

Treating Onychomycoses of the Toenail: Clinical Efficacy of the Sub-Millisecond 1,064 nm Nd:YAG Laser Using a 5 mm Spot Diameter

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ABSTRACT

Background: Onychomycosis is a relatively common fungal infection. Current treatments have limited applicability and low cure rates. Recently introduced laser therapy has shown to be a safe and effective treatment for onychomycosis. In this study, we evaluate a sub-millisecond Nd:YAG 1,064 nm laser for treating onychomycoses of the tonail.

Methods: Thirteen subjects (9 female, 4 male) with 37 affected toenails received 1 to 3 treatments 4 and/or 8 weeks apart with a sub-millisecond 1,064 nm Nd:YAG laser. Diagnosis of onychomycosis was confirmed with microscopy. Average follow-up time was 16 weeks post-final treatment. Photos were taken and degree of turbidity was determined using a turbidity scale (ranging from "0 = clear nail" to "10 = completely turbid nail") at each visit. Improvement in turbidity was determined by comparison of turbidity scores at baseline and 16-week follow-up on average. Efficacy was assessed by an overall improvement scale (0 to 4), which combined improvement in turbidity scores and microscopic examination. Overall improvement was classified as "4 = complete clearance" if the turbidity score indicated "0 = clear nail" accompanied by a negative microscopic result. No microscopic examination was performed unless the turbidity score showed "0 = clear nail."

Results: Treatments were well tolerated by all subjects and there were no adverse events. Of the 37 toenails treated, 30 (81%) had "moderate" to "complete" clearance average of 16 weeks post–final treatment. Nineteen toenails (51%) were completely clear and all tested negative for fungal infection on direct microscopic analysis. Seven (19%) toenails had significant clearance and four (11%) had moderate clearance.

Conclusions: The preliminary results of this study show this treatment modality is safe and effective for the treatment of onychomycosis in the short term. Additional studies are needed to more fully assess the clinical and mycological benefits as well as optimize the treatment protocol and parameters.

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INTRODUCTION

Onychomycosis is a relatively common fungal nail infection that causes nail turbidity, trachyonychia, discoloration, and brittleness. Twelve million individuals in Japan are estimated to have tinea unguium.[1] This is consistent with the reported prevalence of onychomycosis in the United States (US), which ranges from 14%[2] to 28% in persons over 60 years of age.[3] Although oral and topical antifungal medications are currently the first line of treatment for onychomycosis,[4] their efficacy is limited. The efficacy of oral antifungals ranges from 14% to 50%[5,6] with the recurrence (relapse or reinfection) rate of 10% to 53%.[5] On the other hand, the efficacy of topical medications is between 5.5% and 8.5% due to their inability to fully penetrate the nail bed.[7-12] Alternative treatment options include surgical avulsion of the infected toenail by clips or grinder,[13] chemical avulsion by morpholine salicylate and uric acid, or a combination ointment.[14] Surgical avulsion, while an alternative, has limited efficacy[15] and is rarely used as it causes undue pain and may lead to post-operative complications, especially in diabetic or immunocompromised patients.

The use of phototherapy for treating onychomycosis over the past decades was first reported in the literature with the use of a carbon dioxide (CO_2) laser.[16] Early studies with this CO_2 laser report a 67% cure rate with a 22% recurrence rate at 6 months follow-up, with 22% of patients reporting mild pain during the treatment.[17] This level of pain was considered acceptable as it was less than the pain experienced with other more invasive treatment modalities.[18] However, the CO_2 laser energy was only absorbed at a shallow depth from the skin surface, making it less effective for treating subungual my-

cotic infections.[19] Similarly, the N_2 laser was evaluated, but did not have sufficient energy output to effectively address the infection in the deeper layers.[19] The pulsed Nd:YAG laser with a maximum energy of 10 J per pulse, a pulse duration of 1 ms, and a beam diameter of 5 mm, was also evaluated for use on onychomycosis and was found to be more effective than the CO_2 and N_2 lasers for penetrating thicker skin (> 0.5 mm), making it a more effective option for treatment of subungual mycotic infections. However, this early YAG laser required a longer treatment time than the CO_2 laser and did not irradiate the total infected area.[19]

More recently, advancements in laser technology have resulted in effective treatments of onychomycosis with relatively minimal patient discomfort.[3,11,20] In this study, we evaluated the preliminary data on the safety and efficacy of the sub-millisecond Nd:YAG 1,064 nm laser in treating onychomycosis average of 16 weeks post-final treatment.

