The Efficacy of Laser Onychomycosis Treatment with Er:YAG in Non-ablative Mode

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ABSTRACT

Onychomycosis is a fungal infection of the nail that affects approximately 10-30% of the world’s population. Although systemic antifungal therapy today represents a recognized standard, it is not recommended for all patient groups due to the cause of side effects. Therefore there is a great need to develop less invasive therapeutic options for the treatment of onychomycosis. Recently, Er:YAG with a novel thermal SMOOTH mode was introduced for non-ablative treatments. In this study involving 7 patients, a new method using an Er:YAG laser in non-ablative mode was compared with the well-established therapy using Nd:YAG laser. Preliminary results have shown that using the Er:YAG laser in the non-ablative regime results in a significantly higher temperature at the site of the fungal infection (Figure 3), compared to Nd:YAG treatment, before the pain threshold was achieved. Er:YAG treatment was better tolerated compared to Nd:YAG treatment. Er:YAG laser in non-ablative mode has a high potential for the effective treatment of onychomycosis since very encouraging rates of mycological and clinical cure were observed after two treatment cycles.

Key words: onychomycosis, Er:YAG laser, port wine stain, hemangioma.

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1. INTRODUCTION

Onychomycosis is a fungal infection of the nail that affects approximately 10-30% of the world’s population. It most frequently occurs in the elderly, immunocompromised individuals, smokers and patients with peripheral vascular disease, and in people with a family history of onychomycosis [1]. Clinical signs include discoloration, thickening, changes in the surface of the nail and withdrawal from the nail bed.

The most common cause of onychomycosis are dermatophytes of the genus Trichophyton, Epidermophyton and Microsporum, representing more than 90% of all cases of fungal nail infections. To a lesser extent, yeasts (eg. Candida) and saprophyte mold (Aspergillus niger) can also represent a cause of fungal nail infection. The most common infection starts at the end of the nail and spread to the side and under the nail plate to the nail root and deeper into the nail bed [2]. In the past, a variety of systemic and local therapies have been used for the treatment of onychomycosis, and today the most common and widely accepted method of treatment of fungal nail infections is antifungal oral systemic therapy, sometimes combined with topical antifungals. Since the nail plate is an extremely compact structure, the penetration of topical antifungals is difficult, which significantly reduces the efficiency of local antifungals [3]. On the other hand, however, systemic antifungal therapy is usually accompanied by many undesirable effects associated with the necessary long-term use of antifungals, which can affect the liver and kidneys and could interfere with patients other medications or conditions. The most frequently used systemic drugs for the treatment of onychomycosis are terbinafine, itraconazole, fluconazole and griseofulvin. However, the efficacy of systemic therapy is low, between 68 and 80%, and reduces with the age of the patients due to slower metabolism and circulation of the nail bed [4-7]. Especially problematic are some of the side effects of systemic antifungals. The FDA has even issued warnings about the side effects of terbinafine in itraconazole [8,9]. The side effects often include nausea and headaches, and although rare, can cause liver failure and heart problems, which may even lead to death. Therefore, in elderly patients and patients with a weakened immune system, monitoring of liver enzymes during treatment is obligatory. In addition, systemic antifungal drugs can interact with other drugs, which may cause additional side effects. Although systemic antifungal therapy today represents a recognized standard, it is not recommended for all patient groups due to the above described risks. Special caution is in particular required in the elderly, children, and patients with an impaired immune system, women during pregnancy and lactation, and in patients with congestive heart failure.
There is therefore a great need to develop less invasive and more effective therapeutic options for the treatment of onychomycosis. Recently, a new technique of treatment for fungal nail infections based on photodynamic therapy [10,11] and laser [12–15] has been introduced. Fungi are heat-sensitive above 55°C (40–60°C), so absorption of laser energy that results in a sustained photothermal heating of the mycelium results in a fungicidal effect [16,17]. Numerous studies have shown that laser therapy for onychomycosis enables faster treatment with a very low rate of potential unwanted effects[12–15]. Laser therapy using Nd:YAG laser is an FDA recognized method and is useful for all patients, especially for the elderly and immunocompromised patients and patients with liver disease for which the standard methods with the use of systemic antifungal agents pose a significant risk [13].

