Brief Overview about Laser Treatments for Onychomycosis

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Abstract

Onychomycosis is an infection of the nail unit caused by fungi (dermatophytes, non-dermatophyte molds, and yeasts), presenting with discoloration of the nail, onycholysis, and nail plate thickening. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected. The term "onychomycosis" is derived from the Greek words "onyx" meaning nail and "mykes" meaning fungus. Onychomycosis is the most common disorder affecting the nail unit and accounts for at least 50% of all nail diseases. The advancement of laser/photodynamic therapies and their application in onychomycosis has emerged as a new therapeutic paradigm as they successfully negate systemic adverse effects, drug interactions, and frequent application. Their ultimate success depends on their retention, payload, and final disposition at the targeted site of action. It appears that laser/photodynamic therapies could address the problems associated with treating onychomycosis, and offer a novel drug delivery platform for its successful treatment. Promising laser-based treatments for onychomycosis have been reported in recent years. Such therapies include Nd:YAG laser treatment and diode lasers with wavelengths of 870/930 nm

Keywords: Laser Treatments, Onychomycosis

Introduction

Onychomycosis is an infection of the nail unit caused by fungi (dermatophytes, non-dermatophyte molds, and yeasts), presenting with discoloration of the nail, onycholysis, and nail plate thickening. Any component of the nail unit, including the nail plate, nail matrix, and nail bed can be affected. The term "onychomycosis" is derived from the Greek words "onyx" meaning nail and "mykes" meaning fungus. Onychomycosis is the most common disorder affecting the nail unit and accounts for at least 50% of all nail diseases **(1).**

Laboratory confirmation of the clinical diagnosis of onychomycosis prior to initiating treatment is cost effective and is recommended. In recent years, newer techniques enabling accurate and sensitive diagnosis of onychomycosis and novel treatments of this condition have emerged. The purpose of this communication is to provide readers with an update on current approaches to diagnosis and treatment of onychomycosis **(2).**

Onychomycosis can be caused by dermatophytes (tinea unguium), non-dermatophyte molds and yeasts. Approximately 90% of toenail and 75% of fingernail onychomycosis are caused by dermatophytes notably Trichophyton mentagrophytes and Trichophyton rubrum **(3)**.

The remaining dermatophyte infections are caused by Epidermophyton floccosum, Microsporum species, Trichophyton verrucosum, Trichophyton tonsurans, Trichophyton

violaceum, Trichophyton soundanense, Trichophyton krajdenii, Trichophyton equinum, and Arthroderma species **(4)**.

Non-dermatophyte molds that can cause onychomycosis include *Aspergillus* species, *Scopulariopsis* species, *Fusarium* species, *Acremonium* species, Syncephalastrum species, Scytalidium species, Paecilomyces species, Neoscytalidium species, Chaetomium species, Onychocola species, and Alternaria species. Non-dermatophyte molds account for approximately 10% of onychomycosis cases globally. Onychomycosis caused by yeasts is uncommon **(5)**.

Candida albicans accounts for approximately 70% of onychomycosis caused by yeasts. Other Candida species include Candida tropicalis and Candida parapsilosis. Patients with chronic mucocutaneous candidiasis and immunodeficiency are more likely infected with the yeast organism, especially in the fingernails **(6)**.

Epidemiology

The overall worldwide prevalence of onychomycosis in the general population is approximately 5.5%, based on recently published epidemiological studies **(6)**.

A 2013 systemic review of 11 population-based and 21 hospital-based studies showed that the mean prevalence of onychomycosis in North America and Europe was 4.3% (95% confidence interval: 1.9 to 6.8) in the population-based studies and 8.9% (95% confidence interval: 4.3 to 13.6) in the hospital-based studies. There is evidence that the prevalence is rising, possibly because of longer life expectancy, use of occlusive modern footwear, increased prevalence of obesity, and increased urbanization **(7)**.

The condition is much more common in adults than in children and the prevalence increases with age. The prevalence in children in North America is approximately 0.4%, whereas the prevalence may be as high as 35% in the elderly (> 65 years of age) **(6)**.

Toenail onychomycosis is more common in males whereas *Candida* fingernail onychomycosis is more common in females. Other predisposing factors include fungal infection elsewhere on the body (in particular, tinea pedis), chronic paronychia, previous onychomycosis, wearing of occlusive and tight shoes, hyperhidrosis, participation in sports or fitness activities, nail trauma, poor nail grooming, use of commercial swimming pools, communal bathing, living with family members with fungal infection, poor health, genetic factors, immunodeficiency (in particular, acquired immune deficiency syndrome and transplant patients), diabetes mellitus, obesity, Down syndrome, psoriasis, smoking, peripheral vascular disease, venous insufficiency, hallux valgus, and asymmetric gait nail unit syndrome **(8)**.