The primary clinical endpoint of this study was the overall improvement in onychomycosis as assessed by the level of clinical improvement in the appearance of the toenail and negative microscopic result if the toenail is completely clear. The secondary clinical endpoint was the incidence of adverse events.

METHODS

Subjects

This report provides the preliminary results of our prospective study, which investigates the safety and efficacy of the sub-millisecond Nd:YAG 1,064 nm laser in the treatment of onychomycosis. The treatments were conducted at Juntendo University Urayasu Hospital, Japan. The protocol was approved by the Juntendo University Urayasu Hospital institutional review board and all subjects provided written informed consent prior to participating in the study.

Thirteen subjects (9 female, 4 male) with an average age of 68 (range 37-88 years) enrolled in the study as they presented themselves to the hospital's outpatient dermatology clinic. A total of 37 toenails that displayed turbidity (the great toe to the fifth toe) were selected. To qualify for enrollment, a clinical diagnosis of fungal infection was confirmed with microscopic examination of the toenail clippings from 37 toes.

Direct microscopic analysis consisted of the examination of septate hyphae in a preparation of 15% potassium hydroxide (KOH) and 40% dimethyl sulfoxide (DMSO) (Zoom®, Hisamitsu Pharmaceutical Co., Tokyo, Japan). For microscopic analysis, the toenails were clipped after cleansing with alcohol to remove bacteria and debris. The specimen was placed on the slide and the solution of KOH and DMSO was dropped on the specimen. An electric hot plate set at 60° C to 80° C was used to heat the prepared slide for 2 to 5 minutes to speed up the incubation. The specimen was examined under X 100 (10 x 10) magnification. Each slide was examined by three dermatologists to confirm the diagnosis at baseline and 16 weeks post-final treatment.

Patients with a confirmed diagnosis of onychomycosis who had taken oral antifungal medication within a year or topical antifungal medication within a week of planned enrollment were excluded from the study. Those who had a serious generalized medical condition and those who had the potential to become pregnant during the study duration were also excluded from study participation.

Table 1 provides the baseline demographics, relevant medical history, and the type and extent of fungal infection each subject received. Of the 13 subjects enrolled, 9 presented with distal and lateral subungual onychomycosis (DLSO), 2 with total dystrophic onychomycosis (TDO), and 1 with proximal subungual onychomycosis (PSO). One subject presented with concomitant total dystrophic onychomycosis (TDO) in both great toes and superficial white onychomycosis (SWO) in 2nd and 3rd toes on both feet (Table 1). All subjects had previously used topical antifungal treatments and 4 of the 13 subjects had used an oral antifungal for more than a year prior to enrollment in this study.

Treatment

A sub-millisecond 1,064 nm Nd:YAG laser was used applying a 5 mm spot diameter, with the energy fluence set at 14 J per cm^2, an exposure time per pulse of 300 μs (0.3 ms) and a repetition rate of 5 Hz. The treatment consisted of administering 100 to 200 pulses to the great toenail, and 20 to 100 pulses on the second to fifth toenails (Figures 1 and 2), without the use of cooling sprays, gels, or topical anesthetics. Each infected toenail was treated in a criss-crossed pattern with two alternating passes of laser pulses to cover the full nail surface; one pass was applied vertically and the other horizontally (Figure 2). Treatment time was approximately one to two minutes per toenail. Seven subjects were treated a total of three times, five subjects were treated twice, and one subject was treated once. Treatments were performed 4 and/or 8 weeks apart. Toenails that showed no clinical evidence of infection at baseline were not treated.

Photographs

All 13 subjects had their standardized photographs taken at baseline and at 4, 8, 12, 16, 20, and 24 week time points using a digital single-lens reflex (SLR) camera (EOS7D, Canon K.K., Tokyo, Japan).

Assessment of Outcomes

The overall improvement, which is the primary clinical endpoint of this study, incorporated two prior assessments into one score: 1) Level of improvement in turbidity score 2) Direct microscopy performed if the turbidity score indicated 100% clear nail at the final follow-up visit. [Overall Improvement Score = Level of improvement in Turbidity Score + Direct microscopy (if 100% clear nail was observed at the final follow-up visit)].

TABLE 1.