Nd:YAG laser with a wavelength of 1064 nm is very well absorbed in the dark pigments such as melanin and porphyrins. Melanin is a component of the fungal cell wall and one of the key mechanisms of fungal virulence [18]. Due to the high absorption of laser energy in fungal pigments, fungi are exposed to high local temperatures resulting in an inhibition of fungal growth, and at the same time causing cell damage leading to cell death [19,20]. Although therapy with Nd:YAG laser represents a safe and effective treatment option, Nd:YAG laser is highly absorbed in hemoglobin and can penetrate through the nail plate into the nail bed and deeper into the dermis, which can cause tissue damage of the nail bed if treatment parameters are chosen incorrectly. Studies have shown that even slight hyperthermia can trigger the signaling pathway, which through various mechanisms can lead to apoptosis [21,22]. Recently, Er:YAG with a novel thermal SMOOTH mode was introduced for non-ablative treatments. Since Er:YAG is highly absorbed in water, allowing better temperature control, it can be predicted that higher temperatures can be achieved at the site of the fungal infection without damaging the surrounding tissue.

The purpose of this study is to determine the efficacy and safety of Er:YAG laser therapy in non-ablative mode for the treatment of onychomycosis. A new method using an Er:YAG laser in non-ablative mode was compared with the well-established therapy using Nd:YAG laser.

II. MATERIALS AND METHODS

a) Temperature measurements

Preliminary temperature measurements were conducted on a single nail to compare the nail heating with Nd:YAG and Er:YAG in non-ablative mode. With both lasers, energy was delivered on the same spot using a sequence of pulses until the pain threshold was achieved. Surface temperature was measured using Flir ThermalCAM P45 (S/N 2301323). SMOOTH pulses using Er:YAG laser with a 7 mm spot size and 3 J/cm² fluence was compared with Nd:YAG using a 6 mm spot size with 35 J/cm² fluence and 35 ms pulse duration.

b) Clinical evaluation:

7 patients with symmetrical nail plate involvement (56 nails) were enrolled in the study. The suitability of participants was assessed based on inclusion and exclusion criteria. All patients were informed about the risks and benefits of the proposed laser therapy as well as about other treatment possibilities and an informed consent form was signed by all subjects. Onychomycosis was diagnosed clinically, dermatoscopically and microbiologically, and an OSI (Onychomycosis Severity Index) numeric score was determined [23]. Exclusion criteria included the use of isotretinoin and/or vasodilators or topical and/or systemic antifungal agents 6 months before recruitment, pregnancy or breastfeeding, permanent or semi-permanent discoloration of the nail plate or other skin lesions present at the treatment site such as psoriasis, subungual hematomas.

Er:YAG laser therapy in non-ablative mode for the treatment of onychomycosis (left foot) was compared with the well-established therapy of Nd:YAG laser (right foot) to assess the effectiveness and safety of the proposed therapy. Both treatments consisted of two treatment cycles with a 2-month interval between the cycles. One treatment cycle included 4 laser sessions with 1-week intervals between consecutive sessions. There was no post-op care prescribed, except the guidelines on the prevention of the reinfection given to all patients.

Table 1: Treatment parameters used.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nd:YAG</th>
<th>Er:YAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wavelength (nm)</td>
<td>1064</td>
<td>2940</td>
</tr>
<tr>
<td>Fluence (J/cm²)</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Spot size (mm)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pulse duration (ms)</td>
<td>SMOOTH</td>
<td>25</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No of passes</td>
<td>3</td>
<td>15</td>
</tr>
</tbody>
</table>

c) Er:YAG treatment

28 onychomycotic nails (50% - left foot of each patient) were treated using Er:YAG laser in non-ablative mode (Table 1). A pack of 4-15 pulses, depending on the pain threshold of the individual patient and nail thickness, was delivered at one spot of the nail. Successive spots were gradually moved in a helical pattern over the whole nail area. The number
of pulses was reduced around the area of the nail matrix. For better detection of the pain threshold, no anesthesia or pain relief was applied.

d) Nd:YAG treatment

For comparison, onychomycotic nails on the right foot of each patient (28 nails; 50%) were treated using Nd:YAG (Table 1). The entire nail plate was treated in a successive spiral pattern as previously described [12]. Three passes with two-minute intervals were applied to every infected nail. Anesthesia or pain relief was not required during or after the treatment.

