals for reasons medically indicated. One RCT compared effectiveness of varied treatment durations and found no significant difference between the two groups.

KEY WORDS: Onychomycosis, Tinea Unguium, Laser Therapy.

INTRODUCTION

Onychomycosis (Tinea Unguium) is a trichophyton infection of one or more (but rarely all) fingernails or toenails.[4] The fungal infection most commonly causes brittleness, yellowish discoloration, and hypertrophic changes causing a deformity in the nail.[4] Rarely does it cause pain. Most commonly, it is more a cosmetic concern; however, secondary infection is of concern in diabetics and in the immunocompromised patient.[4]

The overall prevalence rate is 2% to 3%[2]; however, the prevalence rate increases to 14% to 28% in persons over the age of 60.[3] Onychomycosis is most often an incidental finding during a routine physical exam and rarely the main reason for a patient visit to their healthcare professional. Onychomycosis is the most common inflammatory disease of the nails, representing 15-40% of all nail disturbances.[6] It is most commonly caused by *T. rubrum*[4] and *T. mentagrophytes*.[5] Other etiologies like yeasts and fungi are also common causes.[5] Nails become lusterless, brittle, hypertrophic, and the substance of the nail becomes friable.[4]

Total annual cost could not be determined; however, they estimated the cost of diagnosis, drug acquisition, and management of adverse reactions per person using Griseofulvin, itraconazole (continuous therapy), Itraconazole (pulse therapy), and fluconazole is $4917, $2072, $1072, and $1042 respectively.[5] Recently Laser therapy has been studied in the treatment of onychomycosis and the estimated cost is $750 to $1,000 per person. Although less expensive, insurance companies have not yet recognized laser therapy as an alternative treatment and do not cover the cost.

From 1994 to 2004 in the USA, there were 51 million visits for superficial fungal infections in which Onychomycosis represented 23.2% of all dermatophyte visits.[6] This adds up to approximately 1,219,820 visits per year or 433 per 100,000 doctor appointments.[6]

Until recently, oral antifungals and/or surgical removal of the nail were the mainstay of treatment. Although oral antifungals are found to be extremely effective, they do carry with them a side effect profile of hepatotoxicity. As mentioned earlier, onychomycosis is seen more commonly in the elderly; therefore, oral antifungals are rarely an option. Surgical removal is invasive and carries the risk of secondary infection which limits the use in the diabetic and/or immunocompromised population. Prior to a newly FDA approved topical antifungal, topicals were rarely used due to their inability to penetrate the nail; therefore, were deemed ineffective in the treatment of onychomycosis.

Although the treatment options mentioned above are effective, they are known to be hepatotoxic, invasive, and carry a higher cost. There is a reported 10% to 53% recurrence or relapse rate[3] which therefore requires longer duration treatments making patient compliance a concern, higher costs to insurers, and more importantly, the associated hepatotoxicity. Laser therapy has shown some promise in the non-invasive and non-hepatotoxic treatment of onychomycosis. Thus far, numerous studies have been conducted and results vary slightly on type of laser and duration of treatment; however, regardless of the treatment, all studies are showing positive nail clearance and negative fungal cultures post treatment. Also, the use of laser therapy has no known side effects and if anything, slight warmth at treatment site might be noted.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not, "Is Laser Therapy an effective alternative treatment for onychomycosis in patients where the hepatotoxicity of oral antifungals is of concern?"

METHODS

The population age range for the review ranged from 18 to 75 years of age with diagnostic evidence of Onychomycosis. The studies involved the interventional use of the Noveon Dual-wavelength near-infrared diode laser, Pinpointe Footlaser long-pulse Nd: YAG 1064-nm laser, and Sub-millisecond 1064-nm ND: YAG lasers. The comparison groups in the two RCTs received either a Sham treatment, lower dose treatment, or a shorter duration of treatment. In the Prospective Cohort study, no comparison group was utilized. The outcomes were measured clinically and by mycological assessments. Photographs were taken at prescribed intervals to determine nail clearance along with fungal cultures being tested post-protocol. The three studies consisted of two Randomized Control Studies and one prospective cohort study.

