Treatment of Onychomycosis Using a 1064nm Nd:YAG Laser

Hiromitsu Noguchi¹,², Keishi Miyata³, Takashi Sugita¹, Midori Hiruma⁴, Masataro Hiruma⁵

¹ Noguchi Dermatology Clinic
² Department of Immunology, Allergy & Vascular Biology, Kumamoto University
³ Department of microbiology, Meiji Pharmaceutical University
⁴ Department of Dermatology, Juntendo University School of Medicine
⁵ Ochanomizu Institute for Medical Mycology and Allergology

ABSTRACT

We investigated the efficacy of 1064nm Nd:YAG laser for the treatment of onychomycosis caused by dermatophytes. The study population consisted of 12 patients (6 male, 6 female; average age 53.5 years), with onychomycosis confirmed by fungal culture and/or real-time PCR identification of the pathogen. The causative agent was identified as *Trichophyton rubrum* in 11 cases and a mixture of *T. rubrum* and *T. mentagrophytes* in 1 case. For each patient, laser treatment was given to a single hallux nail, with turbidity at baseline affecting < 75% of the nail surface and thickness at baseline <3mm. Treatment was given in 3 sessions at 4-week intervals, and nail turbidity was evaluated 3 and 6 months after the first laser treatment. After 6 months the efficacy results were as follows: 3 cases, turbidity significantly improved (> 70%); 2 cases, turbidity improved (50-70%), 1 case, turbidity slightly improved (30-50%); 5 cases, no change in turbidity (< 30% improvement); and 1 case, turbidity worsened. Overall, the total lesion area with turbidity in 12 patients decreased from 664.4mm² to 481.0mm², corresponding to a 27.6% improvement after treatment. Pain during laser treatment was well tolerated, and all patients underwent all 3 treatments. These results suggest that the 1064nm Nd:YAG laser could be a useful treatment alternative for patients with mild onychomycosis.

Key words: Onychomycosis, fungal nail infection, tinea unguium, 1064nm Nd:YAG laser

Introduction

Dermatophytes, such as *Trichophyton rubrum* and *T. mentagrophytes*, are the most common pathogens causing onychomycosis, a fungal infection of the nails. In Japan, the recommended treatment for fungal nail infection caused by dermatophytes (i.e., tinea unguium) is oral terbinafine hydrochloride, given as a daily treatment at 125mg per day for 6 months, or oral itraconazole given intermittently for 3 months as "pulse" therapy, with 400mg per day for 7 days, followed by a 21-day interval without treatment. However, in elderly patients taking multiple medications or in patients with impaired liver function, the use of oral antifungal medication is sometimes risky or contraindicated.

Nd:YAG lasers at a wavelength of 1064nm, in the near-infrared light range, emit optical energy that can penetrate the skin surface to a depth of 3-5mm and coagulate tissue, raising temperature up to 60°C in tissue at a depth of 3mm. Dermatophytes can be killed by exposure to temperatures over 50°C, raising the possibility that laser treatment might be effective in treating fungal disease. Infrared lasers that raise tissue temperature to 60°C can cause protein denaturation and

Address for correspondence: Hiromitsu Noguchi
Noguchi Dermatology Clinic
E-mail: derma@nogcli.jp
Received: 21, February 2013, Accepted: 21, August 2013
collagen coagulation, but thermal damage is usually reversible if the laser exposure time per area is less than 10 seconds in areas that reach the threshold temperature of 57°C. Recent reports have described the successful use of longer-wavelength Nd:YAG laser in treating onychomycosis.

In the study reported here, we examined the efficacy of 1064nm Nd:YAG laser treatment given in 3 sessions at 4-week intervals for the treatment of onychomycosis.

Patients and methods

Study design

The aim of the study was to evaluate the efficacy of 1064nm Nd:YAG laser treatment for patients with onychomycosis. Patients with onychomycosis who visited Noguchi Dermatology Clinic from November 2011 to February 2012 were allowed to select the type of therapy that they preferred: conventional therapy with oral medication or topical treatments, or experimental 1064nm Nd:YAG laser treatment, which was offered without charge to patients who met the inclusion/exclusion criteria. Written informed consent was obtained from all patients prior to study enrollment, and the study was approved by the ethics committee of our facility.

The inclusion criteria were as follows: (i) diagnosis of onychomycosis affecting hallux nails, with fungal detection by direct microscopy; (ii) identification of pathogens by fungal culture or by real-time PCR; (iii) age ≥ 20 years and (iv) consent to participate in the study. Exclusion criteria were the following: (i) use of systemic antifungal medications during the previous year; (ii) hallux nails with turbidity affecting 75% of the entire nail surface and nail thickness of ≥ 3mm (iii) pregnancy or likely to become pregnant; (iv) age < 20 years old; and (v) physician’s recommendation not to participate in the study. Patients with hallux nails with turbidity affecting > 75% of the entire nail surface area with nail thickness < 3mm were excluded from the study.