The effectiveness and safety of the laser therapy was determined by repeated clinical, dermoscopic and microbiological examination of patients before, 1 month and 3 months after completion of the laser therapy (Figure 1). Samples for mycological tests were taken 1 month after the 1st cycle of the treatment. Two months after the completion of 1st cycle, the 2nd cycle was applied to all the patients. The efficacy of the treatment was clinically examined, and photographs and the nail severity index (OSI numeric score) [23] were recorded. Dermoscopy was done on six to nine points of the nail (Fig. 2). Microbiological evaluation for the presence of fungi using the DermAX TA / MA test (Axonlab AG, Germany) was performed before treatment and at every follow-up visit. The fungal culture taken from infected nails was incubated on both sides of the test plate at 37° C for 7 days. To assess the improvement in the quality of life, a standardized questionnaire was completed by the patients before and at the 3-month follow-up. Pain during treatment was also assessed and side effects were monitored during the study. 5 patients with 38 onychomycotic nails completed the study, while 2 patients (18 nails) were lost during follow up.

III. RESULTS

a) Temperature measurement:

Preliminary results have shown that using the Er:YAG laser in the non-ablative regime results in a significantly higher temperature at the site of the fungal infection (Fig. 3), compared to Nd:YAG treatment, before the pain threshold was achieved. The wavelength of the Er:YAG laser is highly absorbed in the water and therefore provides better temperature control of the surrounding tissue without damaging it. The Er:YAG laser in the non-ablative regime also allows for a longer thermal effect at the site of the infection, compared to the thermal effect achieved by using Nd:YAG laser, which further increases the effectiveness of the therapy itself (Fig. 3).

Figure 1: Study diagram

Figure 2: Example of dermoscopic onychomycosis evaluation.

Figure 3: Temperature measurement on the nail surface achieved with two different lasers. A: Nd:YAG laser using standard treatment parameters. B: Er:YAG laser in thermal mode.
According to the measured temperatures related to pain threshold, a mode of actions with the different lasers was suggested. The existing laser therapies such as Nd:YAG are based on utilizing a wavelength that penetrates substantially through the nail plate and is absorbed in the underlying fungus-infected tissue. Absorption of the laser energy is then expected to result in a sustained heating of the mycelium and fungicidal effects, as fungi can be heat-deactivated at temperatures above 40-60 °C. Typically, laser wavelengths that are not strongly absorbed by the nail are also not strongly absorbed in the infecting fungi. The 1064 nm wavelength Nd:YAG laser penetrate through the mycelium and is absorbed in the underlying tissues, resulting in non-specific bulk heating of the toe (Figure 4a). This can cause pain and thermal damage to deep-lying healthy tissue. Using the Er:YAG laser, the nail is irradiated by a 2940 nm wavelength that is strongly absorbed at the nail surface, and does not get substantially transmitted to the nail bed. This leads to the release of heat at the nail surface, which is diffused through the nail to the underlying nail bed, causing a temperature rise within the nail bed (Figure 4b). Laser energy is delivered in the amount necessary to heat the whole thickness of the nail and the upper surface of the nail bed to temperatures that induce deactivation and death of the infecting fungus. At the same time, side effects due to tissue damage are minimized, as the heating is directed only at the infected part of the nail bed and does not reach significant levels in healthy underlying tissues. This significantly decreases discomfort and pain compared to standard treatments.

**b) Clinical results:**

5 patients (four male and one female) with a mean age of 51.5 years (between 31 and 69) with diagnosed onychomycosis (38 onychomycotic nails) by mycological tests and comparable OSI numeric scores on both feet completed the study. All patients had Distal Subungual and Lateral type of onychomycosis (DSLO) (Table 2). On both sides, the severity of the nail infection was determined with OSI score. The mean OSI index before treatment on the Er:YAG-treated side was 27.4 and on the Nd:YAG side 25.8 (Table 2). According to the high OSI index determined before treatment, a poor response could be expected since a high OSI index represents a poor prognostic factor for all treatment options [24].

3 months after both cycles of the treatment protocol was completed, the average OSI index decreased to 19.8 points on the Nd:YAG side and to 19 points on the Er:YAG side. In two patients, on the Er:YAG-treated side, the OSI index decreased from severe to mild onychomycosis according to the OSI index while on the Nd:YAG side, the decrease was from severe to moderate onychomycosis. In one patient the OSI index increased in both treatment groups due to reinfection associated with noncompliance with post-treatment guidance given to all the patients.

Better results were also observed with patients with a lower OSI index. That seems reasonable as severe cases are accompanied by dermatophytoma or significant subungual hyperkeratosis, which requires more time for the nail plate to restore. Poor prognostic indicators also include total dystrophic onychomycosis, the involvement of the lateral edge of the nail plate, and the involvement of the matrix [24].