Baseline demographics and medical history, fungal nail involvement and number of infected toenails

Subject	Gender	Age	Duration of infection (years)	History of topical treatment used	History of oral fungal medication used	Type of fungus*	Number of infected toenails
1	F	84	5	Yes	No	DLSO	2
2	F	75	15	Yes	No	DLSO	6
3	F	39	3	Yes	Yes	PSO	1
4	M	77	10	Yes	No	TDO	2
5	F	77	13	Yes	No	TDO	3
6	F	59	7	Yes	Yes	DLSO	4
7	F	88	10	Yes	Yes	DLSO	2
8	F	63	1	Yes	No	DLSO	1
9	F	71	4	Yes	No	DLSO	2
10	F	37	7	Yes	Yes	DLSO	1
11	M	82	10	Yes	No	DLSO	5
12	M	68	10	Yes	No	TDO (great toes) SWO (2nd, 3rd toes)	6
13	M	62	7	Yes	No	DLSO	2

*DLSO: Distal and lateral subungual onychomycosis; PSO: proximal subungual onychomycosis; TDO: total dystrophic onychomycosis; SWO: superficial white onychomycosis

FIGURE 1. Hand piece was held 1 to 2 cm off the toenail surface.

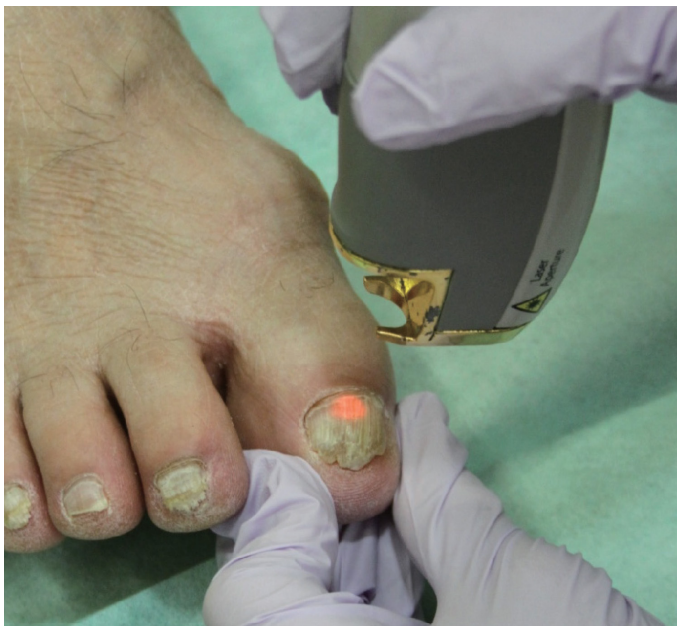
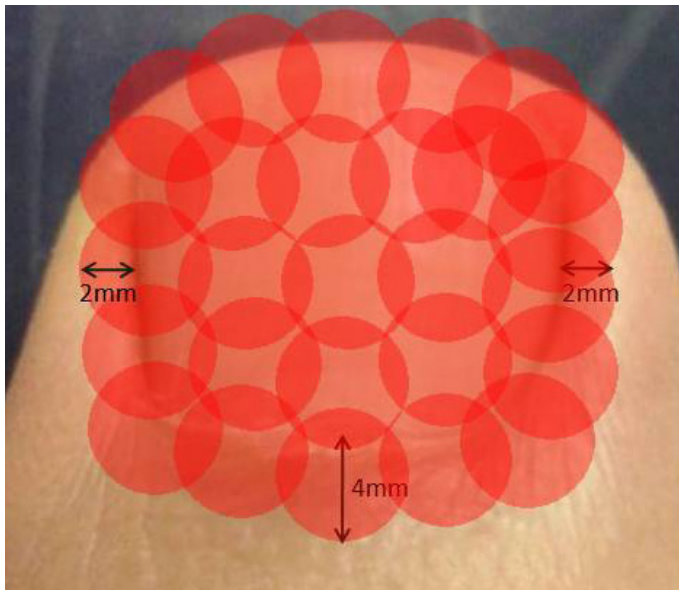