A detailed search using Cochrane Systematic Reviews and PubMed databases were completed by the author using the keywords "Onychomycosis," "Tinea Unguium," "Laser Therapy." Articles were selected based on their relevance to clinical practice and importance to patient-oriented outcomes (POEMs-Patient Oriented Evidence that Matters). All articles chosen for this review were peer-reviewed and published in well-known journals. Inclusion criteria consisted of articles that were either RCTs or Primary studies published after 2000 in which no other systematic review, meta-analysis, or review article was found on the COCHRANE database answering the same question. Studies excluded were those with patients treated with other treatment modalities such as oral antifungals, topical antifungals, or surgically removed nails. A summary of statistics reported or used were RBI, ABI, NNT, and P-values. Table 1 displays the demographics and characteristics of these articles.

Table 1 – Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclsusion Criteria	Exclusion Criteria	W/D	Interventions
Kimura[3] (2012)	Prospective Cohort Study	13	37-88	Positive fungal infection diagnosis via KOH and microscopic examination.	If they were prescribed oral antifungals within 1 year of study, topical antifungals within 1 week of study, had a serious generalized medical condition, or the potential to be pregnant.	0	Sub-millisecond 1,064-nm ND: YAG Laser
Landsman[1] (2012)	Single-Blind RCT	34	18-70	At least one great toe with distal, lateral, or superficial white onychomycosis that did not involve the lunula or extend to the eponychium. Positive laboratory confirmation of onychomycosis. Fitzpatrick skin color grading: 1-4.	Fitzpatrick Skin Color Grading 5 & 6 (Darkest shades), patients with a history of psoriasis, lichen planus, or a history of trauma to toe involved, immunocompromised, or patients who received prescription antifungal medications within the last 6 months.	0	Noveon Dual-Wavelength near-infrared Diode Laser.
Zhang[2] (2012)	Single-Blind RCT	33	18-75	Clinical Diagnosis of onychomycosis. Positive results of fungal direct microscopic examination. Positive fungal culture with Sabouraud's medium.	If they were prescribed topical antifungals within 1 month, systemic antifungals within 6 months, stopped or altered treatment plan, pregnancy, hematoma, nevoid, psoriasis, lichen planus, atopic dermatitis, or bacterial infection.	0	Pinpointe Footlaser long-pulse ND: YAG 1064-nm laser.

OUTCOMES MEASURED

The outcomes measured were POEMs. Outcomes were measured in a variety of ways to include Clinical assessment, photographic images, laboratory studies, patient satisfaction, and safety. Landsman et al used three criteria in the evaluation of outcomes: nail clearance,

mycological assessment, and safety. Photographs were taken on day 0, 14, 42, 120, and 180. They graded the nail clearance as follows: completely cleared, markedly improved, slightly to moderately improved, or unchanged. The photographs were reviewed by the investigators and an independent panel to ensure integrity of the study. Fungal cultures utilizing acid-Schiff staining were taken at baseline and periodically throughout the study and graded accordingly. In determining nail clearance, outcomes were measured based on at least 3mm of clear linear growth. Adverse effects noted during the trial were documented. Zhang et al used four categories of outcome measurement: nail clearance, mycological effects, patient satisfaction, and safety. Nail clearance in which nail samples were taken before treatment and at weeks 8, 16, and 24 and were graded by percentage of nail clearance. Four categories were used: 1. Full-grown new nail with < 5% defects. 2. Significant effect with >60% newly grown nail. 3. Improvement with >20% and <60% newly grown nail. 4. Inefficacy with <20% newly grown nail. During nail sampling, fungal cultures were also taken to determine mycological effect of treatment. Subjective data was collected and used to determine patient satisfaction and were graded as follows: not satisfied, generally satisfied, satisfied, and very satisfied. Any adverse effects noted during the trial were documented. Kimura et al focused their study on two assessments that were summed up into one score. The two assessments were based off level of improvement in Turbidity score and mycological assessment. Assessment of turbidity was conducted at baseline and 16 weeks post study. Utilizing photographs, the investigator and two separate dermatologists analyzed the photographs. Mycological assessments were conducted using a KOH prep. Combined assessments were given a score of 0 to 4 with 0 representing no nail clearance and 4 representing complete nail clearance. Any adverse effects noted during the trial were documented.