A study in Egypt found that Fingernail onychomycosis was recognized in 68% of cases and toenail onychomycosis in 32%. The rate of affected fingernails was higher in females in which yeasts were the most isolated agent, and yeasts were the most common etiological agent causing onychomycosis **(9)**.

Pathogenesis

Onychomycosis is acquired through direct contact of the nail with dermatophytes, non-dermatophyte molds, or yeasts. Because the nail unit does not have effective cell-mediated immunity, it is susceptible to fungal infection. Fungal production of enzymes that have proteolytic, keratinolytic, and lipolytic activities help to degrade the keratin in the nail plate and facilitate fungal invasion of the nail **(4)**.

Factors that compromise barriers to fungal infection may increase the risk for fungal infection. The site and pattern of fungal invasion account for the production of different clinical subtypes of onychomycosis. The formation of fungal biofilms allows the fungi to evade current antifungal therapies and contribute to antifungal resistance **(10)**.

Clinical manifestations

Typically, onychomycosis presents as a white or yellow-brown discoloration of the nail. Violaceous, green, and black discoloration of the nail plate have also been observed. Other clinical manifestations include subungual hyperkeratosis, detachment of the nail from the nail bed (onycholysis) and thickening of the nail plate (onychauxis) **(10)**.

Laser Treatments for Onychomycosis

The advancement of laser/photodynamic therapies and their application in onychomycosis has emerged as a new therapeutic paradigm as they successfully negate systemic adverse effects, drug interactions, and frequent application. Their ultimate success depends on their retention, payload, and final disposition at the targeted site of action. It appears that laser/photodynamic therapies could address the problems associated with treating onychomycosis, and offer a novel drug delivery platform for its successful treatment **(11)**.

Promising laser-based treatments for onychomycosis have been reported in recent years. Such therapies include Nd:YAG laser treatment and diode lasers with wavelengths of 870/930 nm **(12)**.

Advantages of laser treatment

Lasers offer some advantages over drug-based options, such as shorter and fewer treatments, and no systemic side effects **(10)**.

Disadvantages

Treatment costs are generally high, sessions are generally not covered under most insurance plans, and monthly visits are required for as long as 9 months **(13)**.

The FDA-approved lasers are all 1064 nm Nd:YAG lasers, both short-pulsed and Q-switched lasers; other lasers in development include carbon dioxide lasers, and the diode 870, 930 nm laser. Some lasers have also been approved for onychomycosis treatment by health regulatory bodies in Canada, Europe, Australia, Korea, South America and Japan **(10)**.

Mechanism of action

This non-pharmaceutical treatment employs the principle of selected light thermolysis to bring about fungicidal activity in nail fungi by bringing them to an inhospitable temperature. Fungal mycelia in injured tissue are hypothesized to preferentially absorb laser energy, leading to a rapid increase in temperature and fungal cell death; however, the precise mechanism of action is still poorly characterized **(14)**.

The laser treatment of onychomycosis has been approved by the Food and Drug Administration, but only for cosmetic purposes (the temporary growth of clear nail), not for mycological or total cure **(14)**.

Neodymium-doped yttrium aluminum garnet lasers (Nd:YAG)

Nd:YAG lasers have a pulse duration in milliseconds and penetrate as deeply as the lower nail plate due to their longer wavelength, thus efciently inhibiting fungal growth. Due to the production of non-specifc heating, a cooling system is generally employed with such systems **(11)**.

Several output modes are available for the Nd:YAG laser, including long- and short-pulsed and Q-switched modes, as well as 1,064, 940, 1,320, and 1,440 nm wavelengths **(15)**.

Short-pulse Nd:YAG lasers have a pulse duration in microseconds; the shorter pulse allows rapid cooling and therefore a cooling system is not required. Q-switched Nd:YAG lasers have a pulse duration of nanoseconds and are able to emit the highest peak power per pulse of all the available Nd:YAG lasers **(11)**.

A potassium titanyl phosphate (KTP) filter allows for frequency doubling and thus 532 nm light. Due to its longer wavelength, the 1,064 nm Nd:YAG is thought to deeply penetrate tissue and target fungal overgrowth in the nail bed. The 532 nm Nd:YAG may also be better at targeting the fungal pigment xanthomegnin, which has a peak absorption between 406 and 555 nm **(15)**.

- **Long pulse Nd:YAG lasers**

It is suspected that due to its longer wavelength, long pulse Nd:YAG laser is able to more deeply penetrate tissue and efficiently target fungal overgrowth in the nail bed. The pulse duration for these lasers is in the millisecond range. These lasers can cause a high degree of non-specific heating and may need to be operated in the presence of a dedicated cooling system **(16)**.

