New guidelines for Nd:YAG treatment of onychomycosis based on 12-month follow-up and clinical literature study

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Background
Onychomycosis is a persistent fungal infection of the nail bed and plate and the prevalence is estimated to be 2%-8% of the global population, rising to 14%-28% in those over 60 years. Onychomycosis affects approximately one-third of diabetics and is 56% more frequent in people suffering from psoriasis.

Onychomycosis is often caused by Trichophyton rubrum, which invades the nail bed and the underside of the nail plate, beginning at the hyponychium, and then migrates proximally through the underlying nail matrix resulting in extensive disease.

Results of 4 and 12 month follow-up
Eleven Caucasian patients of Fitzpatrick phototypes I – III, (mean age: 60.4 years, range: 31-84 years), were included in a randomized, paired study of Ellipse Nd:YAG treatment of fungally infected toe nails. Patients who had taken oral antifungal medication within a year or topical antifungal medication within a week were excluded from the study. In total 53 nails were treated, 27 with a sub-millisecond pulse duration of 0.3ms and fluence 16J/cm² and 26 nails were treated with pulse duration 35ms and fluence 37J/cm². All nails were treated with a 4mm spot size, an overlap of 30-40% and 5 passes. Three treatments were performed with 2 months intervals.

The objective evaluation in this investigation was performed as a turbidity score (T-score) based on close-up photos of each treated nail, with a high resolution digital camera. In contrast to earlier studies where T-score was evaluated as the length ratio of the infected and uninfected part of the nails, the T-score in this study was based on the ratio between the infected and uninfected area of the individual nail. The area evaluation gives a more precise measurement as it takes lack of symmetry into account.

At the 4-month follow-up the same statistical response rate (74.1% versus 83.3%) for patients treated with the sub-millisecond and millisecond pulse were registered. However, by the 12-month follow-up there was a 63.0% - 50.0% (13 percentage points higher) response rate for the sub-millisecond pulses compared to the millisecond pulses. Improvements for both modalities were found to be statistically significant at 4 as well as 12 month follow-up (P<10⁻⁴ and P<0.04, respectively).

The main conclusion of this investigation is that the long time effect of treatment of onychomycosis with pulse duration in the sub-millisecond area (0.3-0.5ms) tends to be superior to treatment with 35ms pulse duration.

Literature study
Treatment of onychomycosis with Nd:YAG lasers emitting a wavelength of 1064nm is a relative new treatment modality. Highly different treatment parameters with pulse durations varying from 0.3ms to 35ms, fluences from 5J/cm² to 324J/cm², numbers of passes from 1 to 5 and pulse rates from single shot to 5Hz, have been used. Also, the numbers of treatments and treatment intervals is greatly different from study to study.

In Table 1 below, ten clinical studies published in the period 2010-2014 are listed together with parameters used and treatment setups. The studies obtaining the highest clearance rates are placed at the top of the list (last column).

The four investigations at the top of the list all report clearance rates higher than 80%. Treatment parameters used range over the entire area stated above, with respect to pulse duration and fluence used. However, the only common parameter for these successful investigations is the very short time interval of 1 to 3 weeks between treatments.

The numbers of treated nails in these studies is very high, 194, 413, 21 and 16 nails, and the follow-up periods used are relatively long (6 months); both adding to give a good statistical background for evaluation.

If not all fungal spores are destroyed by a single treatment, then the remaining spores will be able to flourish. To ensure a decreasing colony, the laser treatment has to be performed with shorter intervals than the time required for the fungal spores to re-establish the colony. This theory fits well with fact that the highest clearance rates were obtained by studies using short intervals between treatments. Therefore it is recommended to decrease the treatment interval from the previously recommended two months to 2 weeks (or 1-3 weeks to ensure maximum patient compliance).

The mode of action for laser treatment of onychomycosis is not yet known for sure, but has a high probability of being selective photothermolysis. Therefore the outcome might improve by increased temperature in the nail plate. This can be obtained by using higher pulse frequency 2-3Hz, and by increasing the fluence up to 22J/cm², while still taking patient comfort into account.

Treatment Guidelines
- Verify that the patient really suffers from onychomycosis by mycological microscopic examination and/or fungal culture with Sabouraud’s medium. Onychomycosis can easily be a mistaken
diagnose for a patient suffering from psoriasis and in such cases, general treatment of onychomycosis including laser treatment will have no effect.

- Thick nail will have a negative impact on the efficacy, as it might be difficult to reach the necessary flux in the lower part of the nail plate. Therefore we recommend having thick nails ground down to 1-1.5mm thickness before laser treatment is performed.
- Perform 4-5 treatments with 1-3 weeks interval.
- Use pulse durations 0.3-0.5ms and 4 consecutive passes on each nail, before changing to the next nail.
- Use a fluence of at least 16J/cm². Higher fluence will improve the result, so increase the fluence up to 22J/cm², if the patient can accept it.
- Follow-up 3 months post treatment. If in doubt that all fungus has disappeared, perform an additional treatment.
- Ask the patient to come for a check-up every 6 months until all nails have completely recovered and perform an additional treatment.
- Laser treatment might benefit from the combination of home treatment with a water based nail lacquer such as Onytec, Ciclopoli or equivalent, with 8% ciclopirox as the active compound, applied to the nail at night for up to one year.