For each patient, a single hallux nail, from either the right or left foot, was selected for treatment. If hallux nails on both feet were affected, the nail with the more severe turbidity was selected for treatment.

Patient evaluation

Data recorded for each study participant included age, sex, and history of underlying illnesses. Lesions were classified as distal lateral subungual onychomycosis (DLSO), proximal subungal onychomycosis (PSO), superficial white onychomycosis (SWO), or total dystrophic onychomycosis (TDO).

Nail thickness was measured using a digital caliper. The extent of turbidity on affected nails was quantified by determining the surface ratio between the turbid area and the whole area using image analysis software Image J 1.44p (NIH, Bethesda, MD, USA). The turbidity percentile for each nail was recorded.

Fungal culture and identification

Sabouraud’s dextrose agar containing cycloheximide and chloramphenicol (Eiken Chemical Tochigi, Japan) was used for fungal culture. Samples from affected nails were frozen in liquid nitrogen. For molecular analysis, samples were ground using an Auto Mill (Tokken Inc., Chiba, Japan) and fungal DNA was extracted using ISOPLANT (Nippon Gene Co., Toyama, Japan). Fungal DNA was detected by real-time PCR with T. rubrum or T. mentagrophytes species-specific primer and probe.

Treatment protocol

Long-pulsed 1064nm wavelength Nd:YAG laser (GentleYAG; Candela Corporation, Wayland, MA, USA) was used for 3 treatments at 4-week intervals. The laser was set to 10J/cm² with a 0.5 msec pulse duration and a spotsize of 6mm in diameter. The pulse duration was selected not to exceed the thermal relaxation time for tissue, which was previously determined to be approximately 0.7msec, in order to confine the heat within the target tissue. The repetition rate was 2 Hz, and no epidermal cooling spray, gel, or local anesthesia was used.

The surface of the affected nail was irradiated by 4 passes in a crisscross pattern (first and third passes vertically, second and fourth passes horizontally). The distance gauge of the laser handpiece was placed on the nail surface and remained in contact during laser irradiation to sustain sufficient energy delivery. The irradiated area included the entire nail surface and the surrounding area with 2mm margins from both sides of the nail plate and 4mm margins above the supra nail skin. Pain was evaluated by asking the patient how much pain they were experiencing.
during the treatment and rating the response using a numerical rating scale (NRS) of 0 to 10, with a score of 0 representing no pain and a score of 10 representing the most pain the patient had ever experienced.

Evaluation of efficacy

Nail turbidity was evaluated 3 and 6 months after the first laser treatment. Based on changes in nail turbidity, treatment efficacy was described using the following six categories: (i) Cure: healthy nail plate is completely recovered; (ii) Significantly Improved: turbidity improved > 70%; (iii) Improved: turbidity improved 50-70%; (iv) Slightly Improved: turbidity improved 30-50%; (v) No Change: turbidity improved < 30%; (vi) Worsened: increased area of turbidity. Negative conversion of fungi by direct microscopy was used as the index for determining the mycological effect from laser treatment.

Results

1. Patient background

Twelve patients (six men and six women) enrolled in the study (Table 1). The patients ranged in age from 30 to 88 years, with an average age of 53.5 years. Eight patients (66.7%) had tinea pedis. Six of the 12 (50%) patients had an other chronic disease, such as hypertension, diabetes, hepatitis C, or depression.

Three right and 9 left hallux nails were examined. In all cases the lesion type was DLSO. The average nail thickness was 1.61mm, and the average total surface area was 159.1mm$^2$. The average area of turbidity was 49.9mm$^2$, and the average percentile of turbidity in a whole nail surface before treatment was 31.5%.

We identified Trichophyton rubrum as the causative pathogen in 11 cases. In the remaining case, a mixture of T. rubrum and T. mentagrophytes was found. The method of identification was fungal culture in 3 cases (25.0%) and real-time PCR in 9 cases (75.0%).

2. Treatment results

Three of the patients (25.0%) showed a significant improvement following laser treatment. Two patients showed improvement (16.7%), and one patient showed slight improvement (8.3%). Five patients showed no change (41.7%), and one patient worsened (8.3%). Figures 1 and 2 illustrate cases that had Significantly Improved and Improved, respectively.