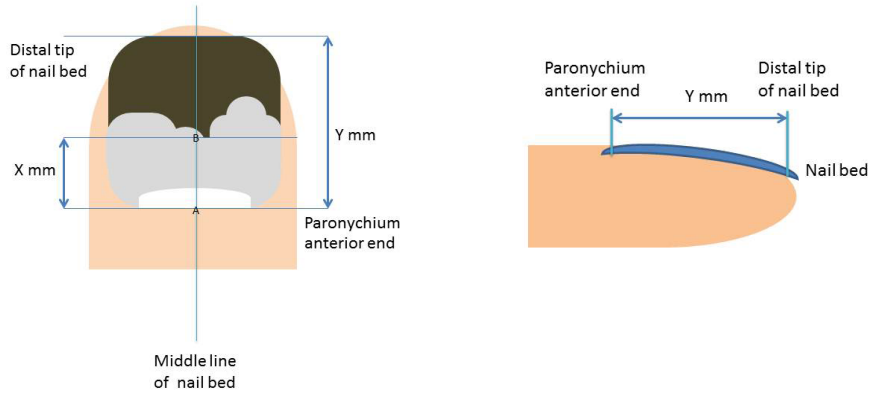
FIGURE 2. Infected toenail area was irradiated extending 2 mm over the medial and lateral nail fold and 4 mm over the proximal nail fold.



1. Assessment of Turbidity

Toenail turbidity was assessed on baseline and final follow-up photos (average of 16 weeks post- final treatment) using a turbidity scale (0-10) (Table 2). Turbidity scores were calculated using the formula (1-X/Y) × 10 (Figure 3) where X (mm) represents the length of uninfected toenail growth proximal to turbidity and Y (mm) is the total length of toenail extending from paronychium anterior end to distal tip of nail bed. Measurements were done on the middle line as shown in Figure 3 on both baseline and final follow-up photos.[10] Three dermatologists including the treating dermatologist performed the measurements and the turbidity scoring. The subjects were randomly divided between the dermatologists for scoring.

FIGURE 3. Calculation of turbidity score of the infected area = (1-X/Y) × 10



A = The line that middle line of nail bed crosses Paronychium anterior end
B = The border line of uninfected toenail and turbidity nail
X = Length of uninfected toenail growth proximal to turbidity
Y = Total length of toenail

TABLE 2.

Turbidity Scale (0–10)	
Score ranges	**Definition**
0	Clear nail
0 < Score ≤ 3	Slight turbidity
3 < Score ≤ 6	Moderate turbidity
6 < Score < 10	Severe turbidity
10	Completely turbid nail
2	Significantly more effective than usual
3	Best effect ever or imaginable

2. Assessment of Overall Improvement

The degree of clinical improvement was determined by comparing the turbidity scores at baseline and at the final follow-up visit. The same group of three dermatologists who did the turbidity scoring also assessed the overall improvement on the same group of subjects they were randomly assigned for scoring. If there was complete resolution of turbidity at final follow-up (turbidity score of 0), a direct microscopic examination was performed using KOH preparation. Overall treatment efficacy was assessed using the overall improvement scale (0-4) where 0 represented "no clearance" and 4 represented "complete clearance" with negative microscopic result (Table 3). No microscopic examination was performed unless the turbidity score showed "0 = clear nail."

Statistical Analysis

Statistical analysis was performed using Minitab statistical package, version 15.1.20.0 (Minitab Inc., State College, PA). The data was presented using descriptive statistics as frequency distributions (presented in bar charts and tables) and individual data (tabulated in tables).

TABLE 3.

Overall Improvement Scale (0–4)	
Score	**Definition**
4	Complete clearance with negative microscopic result*
3	Significant clearance
2	Moderate clearance
1	Slight clearance
0	No clearance

*Direct microscopy was performed.

