Self-controlled Study of Onychomycosis Treated with Long-pulsed Nd:YAG 1064-nm Laser Combined with Itraconazole

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Abstract

Background: Onychomycosis is a fungal infection of the nail plate and subungual area. In this study, we examined the efficacy of laser treatment using self-controlled study programs involving a long-pulsed Nd:YAG 1064-nm laser combined with oral medication.

Methods: Self-controlled strategies were followed in this study. The patients received treatment with oral itraconazole in conjunction with long-pulsed Nd:YAG 1064-nm laser treatment at the nails of the unilateral limb once a week for a total of four times. A total of 84 affected nails were divided into Group A (mild to moderate) and Group B (severe) according to disease severity. Affected nails with the same Scoring Clinical Index for Onychomycosis scores were selected to compare the therapeutic effects of the pure medication treatment group and the combination treatment group with a 24-week follow-up period.

Results: In Group A, at the 8th, 16th, and 24th weeks of follow-up, the efficacies in the pure medication treatment group were 81.0%, 81.0%, and 90.5%, respectively, while those in the combination treatment group were 100%, 95.2%, and 90.5%, respectively. The differences between groups were not significant (8th week: χ² = 4.421, P > 0.05; 16th week: χ² = 2.043, P > 0.05; 24th week: χ² = 0.00, P > 0.05). In Group B, at the 8th, 16th, and 24th weeks of follow-up, the efficacies in the pure medication treatment group were 61.9%, 66.7%, and 52.4%, respectively, while those in the combination treatment group were 95.2%, 90.5%, and 100%, respectively. The differences between groups at the 8th and 24th weeks of follow-up were statistically significant (8th week: χ² = 6.929, P < 0.05; 24th week: χ² = 13.125, P < 0.05).

Conclusions: For patients with mild or moderate onychomycosis, we recommended a pure medication treatment or combination treatment with medication and laser. For those patients with severe onychomycosis, we recommended a combination of medication and laser therapy.

Key words: Itraconazole; Laser Treatment; Nd-YAG Laser; Onychomycosis

Introduction

Onychomycosis is a fungal infection of the nail plate and subungual area. The global incidence is relatively high, at around 2–18%.[1] The current main therapy of onychomycosis is topical or oral antifungal medication. Since it is difficult for topical antifungal agents to penetrate the nail plate to the nail bed, the treatment period is long and the efficacy is normally poor.[2] Although the efficacy of oral antifungals is good, its effectiveness is only 60–70%,[3,4] and its potential side effects, such as liver and kidney dysfunctions, restrict its usage.[5] Therefore, it is very difficult to cure onychomycosis.[6] Laser therapy for onychomycosis is a new breakthrough due to its fewer side effects. The number of professional lasers approved by the US Food and Drug Administration is continually increasing, most of which are the long-pulsed Nd:YAG 1064-nm lasers.[7–9] Many researchers believe that the laser treatment of onychomycosis is safe and effective.[10–12] Recently, however, Hollmig et al.[13] stated that the use of Nd:YAG 1064-nm laser equipment is invalid for the treatment of onychomycosis. Adopting a self-controlled method, we studied the efficacy of Nd:YAG laser and its potential side effects, such as liver and kidney dysfunctions, restrict its usage.[5] Therefore, it is very difficult to cure onychomycosis.[6] Laser therapy for onychomycosis is a new breakthrough due to its fewer side effects. The number of professional lasers approved by the US Food and Drug Administration is continually increasing, most of which are the long-pulsed Nd:YAG 1064-nm lasers.[7–9] Many researchers believe that the laser treatment of onychomycosis is safe and effective.[10–12] Recently, however, Hollmig et al.[13] stated that the use of Nd:YAG 1064-nm laser equipment is invalid for the treatment of onychomycosis. Adopting a self-controlled method, we studied the efficacy of Nd:YAG laser therapy.
1064-nm laser therapy combined with oral medication as a treatment for onychomycosis.

**Methods**

**Inclusion criteria**
The patients were 18–75 years old and had typical clinical manifestations of onychomycosis, including positive fungal direct microscopy and/or fungal culture. The patients signed written informed consent and voluntarily accepted follow-up. None had taken external medication within 1 month or systemic antifungal drugs within the previous 6 months. The affected nails were on the hands or feet, and the severities of bilateral onychomycosis were similar, which meant that the Scoring Clinical Index for Onychomycosis (SCIO) of at least one pair of affected nails of patients with bilateral onychomycosis was consistent.[14]

**Exclusion criteria**
The following patients were excluded from the study: those who terminated the treatment on their own initiative, changed the treatment strategy, or failed to complete timely follow-up; patients who took other drugs that might affect efficacy during the treatment period; those who persistently or semi-persistently demonstrated nail discoloration, including a nail pigmentation anomaly caused by therapeutic or cosmetic purposes, such as topical antifungal solution castellani, nail stains, polish (such as magnesium- or iron-containing substances), or caused by occupational exposure to dyes or asphalt; those who took a photosensitizer for almost 6 months; pregnant or lactating women; those who had a subungual hematoma or mole-like tissue; those whose affected nail was caused by a combination of diseases, such as nail plate psoriasis, lichen planus, and atopic dermatitis; those with liver or kidney dysfunctions; those who needed to take drugs that cannot be taken in conjunction with itraconazole capsules; and those who were considered ineligible to participate in the trial by clinicians. Treatments terminated due to adverse reactions were not included in the efficacy but were included in the incidence of adverse reactions.