Total lesion area with turbidity in 12 patients decreased from 664.4mm$^2$ to 481.0mm$^2$ with 27.6% improvement after the laser treatments. The average number of laser shots per treatment given to each patient over the entire treatment period was 172.5. For the first treatment, an average of 160.0 shots was given, increasing to an average of 175.0 for the second treatment and 182.2 for the third treatment. With regard to pain level, NRS scores for 1st, 2nd, and 3rd treatments were 6.6, 3.7, and 4.6, respectively; the average score overall was 5.1. Pain during the laser treatment was well tolerated and all patients underwent all 3 treatments.

Of the 3 patients who showed significant improvement, we continued to follow one for the next 6 months. At a follow-up visit 12 months after the last laser treatment, we confirmed that the patient was cured. The other 2 patients who showed significant improvement were cured after receiving 6 more treatments at 1-month intervals. Finally, the 2 patients who showed improvement switched to oral medication following the laser treatment.

Calculation of the total laser energy irradiated on the nail plate showed an average total laser energy per nail of 3.2J/mm$^2$ for the 12 patients. Notably, fluence was higher for the 3 patients with significant improvement, at 4.5J/mm$^2$, 5.0J/mm$^2$, and 3.5J/mm$^2$, compared to an average fluence of 3.2J/mm$^2$.

Discussion

Dermatological uses of the 1064nm Nd:YAG laser include laser-assisted hair removal, treatment of facial and leg telangiectasia, and skin rejuvenation. Podiatrists recently started using lasers of this wavelength for onychomycosis treatment in the United States. Four separate models received FDA marketing approval in 2012, including a 1064nm Q-switched Nd: YAG and a 980 nm diode laser, in addition to a 1064nm Nd:YAG laser.

For onychomycosis treatment, Kimura et al. reported using a 1064nm Nd:YAG laser (Laser Genesis; Cutera Inc.) set at 5mm spotsize, 14J/cm$^2$, 0.3 msec pulse duration, 5Hz repetition rate, and no epidermal cooling. Their results showed that 5 of 19 hallux nails (26.3%) were cured after 1 to 3 treatments, irradiating 100 to 200 shots per hallux nail at 4-8 weeks intervals. Based on these
Table 1. Cases in the treatment of onychomycosis using a 1064nm Nd:YAG laser

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>Sex</th>
<th>Site</th>
<th>Nail thickness (mm)</th>
<th>Total area (mm²)</th>
<th>Turbidity area pre-laser (%)</th>
<th>Pathogens</th>
<th>Turbidity at 3 Mo (%)</th>
<th>Turbidity at 6 Mo (%)</th>
<th>Improvement rate (%)</th>
<th>Efficacy</th>
<th>Average laser shots</th>
<th>Fluence (J/mm²)</th>
<th>VAS</th>
<th>At 12Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>Left</td>
<td>1.95</td>
<td>93.1</td>
<td>14.1</td>
<td>TR</td>
<td>3.2</td>
<td>4.2</td>
<td>72.4</td>
<td>Significantly improved</td>
<td>160.7</td>
<td>4.9</td>
<td>6.3</td>
<td>Cured</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>F</td>
<td>Left</td>
<td>1.53</td>
<td>190.8</td>
<td>65.0</td>
<td>TR</td>
<td>39.8</td>
<td>31.7</td>
<td>7.0</td>
<td>No change</td>
<td>158.7</td>
<td>2.3</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>M</td>
<td>Left</td>
<td>0.68</td>
<td>290.0</td>
<td>70.5</td>
<td>TR</td>
<td>23.5</td>
<td>11.5</td>
<td>52.7</td>
<td>Improved</td>
<td>209.3</td>
<td>2.0</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>F</td>
<td>Right</td>
<td>2.84</td>
<td>109.8</td>
<td>39.4</td>
<td>TR</td>
<td>9.5</td>
<td>4.0</td>
<td>88.9</td>
<td>Significantly improved</td>
<td>194.3</td>
<td>5.0</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>M</td>
<td>Right</td>
<td>1.33</td>
<td>171.4</td>
<td>60.9</td>
<td>TR</td>
<td>31.0</td>
<td>33.9</td>
<td>4.8</td>
<td>No change</td>
<td>129.3</td>
<td>2.1</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>Left</td>
<td>0.6</td>
<td>177.0</td>
<td>41.8</td>
<td>TR</td>
<td>5.3</td>
<td>9.4</td>
<td>61.2</td>
<td>Improved</td>
<td>178.7</td>
<td>2.9</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>83</td>
<td>F</td>
<td>Left</td>
<td>1.77</td>
<td>138.4</td>
<td>59.8</td>
<td>TR</td>
<td>28.5</td>
<td>45.3</td>
<td>-4.9</td>
<td>Worse</td>
<td>166.7</td>
<td>3.4</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>76</td>
<td>M</td>
<td>Left</td>
<td>2.09</td>
<td>186.8</td>
<td>47.5</td>
<td>TR</td>
<td>20.8</td>
<td>18.9</td>
<td>25.0</td>
<td>No change</td>
<td>209.3</td>
<td>3.2</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>F</td>
<td>Left</td>
<td>1.04</td>
<td>158.1</td>
<td>17.4</td>
<td>TR</td>
<td>8.0</td>
<td>2.5</td>
<td>77.2</td>
<td>Significantly improved</td>
<td>195.3</td>
<td>3.5</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>F</td>
<td>Right</td>
<td>2.19</td>
<td>129.4</td>
<td>38.5</td>
<td>TR</td>
<td>24.7</td>
<td>17.3</td>
<td>41.7</td>
<td>Slightly improved</td>
<td>157.0</td>
<td>3.4</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>88</td>
<td>F</td>
<td>Left</td>
<td>2.38</td>
<td>146.2</td>
<td>59.6</td>
<td>TR</td>
<td>32.0</td>
<td>40.6</td>
<td>0.0</td>
<td>No change</td>
<td>163.0</td>
<td>3.2</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>77</td>
<td>M</td>
<td>Left</td>
<td>2.22</td>
<td>197.9</td>
<td>149.8</td>
<td>TR, TM</td>
<td>42.1</td>
<td>62.7</td>
<td>17.1</td>
<td>No change</td>
<td>147.3</td>
<td>2.1</td>
<td>3.7</td>
<td></td>
</tr>
</tbody>
</table>