**Patient Guidelines**

To perform successful onychomycosis treatments it is very important to inform the patients about the background of the disease and what they themselves can do to improve the result.

- Onychomycosis is a fungal infection often seen in connection with foot fungus (athlete's foot).
- Fungus thrives in moist, poorly ventilated areas therefore:
  - Wear light shoes or sandals, made of breathable material, and alternate them often
  - Avoid footwear made of synthetic material
  - Wash feet at least once a day
  - Dry feet carefully especially between toes
  - Let feet dry before putting on socks and shoes
  - Only use cotton or wool socks
  - Both feet and the inside of the footwear can be dusted with anti-fungal powder.

<table>
<thead>
<tr>
<th>Investigation</th>
<th># patients/ nails</th>
<th>Fluence J/cm²</th>
<th>Pulse duration ms # passes</th>
<th># Treatments</th>
<th>Treatment intervals</th>
<th>Follow-up</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kozarev J, 2010&lt;sup&gt;1&lt;/sup&gt;</td>
<td>72 pat 194 nails</td>
<td>35-40 Ø4</td>
<td>35 3 passes temp 45±5ºC</td>
<td>4</td>
<td>weekly</td>
<td>3 months 6 months</td>
<td>95.8% 100%</td>
</tr>
<tr>
<td>Kozarev J, 2011&lt;sup&gt;8&lt;/sup&gt;</td>
<td>162 pat 413 nails</td>
<td>35-40 Ø4</td>
<td>35 1Hz 3 passes</td>
<td>4</td>
<td>weekly</td>
<td>3 months 6 months</td>
<td>Avg.:95.7% Avg.: 98.8%</td>
</tr>
<tr>
<td>Waible 2012&lt;sup&gt;7&lt;/sup&gt;</td>
<td>21 patients</td>
<td>13 6Hz</td>
<td>0.3</td>
<td>4</td>
<td>Weekly</td>
<td>6 month</td>
<td>Negative mycological culture 95%</td>
</tr>
<tr>
<td>Hochmann 2011&lt;sup&gt;10&lt;/sup&gt;</td>
<td>8 pat. 16 nails</td>
<td>233 Ø2</td>
<td>0.65 2 passes</td>
<td>2-3</td>
<td>3 weeks</td>
<td>4-6 months</td>
<td>88% negative culture</td>
</tr>
<tr>
<td>Kimura 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>13 patients 37 nails</td>
<td>14 Ø5</td>
<td>0.3 2 passes 100-200pulse</td>
<td>1-3</td>
<td>4-8 weeks</td>
<td>16weeks</td>
<td>Avg.: 74%</td>
</tr>
<tr>
<td>Zhang 2012&lt;sup&gt;14&lt;/sup&gt;</td>
<td>33 patients 154 nails</td>
<td>240-324 Ø3</td>
<td>30 1Hz 2 passes</td>
<td>8 (78 nails) 4 (76 nails) Weekly Weekly</td>
<td>16 weeks</td>
<td>51% 53% obtained &gt;60% clearance</td>
<td></td>
</tr>
<tr>
<td>Moon SH 2014&lt;sup&gt;13&lt;/sup&gt;</td>
<td>13 patients 43 nails</td>
<td>5 Ø6</td>
<td>0.3 5Hz temp 40-42ºC</td>
<td>5</td>
<td>4 weeks</td>
<td>1 months</td>
<td>Avg. 50.2% 70% negative repeated KOH test</td>
</tr>
<tr>
<td>Weiss D 2011&lt;sup&gt;14&lt;/sup&gt;</td>
<td>7 patients</td>
<td>16 Ø5</td>
<td>0.3</td>
<td>2</td>
<td>6 weeks</td>
<td>12 months</td>
<td>Avg.: 42.3% 70% responders</td>
</tr>
<tr>
<td>Noguchi H 2013&lt;sup&gt;35&lt;/sup&gt;</td>
<td>12 patients 1 hallux nails</td>
<td>10 Ø6</td>
<td>0.5 2 Hz 4 passes</td>
<td>3</td>
<td>4 weeks</td>
<td>6 months</td>
<td>Avg.: 37.7% 92% respond</td>
</tr>
<tr>
<td>Carney 2013&lt;sup&gt;16&lt;/sup&gt;</td>
<td>14 nails</td>
<td>16 Ø5</td>
<td>0.3 5 passes 300 pulse</td>
<td>5</td>
<td>0,1,2,3 and 7 week</td>
<td>24 weeks</td>
<td>Avg.:33%. Area reduction 57% responders</td>
</tr>
</tbody>
</table>

Table 1 Published clinical studies of Nd:YAG treatment of onychomycosis in the period 2010-2014 ranged after clearance rate


4 T-Score: = (1 -X/Y) x 10, where X was the area of the uninfected part of the nail and Y is the total nail area. (T-score = 0 means total clear nail and 10 means total infected nail)