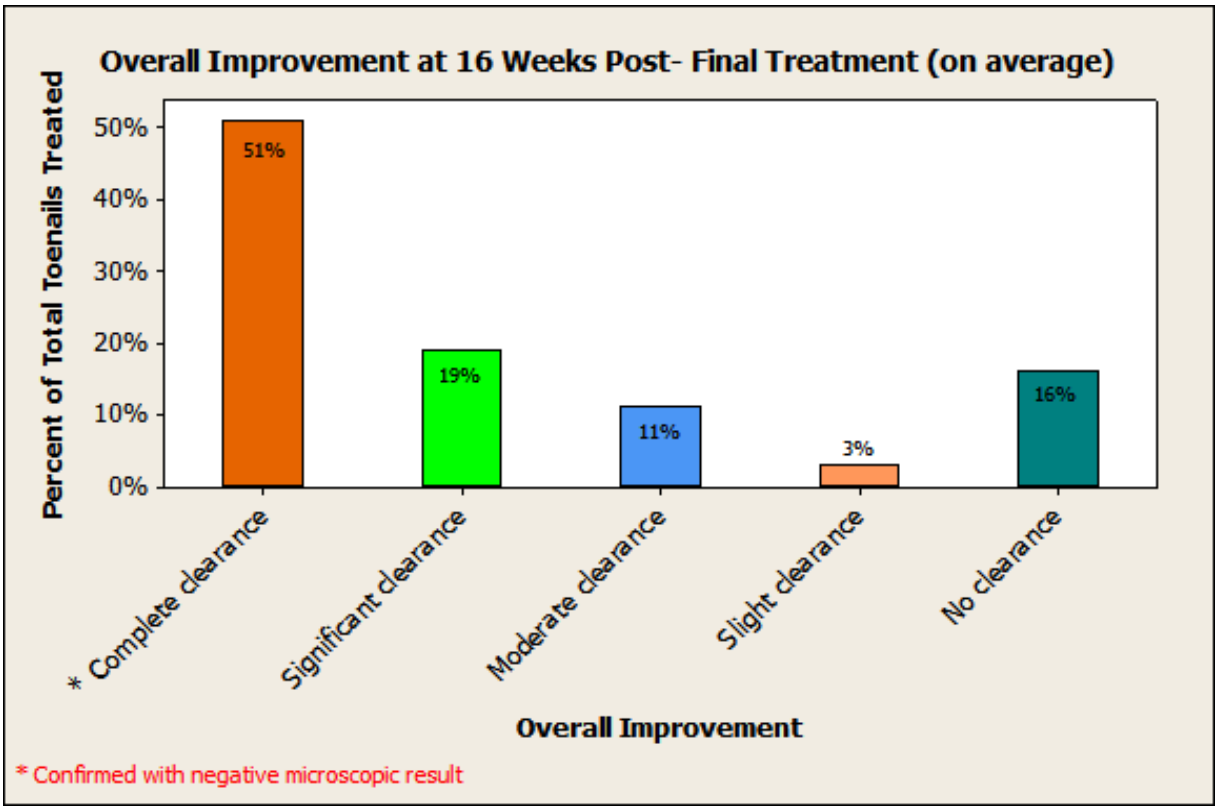
RESULTS

Thirteen subjects with a total of 37 affected toenails received treatments 4 and/or 8 weeks apart and completed 2 to 6 follow-up visits 4 weeks apart post-final treatment. The average number of treatments was 2.4 (1 to 3 treatments) and the average follow-up period was 16 weeks post-final treatment (ranging from 8 to 24 weeks).

The overall improvement observed at 16 weeks post-final treatment is shown in Figure 4. Of the 37 infected toenails treated, 30 (81%) showed either "complete clearance" or "moderate" to "significant" clearance. Nineteen (51%) toenails showed "complete clearance," of which 100% tested negative for fungi on direct microscopy.

Of the six (16%) toenails that showed no improvement at 16 weeks post-final treatment, all had a turbidity score of 10 at baseline and five of six involved the great toes (Table 4). Overall, 78% (29/37) of toenails had a baseline turbidity of 8 to 10, of which 76% (22/29) had a baseline turbidity of 10 (Table 4). However, of the 22 toenails with a turbidity of 10 at baseline, 50% (11/22) showed "complete clearance," and 18% (4/22)

FIGURE 4. Percentage of toenails showing improvement.



showed "significant" to "moderate" clearance." In summary, 68% (15/22) of toenails with a maximum baseline turbidity of 10 resulted in either "complete clearance" or "moderate" to "significant" clearance average of 16 weeks post-final treatment.

Twelve of 13 subjects had involvement of at least one great toenail. Although great toenails with a turbidity of 10 at baseline indicated "slight" to "moderate" improvement at the 16-week follow-up, none showed "complete clearance" (Table 4). Of 19 toenails with complete clearance, only 26% (5/19) involved the great toenails (Table 5). On the other hand, 72% (8/11) of toenails that showed "moderate" to "significant" clearance were the great toenails (Table 5).

Adverse Events

The laser treatment procedures were well-tolerated. While some subjects experienced a mild warming sensation during the laser treatments, there were no adverse events reported during the 24-week observation period.

DISCUSSION

Treatment of onychomycosis with topical and oral antifungal treatments can be challenging for practitioners and frustrating for patients due to relatively high persistence, recurrence, and reinfection rates[3,11] of 10% to 53%.[5] Although oral medications are generally more effective than topical antifungals,[22] treatment is usually protracted and can take up to three months.[23,24] Oral antifungal therapy is also associated with higher risks of liver toxicity, drug interactions, and allergies,[5,7,8] which may limit its use, particularly in certain patient populations.[24] In addition, relatively high reinfection rates can adversely impact treatment compliance.

