Case report

The effectiveness of laser therapy in onychomycosis patients: An evidence-based case report

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Abstract

Background: Onychomycosis may cause nail discoloration, thickening, nail bed separation, and other serious complications. For some cases, oral antifungal treatment is not tolerable because of its potential side effects and drug interactions. Laser therapy is considered as an alternative treatment, owing to the features of simple and effective, with only minor potential side effects. This EBCR was made to collect and appraise studies regarding the effectiveness of laser therapy for onychomycosis, and to suggest laser as an alternative treatment.

Methods: Literature searching strategy was performed using Pubmed and Cochrane Library database to address the clinical problem. Keywords used were “laser” AND “onychomycosis”.

Results: Seventy-nine articles were obtained from the search strategy procedure. After selection based on exclusion and inclusion criteria, and full-text availability, four relevant articles remained.

Discussion: The study by Xu et al. was considered as the most valid study while compared to other three studies. This study used intention to treat analysis and had no loss of follow-up patients. Xu et al. compared mycological and clinical clearance rate between patients receiving laser, oral{terbinafine}, or combination of those two. It showed that laser therapy was less effective when compared to oral antifungal (Number Needed to Harm = 17).

Conclusions: Laser has a lower level of effectiveness while compared to oral terbinafine as the current gold standard therapy for onychomycosis. However, laser therapy can still be used as an adjunctive therapy along with oral antifungal to achieve a better cure rate. More studies are needed to prove this hypothesis.

Keywords: onychomycosis, laser therapy, effectiveness

Introduction

Onychomycosis is a fungal infection of the nail. It may cause nail discoloration, thickening, and nail bed separation. Epidemiologically, it affects 10% of the general population. This number has a tendency to increase in the aged group. It affects 20% of people older than 60 years old, and 50% in those older than 70 years old.¹ Although onychomycosis is widely regarded as a merely cosmetic issue, it should be noted that onychomycosis has potential serious complications, such as cellulitis and foot ulcers. People at risk are the immunocompromised, the elderly, and diabetic patients. Complete eradication of the fungal infection is a key to preventing those complications.¹

Oral antifungals, such as ketoconazole, itraconazole, fluconazole and terbinafine are effective and therefore considered as the gold standard.¹,² However, these antifungals are not
suitable for all patients due to their potency of drug interactions, side effects, and contraindications.²³ Use of topical antifungals is also limited because of lacking ability to penetrate into the nail plate. The failure rate of topical antifungal ciclopirox is more than 60%.³ Laser therapy is considered as another choice of treatment due to its simple and effective features with minimal potential side effects. On the basis of these statements, this evidence-based case report was conducted to determine the effectiveness of laser therapy in onychomycosis patients.

Case Illustration

A 56 years old female patient with discoloration of the right big toenail, which had been neglected for about 5 years, was presented to the clinic. Physical examination revealed yellow-white nail discoloration, onycholysis, and subungual hyperkeratosis. The dermatologist she had visited suggested her to be on oral antifungal for 3 consecutive months for her onychomycosis, which then she refused. She came to the clinic asking information regarding laser therapy for toenail infection, specifically fungal infection. She asked whether such treatment was effective for treating her condition.

Clinical Question

In developing the research question, we use PICOT approach, which is explained below:
Question: In a patient with onychomycosis, is laser therapy effective?
- Patient: Patient with onychomycosis
- Intervention: Laser therapy
- Comparison: -
- Outcome: Effectiveness (mycological and clinical cure)
- Type of question: Therapy

Methods

Search Strategy

Literature search procedures were performed to address the clinical problem using Pubmed and Cochrane Library database on April 25th, 2016. Keywords used were “laser” AND “onychomycosis” (see table 1).

Critical Appraisal

The articles were independently appraised, using standardized criteria. Disagreement between researchers was resolved by a discussion.

Table 1. Literature search strategy

<table>
<thead>
<tr>
<th>Database</th>
<th>Search strategy</th>
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<tbody>
<tr>
<td>PubMed/Medline</td>
<td>(&quot;lasers&quot;[MeSH Terms] OR &quot;lasers&quot;[All Fields] OR &quot;laser&quot;[All Fields]) AND (&quot;onychomycosis&quot;[MeSH Terms] OR &quot;onychomycosis&quot;[All Fields]) AND (effective?[All Fields])</td>
</tr>
<tr>
<td>Cochrane</td>
<td>“onychomycosis” AND “laser”</td>
</tr>
</tbody>
</table>

Articles were reviewed in order from the most recent. (see table 2)

Results

Search and Selection Results

Seventy-nine titles were obtained; the selection of literature was conducted based on title/abstract and elimination of duplicates. Further selection was conducted based on inclusion and exclusion criteria as shown in the flowchart (see figure 1). Four matched articles to the issue were obtained.