RESULTS

The three studies chosen evaluated the effectiveness in laser therapy for the treatment of onychomycosis and did not compare laser therapy to standard treatment practices. All subjects included in each study were assessed prior to treatment and assessed throughout the study at prescribed intervals. All of the studies utilized laser therapy as the intervention, but varied slightly the type of laser utilized and duration of treatment. Each study had similar inclusion and exclusion criteria (see Table 1). Throughout each of the studies, safety and protocols were followed. Temperature of nail beds were monitored, settings on lasers were verified, and all adverse events were documented.

The study conducted by Landsman et al consisted of 34 subjects randomly assigned to a treatment group (n = 25) or a control group (n = 9). Also included in the randomization was number of eligible toes: treatment group (n = 26) and the control group (n = 11). Prior to treatment protocols and to ensure laser accuracy, the laser was calibrated before and after each treatment. Each patient and/or toe received a total of four treatments: days 1, 14, 42, and 120. Each treatment consisted of two does of laser therapy: first dose consisted of a 4-minute exposure using both 870 and 930 nm simultaneously and the second dose consisted of a 2-minute exposure with a 930 nm dose. The control group followed the exact protocols as that for the treatment group, but instead received what they call a "sham treatment". Sham treatment consisted of the same laser, same treatment number, and same durations. All that differed was the setting on the laser which was set at 0 (no energy output).[1]

A variety of outcomes were measured during this study, but for purposes of this review, only two of the three outcomes were used: Nail clearance and Mycological assessment. As mentioned in the outcomes measured section, photographs were used to assess nail clearance and

acid-Schiff staining methods were used for mycological assessment. According to the study, laser therapy was shown to be effective in achieving at least 3mm of nail clearance (p = 0073) when compared to the control group. Also, there was a negative mycological assessment of 64% at day 120 post treatment; however, was not compared to the control group. Combined, there was a 39% that achieved negative fungal cultures and nail clearance of at least 3mm on day 180 of the study.[1]

Table 2 – Results of 870 and 930-nm Laser Therapy[1]

	RBI	ABI	NNT	P-value
Nail Clearance of at least 3mm	5%	40%	3	0.0073

The study conducted by Zhang et al consisted of 33 subjects randomly assigned to group 1 (n = 15) and group 2 (n = 18). Also included in the randomization was number of eligible toes: group 1 (n = 78) and group 2 (n = 76). Group 1 was to receive two courses of treatment (eight sessions) whereas Group 2 was to receive a single course of treatment (4 sessions). There was not a control group in their study. Groups were randomly selected and only varied in their treatment durations. Intervention was accomplished by the use of the Pinpointe Footlaser long-pulse Nd:YAG 1064-nm laser. A full course is defined as having four sessions on days 0, 7, 14, and 21.[2]

A variety of outcomes were measured in this study to include fungal cultures and microscopic examinations, clinical evaluations, patient satisfaction, and safety. Outcomes were measured on days 8, 16, and 24. This study did not focus on whether or not laser therapy is effective, but more the effectiveness of different treatment prescriptions. According to the study, there was not a significant difference in clinical assessment between the two groups (p>0.05). Patient satisfaction was an overall 87% with 4 subjects being unsatisfied. On mycological

assessment, there appeared to be a high recurrence rate with positive cultures appearing higher at week 24. No reported adverse event occurred in any of the 33 subjects. Table 3 summarizes the results of the study by Zhang et al.[2]