This study reports our initial clinical experience with a sub-millisecond Nd:YAG 1,064 nm laser in treating onychomycosis of varying severity in 37 affected toenails of 13 subjects. All patients enrolled in this study had a prior history of ineffective oral and/or topical antifungal medication use. Although the optimal treatment regimen with this therapeutic modality is yet to be defined, all patients received one to three treatments 4 and/or 8 weeks apart.

Nine of the 13 subjects presented with the distal and lateral subungual onychomycosis (DLSO) in 25 toenails, 2 subjects presented with TDO in 5 toenails, 1 subject presented with PSO in 1 toenail, and 1 subject was reported to have had concomitant total dystrophic onychomycosis (TDO) in 2 great toenails and superficial white onychomycosis (SWO) in 4 toenails (2nd and 3rd).

The preliminary clinical results obtained with the use of the sub-millisecond Nd:YAG laser are encouraging irrespective of the stage and severity of the infection. Of the toenails, 81% indicated "moderate" to "complete" clearance an average of 16 weeks post-final treatment (following an average of 2.4 treatments).

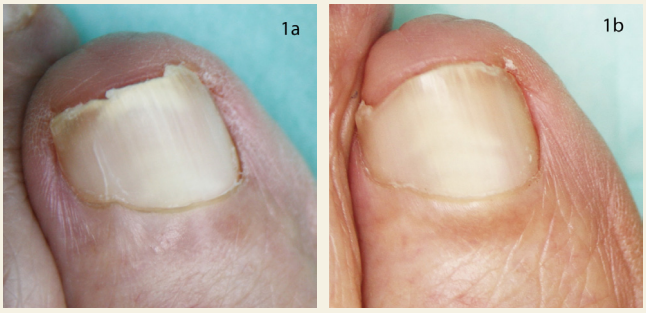
TABLE 4.

Assessment of overall improvement (0–4) at 16 weeks post- final treatment (on average)

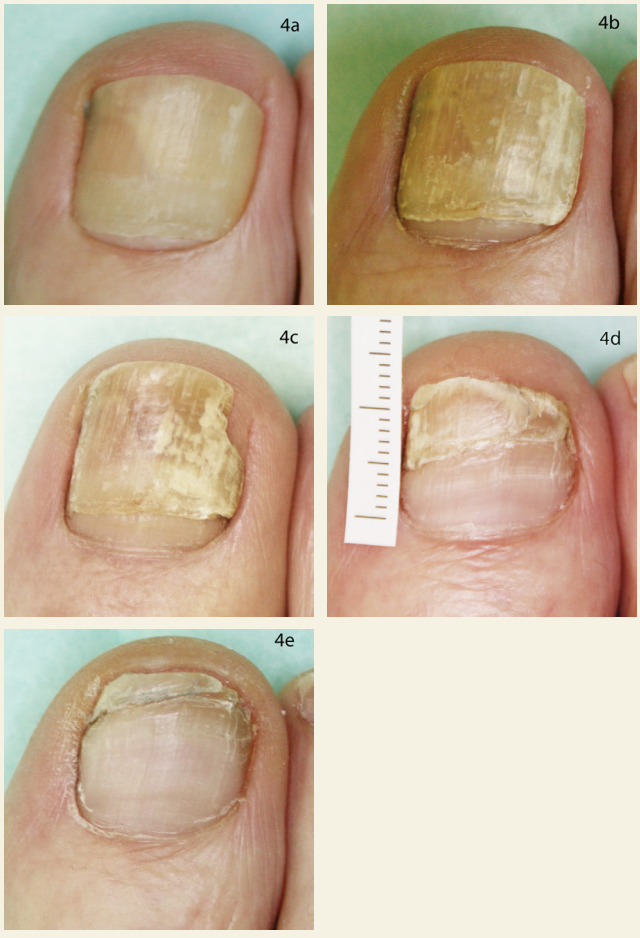
Side	Toenail	Subject	Number of treatments	Follow-up post- final treatment (weeks)	Turbidity score at baseline (0–10)	Turbidity score post-final treatment (0–10)	Overall improvement score (0–4)
Right	Great	1	2	20	6.7	0	4
Right	Great	2	3	8	7.1	0	4
Right	Great	4	2	16	9.4	2.7	3
Right	Great	5	3	8	10	10	0
Right	Great	8	2	20	10	6.8	2
Right	Great	10	2	20	5	0	4
Right	Great	11	3	16	7.4	1.2	3
Right	Great	12	3	16	10	6.7	2
Right	Great	13	1	24	10	10	0
Right	2nd	6	2	20	6	0	4
Right	2nd	11	3	16	10	0	4
Right	2nd	12	3	16	10	0	4
Right	3rd	2	3	8	10	0	4
Right	3rd	5	3	8	10	0	4
Right	3rd	6	2	20	10	0	4
Right	3rd	12	3	16	10	0	4
Right	4th	2	3	8	10	0	4
Left	Great	1	2	20	3.3	0	4
Left	Great	2	3	8	8	0.7	3
Left	Great	3	3	16	10	10	0
Left	Great	4	2	16	8.8	1.3	3
Left	Great	5	3	8	10	8.3	1
Left	Great	7	3	12	8.2	4.3	2
Left	Great	9	3	8	10	10	0
Left	Great	11	3	16	7.4	1.9	2
Left	Great	12	3	16	10	9.3	0
Left	Great	13	1	24	4.7	0	4
Left	2nd	2	3	8	10	0	4
Left	2nd	6	2	20	8.3	0	4
Left	2nd	11	3	16	10	0	4
Left	2nd	12	3	16	10	2.9	3
Left	3rd	2	3	8	10	0	4
Left	3rd	6	2	20	8.3	1.7	3
Left	5th	7	3	12	10	10	0
Left	5th	9	3	8	10	0	4