### Table 2: OSI index before and after treatment with Er:YAG or Nd:YAG laser.

<table>
<thead>
<tr>
<th>After complete Tx protocol: 3-month follow-up visit</th>
<th>Nd:YAG</th>
<th>Er:YAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) Before</td>
<td>51.5</td>
<td></td>
</tr>
<tr>
<td>OS1 index P1 Before</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>OS1 index P1 After</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>OS1 index P2 Before</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>OS1 index P2 After</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>OS1 index P3 Before</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>OS1 index P3 After</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>OS1 index P4 Before</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>OS1 index P4 After</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>OS1 index P5 Before</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>OS1 index P5 After</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Average OSI index Before</td>
<td>25.8</td>
<td>19.8</td>
</tr>
<tr>
<td>Average OSI index After</td>
<td>27.4</td>
<td>19</td>
</tr>
</tbody>
</table>

A 29% mycological cure rate (2 patients) was
observed in both sides 1 month after completion of the 1st cycle. Immediately after the completion of the 2nd treatment cycle, the mycological cure rate increased to 80% for both treatment sides. At the 1-month follow up, the mycological cure rate on the Er:YAG side persisted, while on the Nd:YAG side it decreased to 60%. At the 3-month follow up, the cure rate was still higher on the Er:YAG side (60%) compared to a 40% cure rate on the Nd:YAG side. At the 3-month follow up, reinfection of the fungi occurred in one patient on the Er:YAG treatment side and in two patients on the Nd:YAG side (Table 3).

Table 3: Mycological cure rate

<table>
<thead>
<tr>
<th>Follow up</th>
<th>Nd:YAG</th>
<th>Er:YAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month after 1st cycle</td>
<td>29% (2/7)</td>
<td>29% (2/7)</td>
</tr>
<tr>
<td>Immediately after complete Tx (2 cycles of treatment)</td>
<td>80% (4/5)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>1 month after complete Tx</td>
<td>60% (3/5)</td>
<td>80% (4/5)</td>
</tr>
<tr>
<td>3 months after complete Tx</td>
<td>40% (2/5)</td>
<td>60% (3/5)</td>
</tr>
</tbody>
</table>

At the 3-month follow up, a significant clearance of the nail plate was observed in 3 patients on the Er:YAG treatment side, which was in compliance with the negative culture observed on mycological tests (Figure 3, 4). Surprisingly, a clinical worsening was observed before the 2nd treatment with Er:YAG as well as with Nd:YAG laser, despite negative mycological results detected with the DermAX TA/MA test. This phenomenon may be explained by gas-bubbles generated during the heating or with disintegration of the fungi after the treatment.

For better clinical results, a longer follow up would be necessary since up to 14 months is needed for complete regrowth of the nail plate. A permanent damage of the nail plate can also occur due to a prolonged and aggressive fungal infection.

Both laser treatment procedures were well tolerated by the patients, who described different modes of pain on the two treatment sides. On the Nd:YAG treatment side, a sudden sharp pain was described, while on the Er:YAG treatment side a warm sensation was gradually increasing. 71% of the patients described the pain as more acceptable on the side treated with Er:YAG laser. Only two patients reported that the warm sensation on the Er:YAG-treated side persisted about 30 minutes after the treatment. On the Nd:YAG-treated side, pain subsiding several minutes after the treatment was reported by three patients.

Mild-to-moderate erythema was observed in one
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patient on the Nd:YAG treatment side, but no other side effects were reported on either treatment side.

On the Er:YAG treatment side, the number of pulses varied between patients, i.e. between subsequent spots in the same treatment to achieve the pain threshold which represented the endpoint of the treatment. A high variation of the pulse number was also observed due to differences in environmental temperatures. During winter, up to 50% more pulses were needed to achieve the pain threshold compared to the summer.

IV. CONCLUSION

Based on preliminary results it is suggested that Er:YAG laser therapy in non-ablative mode represents a safe and effective therapy for the treatment of onychomycosis, which was also confirmed clinically. Er:YAG treatment was better tolerated compared to Nd:YAG treatment. Er:YAG laser in non-ablative mode has a high potential for the effective treatment of onychomycosis since very encouraging rates of clinical and clinical cure were observed after two treatment cycles. Further studies will be needed to additionally evaluate thermal Er:YAG treatment for onychomycosis and to further optimize the protocol.

REFERENCES


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