**Patient information**
Nineteen patients in this study (8 men, 11 women; age range, 19.0–63.0 years; mean age, 45.3 years) were recruited from the Dermatology Department of Beijing Friendship Hospital between October 2013 and March 2014. Their disease duration was 5 months to 25 years (mean duration, 12.2 years). The total number of affected nails was 120, with an average of 6.3 for each patient, and 84 (42 pairs) affected nails met the inclusion criteria.

**Grouping**
A self-controlled strategy was followed in this study. The patients received oral systemic treatment, and at the same time, laser therapy was conducted on a unilateral limb’s affected nails. To minimize differences between the pure medication group and the combination treatment group, the following method was adopted to collect the experimental data: those patients who took oral itraconazole regularly were divided into odd- and even-numbered groups. To do this, twenty tags were labeled with twenty consecutive numbers selected from random number table. For patients in the odd-numbered group, the affected nails of the left limb were subjected to laser treatment. For patients in the even-numbered group, the affected nails of the right limb were subjected to laser treatment. One affected nail from the pure medication group and one from the combination treatment group with the same SCIO score were selected to create a matching pair. Each affected nail was paired only once. Only matched pairs were included in the clinical evaluation and mycological examination.

Matched pairs were divided into two groups (Group A, mild to moderate; Group B, severe) according to disease severity. The SCIO scores of Group A (21 pairs) were $6 \leq \text{SCIO} < 12$ while those of Group B (21 pairs) were $\text{SCIO} \geq 12$. Each group was divided into a combination treatment group (laser combined with medication treatment) and a control group (pure medication treatment).

**Therapy**
For the laser therapy, a Miracle Laser™ ML-3420 long-pulsed Nd:YAG 1064-nm laser (Wuhan Miracle Laser Co. Ltd., Wuhan, China) treatment device with $5–15 \text{J/cm}^2$ fluence, 3-mm spot size, 0.3–2.0-ms pulse width, and 1–10-Hz frequency was used. The energy was adjusted according to the nail thickness: the thicker the nails, the higher the energy. The laser beam irradiated the entire nail plate with a spiral movement and increasing laser energy. After the entire nail plate was irradiated, the process was paused for 2 min, then irradiation was conducted again, and the laser irradiation was repeated three times. Treatments were delivered at 7-day intervals for a total of four times.

For the medication therapy, the antifungal itraconazole (Xi’an Janssen Pharmaceutical Ltd., China) was administered orally. Each treatment course consisted of 200 mg twice daily for 1 week followed by a 3-week rest. Fingernails were treated with three courses while toenails were treated with four courses.

Follow-ups were conducted at the 8th, 16th, and 24th weeks. Fungal microscopy and culture examinations were performed. The patients’ adverse reactions, including their duration and extent, were recorded in detail.

**Assessment**
For the mycological assessment, fungal microscopy and culture examinations were conducted before therapy at the 8th, 16th, and 24th weeks of follow-up. The positive rate = positive/total cases $\times 100\%$.

The clinical efficacy assessment consisted of target nail measurements before treatment and at the 8th, 16th, and 24th weeks. Cure was defined as the growth of a new nail with a smooth and brightly colored nail plate and not more than 5% defects. Statistically significant improvement was defined as 60% new nail growth. Improvement was defined as 20% new nail growth $<60\%$ while no change
was defined <20% new nail growth. Efficacy rate = cure rate + significant efficacy rate.109

Among the twenty enrolled patients, only one patient was lost to follow‑up at the early stage due to his migration.

Statistical analysis
SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The Chi‑square test of paired design was analyzed to compare variables and \( P < 0.05 \) was considered statistically significant.

Results
Mycological efficacy
In this study, fungal microscopy and culture were conducted on the target nails of each patient who met the inclusion criteria. The microscopic examination results were all positive. Among the 19 patients, fungal cultures were positive in 10 patients (52.6%), including nine cases of *Trichophyton rubrum* (47.4%) and one case of yeast (5.3%). The positive rates of fungal microscopy and culture are listed in Table 1.

In Group A, the fungal culture results were significantly different between the combination treatment and control groups at the 8th week (\( \chi^2 = 11.667, P < 0.05 \)) but not at the 16th or 24th weeks (8th week: \( \chi^2 = 2.043, P > 0.05 \); 24th week: \( \chi^2 = 0.00, P > 0.05 \)). However, at the 8th and 24th weeks, the difference in clinical efficacy between the combination treatment and control groups in Group B was significant (8th week: \( \chi^2 = 6.929, P < 0.05 \); 24th week: \( \chi^2 = 13.125, P < 0.05 \)) while that at the 16th week was not statistically significant (\( \chi^2 = 3.535, P > 0.05 \)).