FIGURE 5. Progression of improvement at various time points (Subjects 1, 4, 11, 12, and 13).

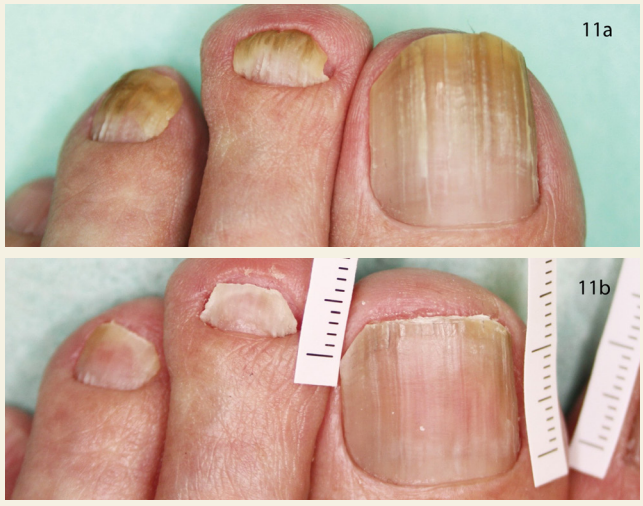
Subject 1: (1a) Baseline, (1b) 4 weeks post-final treatment (2 treatments, 4 weeks apart)



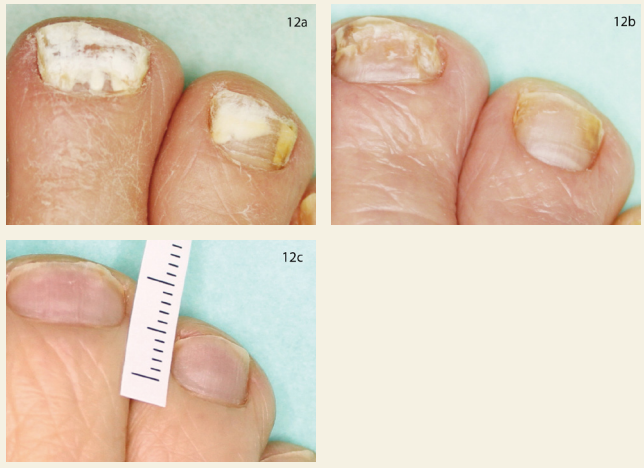
Subject 4: (4a) Baseline, (4b) 4 weeks post-first treatment, (4c) pre- second treatment (at 8 weeks), (4d) 8 weeks post-final treatment and (4e) 16 weeks post-final treatment (2 treatments, 8 weeks apart)



Subject 11: (11a) Baseline and (11b)16 week post-final treatment (3 treatments, 4 weeks apart)



Subject 12: (12a) Baseline, (12b) pre-third treatment (at 8 weeks) and (12c) 16 weeks post-final