TR: *Trichophyton rubrum*, TM: *T. mentagrophytes*
settings, we used a 1064nm Nd:YAG laser (Gentle YAG; Candela Corp.) with 6mm spot size, 10J/cm², 0.5msec pulse duration, 2Hz repetition rate, and no epidermal cooling. Each hallux was treated 3 times with an average of 172.5 laser shots per treatment at 4-week intervals. In our study, 3 of 12 patients (25.0%) showed significant improvement, and in one patient (8.3%) the nail was cured 12 months after the final laser treatment. For the 3 patients who showed significant improvement, it is noteworthy that the average fluence was higher than average (Table 1); therefore, efficacy might be improved by increasing total fluence per treatment.

After study termination, we continued to treat two significantly improved nails; after an additional 6 treatments at 1-month intervals, giving a total of 9 treatments, the nails were cured. This result might suggest that 3 treatments are insufficient and that laser treatment should continue until nails are cured.

In this study, we included nails in which the thickness was < 3mm. If thicker nails are physically ground by a grinder or chemically scraped using topical urea, treatment efficacy could be possibly improved further. The mechanism of action of a 1064nm Nd:YAG laser to destroy dermatophytes is not clearly known; however, the effect of laser exposure of 100J/cm² at this wavelength was confirmed to suppress the expansion of T. rubrum colonies, cause fungal hyphae to become thinner, and damage the cell wall in electron microscopic observations [15]. If the effect of laser exposure is simply to cause physical damage to the fungal structure, it might be possible to treat onychomycosis caused by other fungi besides dermatophytes.

In Japan, oral terbinafine hydrochloride and oral itraconazole are recommended and widely used treatments for tinea unguium [11]. In some cases, however, patients have difficulty with these medications due to side effects, underlying medical conditions, or drug interactions, or may be averse to long-term oral medication. Although
the effectiveness of conventional topical therapy is extremely limited, anti-fungal agents ciclopirox and amorolfine transparent manicure as a base have recently been used in topical preparations for onychomycosis treatment in some countries outside Japan. The active agents in these nail lacquers become condensed and work as a coating on the nail surface when the topical solution evaporates, allowing the agent to stay on the surface for a longer period of time and penetrate deeper into the nail plate. A 1064nm Nd:YAG laser can be used to treat mild onychomycosis and may be equivalent to applying topical nail lacquer alone. No systemic adverse effects have been associated with onychomycosis treatment using a 1064nm Nd:YAG laser, and a monthly treatment regimen might lead to a higher level of patient compliance compared to other treatments. The 1064nm Nd:YAG laser should be considered as a new alternative treatment modality for mild onychomycosis.

Acknowledgement

This study was partly funded by Health, Labour and Welfare Sciences Research Grants for Research on Measures for Intractable Diseases (H25 shinko-ippan006) from the Japanese Government.

References

17) Lecha M, Effendy I, Feuilhade de Chauvin M, Di Chiaccio N, Baran R: Taskforce on Onychomycosis Education. Treatment options--develop-