Critical Appraisal Result

Based on our searching strategy, four RCT articles were included (Xu, et al.; Hollmig, et al.; Ortiz, et al.; Landsman, et al.). Validity, importance, and relevance comparison results are explained in table 3 and 4.

Discussion

From the four included studies, only study by Xu et al.⁵ used intention to treat (ITT) analysis. Samples were divided into three groups: The T group (oral terbinafine), the L group (long-pulsed 1.064 Nd:YAG laser treatment) and the T + L group (both treatments). The strength of this study is that the efficacy of terbinafine and laser therapy can be compared as well as the combination of the two. Mycological clearance rate (MCR) and clinical clearance rate (CCR) were also calculated several times, so the efficacy can be analyzed and compared throughout the period of the study. The limitations of this study are blinding procedure was not stated, and the laser type used in this study has not been recommended for onychomycosis treatment.

The second appraised study, Hollmig et al.⁶ allocated patients into laser and control groups rather than individual toenails, which was thought
to allow a more clinically meaningful analysis. The strength of this study, they counted on individ...
<table>
<thead>
<tr>
<th>Authors</th>
<th>N of nails (N of patients)</th>
<th>Study design</th>
<th>Patient characteristic</th>
<th>Comparison</th>
<th>Laser specification &amp; doses</th>
<th>Diagnostic techniques</th>
<th>Follow-up</th>
<th>Study end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, et al⁵</td>
<td>90 (53)</td>
<td>RCT</td>
<td>16-68 years old.</td>
<td>Oral terbinafine</td>
<td>Contact-cooled long-pulsed 1,064-nm Nd:YAG laser (Lumenis One; Lumenis Ltd, Santa Clara, California) repeated every week until complete mycological recovery or week 24.</td>
<td>Microscopic examination</td>
<td>MCR and CCR at week: 2, 4, 8, 12, 16, 24.</td>
<td>Negative results from microscopic and clinical clearance by a completely normal appearance of the nail or the presence of 5% nail plate involvement at 24 weeks.</td>
</tr>
<tr>
<td>Hollmig, et al⁶</td>
<td>125 (27)</td>
<td>RCT</td>
<td>18-75 years old.</td>
<td>No intervention</td>
<td>1064-nm Nd:YAG laser (JOULE ClearSense; Scitton Inc, Palo Alto, California). Two treatments were given within 2 weeks apart</td>
<td>Culture and PAS</td>
<td>52 weeks</td>
<td>Negative culture and measured clearance at 3 months for all subjects and repeated clearance measurement at 12 months for those treated with laser.</td>
</tr>
<tr>
<td>Ortiz, et al⁷</td>
<td>20 (10)</td>
<td>RCT</td>
<td>Inclusion criteria: active bilateral great toenail onychomycosis, older than 18 years. Exclusion criteria: pregnant, had other toenail disease, had hypertrophic nails, were diabetic, a minimum of a 2-week and 3-month exclusionary medicine wash-out period if on topical antifungals or systemic antifungals before, 6-month washout period for any surgical procedure.</td>
<td>Sham treatment of cryogen cooling</td>
<td>1,320-nm Nd:YAG laser (CoolTouch CT3 Plus; CoolTouch, Roseville, California). For treatments on days 1, 7, 14, and 60.</td>
<td>Culture</td>
<td>180 days</td>
<td>Negative cultures at day 90, improvement on MLCNG at day 90, clinical improvement of the degree of nail plate involvement and overall improvement based on the blinded assessment of clinical photography at 90 days, and subjective improvement of subject satisfaction based on the Nail Quality of Life Questionnaire at day 90. Clinical evaluations, digital photography, and MLCNG repeated on day 180.</td>
</tr>
<tr>
<td>Landsman, et al⁸</td>
<td>59 (34)</td>
<td>RCT</td>
<td>18-70 years old.</td>
<td>Sham treatment with no energy output (the laser power was set to zero)</td>
<td>870 ± 5 nm and 930 ± 5 nm near-infrared spectrum (Noveon; Nomir Medical Technologies Inc, Waltham, Massachusetts) or sham control device. Four treatments were given on day 1, 14, 42, and 120.</td>
<td>Culture or PAS</td>
<td>180 days</td>
<td>Decrease in positive fungal culture and a concomitant decrease in positive microscopy with PAS nail scrapings.</td>
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*CCR: clinical cure rate, MCR: mycological cure rate, MLCNG: maximum linear clear nail growth, N: number, PAS: periodic acid-Schiff stain, RCT: randomized controlled trial*
Table 3. Validity, relevance, and level of evidence (LOE) of appraised journals about laser therapy in treating onychomycosis