Subject 13: (13a) Baseline, (13b) 4 weeks post-final treatment (1 treatment)

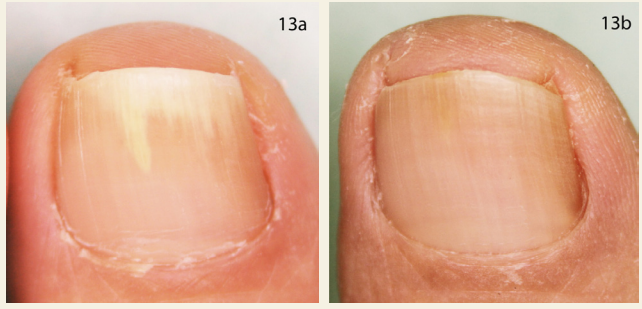


TABLE 5.

Frequency distribution of overall improvement scores [n (%)] by type of toenail at 16 weeks post-final treatment (on average)

	Overall Improvement Score (0–4)				
Type of Toenail (left and right)	0	1	2	3	4*
Great	5 (26)	1 (6)	4 (21)	4 (21)	5 (26)
Other (2nd, 3rd, 4th and 5th)	1 (6)	0 (0)	0 (0)	3 (16)	14 (78)

* Confirmed with negative microscopic result.

The complete clearance was defined as the clinical appearance of clear nail confirmed by negative direct microscopy. Fifty-one percent of toenails had complete clearance, which included a left great toenail with distal and lateral subungual onychomycosis (DLSO) following one treatment (Figure 5. 13b).

Almost all subjects had involvement of at least one great toenail; however, the great toenail constituted only 26% of all toenails with complete clearance. Lower rate of complete clearance on great toenails suggest that the improvement need to be further investigated in studies with longer follow-up periods. Long-term data will allow showing complete clearance on all infected toes, which is also an important goal, both for the patient and the clinician.

Currently, there are few publications available about the treatment of onychomycosis using sub-millisecond 1064 nm Nd:YAG laser.[3,4] A pilot study of a 0.65 ms 1064 nm Nd:YAG with 2 mm spot size showed substantial improvement in the appearance of the nail 4 to 6 months post-final treatment.[3] In contrast to our study, the subjects were asked to use daily antifungal cream to prevent re-infection after treatment. Seven of eight subjects (88%) in this pilot study had negative post-treatment culture following 2 to 3 treatments. In a review paper, Gupta reported preliminary results from two studies about the treatments using a 1064 nm Nd:YAG with 1 mm spot size.[4] In one of the studies, a growth of 2.1 mm to 6.1 mm clear nail was observed at 3 months following a single treatment. The other study, a retrospective analysis of single treatments on 128 toes (64 subjects), indicated a statistically significant mean improvement of 9.8 % in the lesion-free area at 6 months post-final treatment. The preliminary results from these studies, including our study, suggest that treatment of onychomycosis using sub-millisecond 1,064 nm Nd:YAG is promising. Although smaller spot sizes were investigated in studies with other devices compared to 5 mm spot size used in our study, the safety and efficacy of the spot size on the clinical outcome and patient discomfort needs to be investigated in comparative studies. One benefit of a bigger spot size as experienced in our study is that the treatment time is shorter than it is with a small spot size.

There were no adverse events reported during our study, consistent with the use of similar therapeutic modalities reported in the literature.[3,11] The application of laser irradiation in a non-contact mode mitigated concerns of possible recurrence due to contamination.

Although the mechanism of action of lasers in treating onychomycosis is unknown, their effectiveness is thought to result from bulk heating to thick, horny cell layer and internal nail harboring the fungus, which is a weak pathogen that is susceptible to heat. In addition, particular features of the laser wavelength or heating effects may stimulate infected nails to promote more rapid nail growth.

To date, the results of our clinical study suggest that the sub-millisecond Nd:YAG 1,064 nm laser is a safe and effective treatment modality for onychomycosis. However, as this study involves a relatively small patient population followed for a relatively short period, studies involving larger patient populations with longer follow-up times are warranted to determine the optimal treatment protocols and assess performance in the long term. The clinical efficacy and significance of this novel treatment for the management of onychomycosis should be further evaluated in broader patient populations.

DISCLOSURES

Juntendo University Urayasu Hospital, Department of Dermatology has received an equipment loan from Cutera Inc.

Addenda: Future studies will have control groups. In addition, tests will be done to detect for absence of fungus infection and not done only by visual evaluation.

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