Safety evaluations
No serious adverse events were experienced in any of the 19 patients. Most patients had just a little pain with fine tolerability during the whole treatment.

Discussion
Oral antifungal treatment is considered the gold standard for onychomycosis.15 In recent years, researchers have been

### Table 1: Mycological examination results of affected nails before and after onychomycosis treatment

| Time     | Group   | Positive fungal microscopy, \( n \) | Positive fungal culture, \( n \) | \( \chi^2 \) | \( P \)       |
|----------|---------|-------------------------------------|---------------------------------|-------------|------------|
| Before   | Group A | Combination: 21                     | Control: 21                     |             |            |
|          |         |                                     |                                 |             |            |
|          | Group B | Combination: 21                     | Control: 21                     |             |            |
|          |         |                                     |                                 |             |            |
| 8th week | Group A | Combination: 3                      | Control: 12                     | 11.667      | <0.05      |
|          |         |                                     |                                 |             |            |
|          | Group B | Combination: 9                      | Control: 13                     | 0.104       | >0.05      |
|          |         |                                     |                                 |             |            |
| 16th week| Group A | Combination: 2                       | Control: 8                       | 4.286       | >0.05      |
|          |         |                                     |                                 |             |            |
|          | Group B | Combination: 2                       | Control: 10                     | 11.667      | <0.05      |
|          |         |                                     |                                 |             |            |
| 24th week| Group A | Combination: 2                       | Control: 5                       | 2.100       | >0.05      |
|          |         |                                     |                                 |             |            |
|          | Group B | Combination: 2                       | Control: 4                       | 4.421       | >0.05      |

Group A: Mild to moderate onychomycosis severity; Group B: Severe onychomycosis severity.
When the laser reaches the skin, it is selectively absorbed by the melanin in the fungal cell wall, thus creating the antifungal effect. After being selectively absorbed by the target color base, the laser energy may be converted to vibrational and rotational energy consisting of biological molecules, resulting in enhancement of the thermal motion of the biological molecules and a temperature increase in the irradiated local tissue. The average temperature of the nail plates may increase to 43–51°C, which is enough to cause cell degeneration, subject cellular proteins to oxidative stress, induce cell apoptosis, and effectively kill 80–90% of microorganisms.[4] Since laser therapy and medication have different mechanisms of action, we speculate that combination therapy may be more effective and benefit more patients.

A self-controlled strategy was followed in this study. The patients received oral systemic treatment, and at the same time, laser therapy was conducted in the affected nails of a unilateral limb. Affected nails with the same SCIO scores were selected to compare the efficacy differences between the combination treatment and control groups. The patients were divided into the mild or moderate group (Group A) and severe group (Group B) according to disease severity. In the mild or moderate group, at the 8th, 16th, and 24th weeks, the efficacy of the combination treatment group was higher than that of the control group; however, the difference between these two groups was not significant ($P > 0.05$). Therefore, combination therapy or medication only can be used in patients with mild or moderate disease. However, in the severe group, at the 8th, 16th, and 24th weeks, the efficacy of the combination treatment was 30–40% higher than that of the medication-only treatment, and the difference between the two groups was statistically significant ($P < 0.05$). In the severe group, the efficacy of the combination therapy was much greater than that of the medication alone. Thus, we believe that the combination treatment is more effective and that the laser treatment helps improve the efficacy of the medication therapy. We recommend that patients with severe onychomycosis can be treated with oral medication as well as laser therapy to improve efficacy and reduce the treatment duration.

At the 8th, 16th, and 24th weeks, the positive rate of the fungal culture of the combination treatment group was lower than that of the pure medication group; however, the overall difference was not significant ($P > 0.05$), which means that the fungal culture result was not consistent with the efficacy results. We believe that the mechanism of laser treatment of onychomycosis is very complicated and that the mycological test results cannot fully reflect the treatment’s clinical efficacy. The mechanism of laser treatment not only relies on the laser’s direct fungicidal effect but also includes immune system or local microenvironment changes induced by the laser.[10] There was no much difference between the efficacy of the pure medication in this study and that in literature.[21,22] The efficacy of the combination treatment was higher than that of the laser therapy only in the previous research.[1,16,12]
In summary, combined laser and medicine treatment for onychomycosis is effective. Laser treatment can improve the efficacy of pure medicine treatment. For patients with severe onychomycosis, we recommend the use of combination treatment. However, further studies are required to understand whether the efficacy of combination treatment is a simple superposition of laser treatment and drug treatment and whether laser irradiation changes the drug’s effect on the fungi. This study’s primary limitation is its short (4-week) treatment period, which was chosen since laser treatment for onychomycosis is still in the exploratory stage, that might have affected our results.

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Conflicts of interest
There are no conflicts of interest.
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