<table>
<thead>
<tr>
<th>Articles</th>
<th>Validity</th>
<th>Relevance</th>
<th>LOE</th>
</tr>
</thead>
</table>

$^*$LOE used was based on the Oxford Centre for Evidence-based Medicine, 2011

Out of all studies' strengths and weaknesses, each has its superiority as compared to each other. Xu's biggest strength is the use of intention to treat (ITT) analysis with no loss to follow-up patients. Landsman's strength is the clear blinding procedure but with minimal statistical analysis. Ortiz's strength is a more defined patient characteristic, but its small sample and consequentially lack of statistical analysis can provide unreliable results. From all four, Hollmig's was the weakest of all with a lot of loss to follow-up patients, and the blinding procedure was not explained. We give more weight to Xu's study because of its ITT analysis rather than to Landsman's study, which thoroughly explained its blinding procedures. Therefore, it can be concluded that Xu's study is the most valid one.

From Xu's study$^5$, it can be seen that laser has no benefit in treating onychomycosis while compared to oral terbinafine. Table 4 shows that in Xu's study, the event of treatment failure is higher for the analysis rather than nails. Limitations of this study included unclear blinding procedures and many losses to follow-up study participants.

The study by Ortiz et al.$^7$ has several strengths. The patient characteristics are more defined and have several indicators for measurements of effectiveness (one of them are blindly measured). However, this study was only done to 20 nails. This study has no statistical analysis, which possibly because of the small number of sample.

The study by Landsman et al.$^8$ is the only appraised study that specified the blinding procedure and had an independent expert panel to assess clinical outcome together with the internal investigators. The limitations are a lot of loss to follow-up patients; there is a potential conflict of interest because some of the investigators were employees of the company who funded the study, and lack of statistical analysis especially on mycological cure results.
Table 4. Treatment failure rate based on mycological cure at the end of each appraised study about laser therapy in treating onychomycosis

<table>
<thead>
<tr>
<th>Articles</th>
<th>Comparison</th>
<th>Failure of Mycological cure</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu, et al^5</td>
<td>Oral terbinafine</td>
<td>CER 16.7%  EER 22.6%  ARR*(95% CI(%) 5.9% (-13.95% to 25.78%) NNT* 17**</td>
<td>Because the EER result was higher than CER, NNT was read as NNH and ARR as ARI.</td>
</tr>
<tr>
<td>Hollmig, et al^6</td>
<td>No intervention</td>
<td>CER 80%  EER 76.5%  ARR*(95% CI(%) 3.53% (-28.43% to 35.49%) NNT* 29</td>
<td>Results were calculated based on the third month follow up.</td>
</tr>
<tr>
<td>Ortiz, et al^7</td>
<td>Sham device</td>
<td>CER 30%  EER 50%  ARR*(95% CI(%) 20% (-22.04% to 62.04%) NNT* 5**</td>
<td>Because the EER result was higher than CER, NNT was read as NNH and ARR as ARI.</td>
</tr>
<tr>
<td>Landsman, et al^8</td>
<td>Sham device</td>
<td>CER 93%  EER 77%  ARR*(95% CI(%) 16% (-1.62% to 33.74%) NNT* 7</td>
<td>Results were calculated based on day 180 based on mycological and clinical cure rate.</td>
</tr>
</tbody>
</table>

ARI : Absolute Risk Increase
ARR : Absolute Risk Reduction
CER : Control Event Rate
CI : Confidence Interval
EER : Experimental Event Rate
NNH : Number Needed to Harm
NNT : Number Needed to Treat
*intention to treat analysis
**read as NNH

in the laser group compared to antifungal group (NNH = 17). The MCR and CCR of the oral terbinafine group were significantly higher than the laser group at weeks 12 and 16. The MCR and CCR for oral terbinafine results were increased in a time-dependent manner. The lower effectiveness of laser therapy, when compared to oral antifungal in this study, may be caused by the selective photothermal lytic effect of the long-pulsed Nd: YAG laser on the black chromophores.
produced by certain fungi. Meanwhile, oral antifungal mechanism of inhibiting fungal growth does not depend on this particular pigment. However, we also see interesting findings where a group with combination therapy (laser and oral antifungal) gives a better result than oral antifungal alone.

**Conclusion**

Referring to the most valid study, the laser is less effective when compared to oral terbinafine as the current gold standard therapy for onychomycosis. On the other side, more studies with detailed patients’ baseline criteria, less loss to follow-up patients, clear blinding procedure among investigators, and comparison with and current gold standard therapy are needed to accurately assess the effectiveness of laser therapy in the management of onychomycosis.

Referring to our case, we do not have enough evidence to recommend the use of laser therapy as a substitution for an oral antifungal. However, the possibility of using laser therapy as an adjunctive therapy to oral antifungal to achieve better cure rate should be further evaluated.

**References**