Table 3 – Clinical Effectiveness and Positive Fungal Cultures[2]

	Week 8	Week 16	Week 24
Clinical Effectiveness			
Group 1	63%	62%	51%
Group 2	68%	67%	53%
Positive Mycological Assessment			
Group 1	13%	20%	27%
Group 2	11%	11%	11%

The study conducted by Kimura et al was a Prospective Cohort study consisting of 13 subjects that demonstrated turbidity in 37 toenails along with positive microscopic analysis. Intervention utilized in this study was the Sub-millisecond 1064-nm Nd:YAG laser. Treatments consisted of 1 to 2 minutes per toenail with 4 to 8 weeks between sessions. The 13 subjects were treated differently with seven subjects receiving three sessions, five subjects receiving two sessions, and one subject receiving one session.[3]

Two outcomes were measured in this study and summed to provide the investigators with one score. Clinical assessment of turbidity was achieved via photographs taken at baseline and weeks 4, 8, 12, 16, 20, and 24. At week 24, if a subject presented for follow up with 100% turbidity clearance, a microscopic analysis was then performed and the subject was graded accordingly. Overall, 81% of subjects received moderate to complete clearance post treatment. Of the 16% with no clearance, it was noted at baseline they had a turbidity score of 10 which indicated a completely turbid nail. Other than a slight warmness sensation during treatment sessions, no adverse effects were noted significant. Table 4 illustrates the results of overall

improvement at final follow-up with complete clearance also indicating a negative microscopic result.[3]

Table 4: Overall Improvement[3]

Complete Clearance	Significant Clearance	Moderate Clearance	Slight Clearance	No Clearance
51%	19%	11%	3%	16%

DISCUSSION

The results from these studies demonstrate that laser therapy is an effective and safe alternative treatment for onychomycosis. Although none of the studies compared laser therapy directly to already proven treatments, as far as effectiveness goes, these early studies show promise. However, before insurance companies consider compensation for such treatments, further studies should be conducted comparing the two.

Throughout the studies, there were limitations that may have altered the results. According to the Landsman et al study, fungal cultures could result in false positives if not enough new nail growth occurs prior to sample. They believe dead pathogens are still recognized in the nail tissue; therefore, showing positive nail fungus.[1] The Lang et al study believes numerous factors could have contributed to the results. They feel the lack of effectiveness could have been due to treatment duration, treatment depth, laser energy, and different fungal strains having varied sensitivities to laser therapy. Treatment variations based on cultured pathogen must be made to effectively kill fungi as today's medicine does with antibiotics.[2] Also considered a contributing factor was the reoccurrence and relapse rates. Were all subjects taking the same preventative measures? Is recurrent rate high regardless? Like mentioned earlier, recurrence and relapse rates are high even in today's mainstay of treatment.

In doing the initial search, this researcher found there to be few RCTs or other peer-reviewed studies conducted on the effectiveness of laser therapy. The studies reviewed met all requirements of the IRB, followed strict protocols and were randomly selected; however, sample sizes were small and no study compared laser therapy to standard therapies such as oral antifungal use.

CONCLUSION

Laser therapy is an effective alternative treatment for onychomycosis. All three studies showed evidence of effective clearance of nails and negative mycological assessments post-study. Although not directly compared to current treatments, laser therapy has proven to be just as effective if not more effective to the 59% mycological cure rate of oral antifungals.[1] Also, there were no concerning adverse effects noted in any of the studies.

Due to the limited amount of studies, small sample sizes, and no comparison studies, future studies are needed to directly compare laser therapy with today's standard treatments of oral and topical antifungals as well as comparing the many different types of lasers currently being used to treat onychomycosis. Thus far, results appear to be promising and the possibility of having a cheaper, safer, and more effective treatment available to the consumer is in the near future.

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