It Was performed a clinical study in which 72 patients with 194 onychomycotic nails were treated with long pulse Nd:YAG laser using fluences of 35–40 J/cm^2 at pulse duration of 35 msec to develop a nail-plate temperature of 45 ± 5 °C. Laser treatment consisted of four sessions with 1-week interval, during which all

infected nails were irradiated three times with laser light so that the nail plate was fully covered each time. This clinical study demonstrated that fungal nail infections can be effectively and safely treated with Nd:YAG 1064 nm laser because there were no noticeable side effects of treatment and all patients were satisfied with the treatment.

Another study was conducted in Berlin which was a clinical pilot study in which 42 nails from 14 patients who exhibited onychomycosis caused by *Trichophyton* sp., *Aspergilus niger, Candida* sp. and other moulds were treated with a novel 1064 nm Nd:YAG laser therapy in a series of four sessions at 3-month intervals. In 13 (93%) patients, mycological clearance was observed at 3-month follow-up, at 6 and 12 months follow-up all patients were free of onychomycosis **(17)**.

A study conducted in China by **Zhang et al., (18)** to see the effect of long-pulse Nd:YAG 1064-nm laser on onychomycosis found that it is an effective method of treatment. This study concluded that long-pulse Nd:YAG 1064-nm laser is a simple and effective method without significant complications or side effects and is expected to become an alternative or replacement therapy for onychomycosis.

- **Short-pulse Nd:YAG lasers**

Nd:YAG short-pulse laser systems have a pulse duration in the microsecond range. 1064 nm models are the largest class of lasers approved for the temporary increase of clear nail in onychomycosis. Models for this class of laser includes PinPointe Foot Laser, GenesisPlus and VARIA **(16)**.

A pilot study was conducted by **Hochman, (19)** using a novel 0.65-ms pulsed Nd:YAG 1064-nm laser. The purpose of this pilot study was to evaluate the treatment of onychomycosis using a 0.65-ms pulsed 1064-nm laser with a hand piece that does not contact the treatment site and does not require tissue cooling. In this study eight patients were treated over two to three sessions spaced at least 3 weeks apart. Of the eight subjects evaluated, seven had negative posttreatment cultures after the second or third session. Treatments were well tolerated by all subjects with acceptable levels of comfort and without any significant complications or side effects.

A case was reported in which *Candida tropicalis* onychomycosis resistant to standard topical treatments was successfully treated with four sessions of Nd:YAG laser in Short-Pulse mode. The efficacy of treatment was verified at 3 months via negative control sample and was maintained for at least 6 months **(20)**.

- **Q-switched Nd:YAG lasers**

Q-switched lasers have pulse duration in the nanosecond range and they have the highest maximum pulse energy of the commercial solid-state lasers. They emit the highest peak power per pulse of all the Nd:YAG lasers. The Q-Clear laser is the only Q-switched system approved for the treatment of onychomycosis **(16)**.

It Was reported that significant inhibition of fungal growth after treatment with Q-switched Nd:YAG laser (wavelength: 1064 nm, fluence: 4 and 8 J cm^{-2}, as well as wavelength: 532 nm, fluence: 8 J cm^{-2}, spot size: 2 mm). Photometric analysis showed that after 3 and 6 days there was significantly slower growth of treated colonies compared with those that were untreated.

- **Side Effects**

Due to the relatively low absorption of Nd:YAG laser radiation in melanin, treatment errors with too high energy density unfortunately do not show as grey discoloration or blistering in the epidermis, as is known from most other dermatologically effective laser systems. Rather, the side effects are directly related to the dermis and are related to the absorption of Nd:YAG laser radiation in water **(21)**.

In case of unintentional overdosage, a diffuse overheating of the connective tissue occurs with the consequence of a loss of substance in the form of atrophic scarring in the healing process. Bubble formation in the junction zone is more secondary (caused by heat rising from the upper corium) and therefore leads to hypopigmentation and whitish to atrophic scars **(21)**.

Excimer laser

An excimer laser is a form of ultraviolet laser, commonly used in the fabrication of microelectronic devices including semiconductor integrated circuits, besides having applications in eye surgery, and micromachining. In fact, excimer may be used to specify a family of lasers with similar output characteristics like **(22)**:

(i) All emitting powerful pulses lasting nanoseconds or tens of nanoseconds, with wavelengths in or near the ultraviolet.

(ii) The lasing medium is a diatomic molecule, or dimer, having component atoms bound in the excited state, and not in the ground state. The term excimer means excited dimer, having molecules in the form of rare gas halides like ArF, KrF, XeF and XeCl, which interestingly, though not existing in nature, can be easily produced by passing an electrical discharge through a suitable gas mixture of rare gas ~1-9%, a halogen donor concentration ~ 0.1 to 0.2%, and He or Ne gas, the last being used for assisting the energy transfer.

Mechanism of action

The 308-nm wavelength, which is very close to 311 nm, used in nb-UVB phototherapy, is considered to have a similar mechanism of action with the latter. The radiations of the UVB spectrum show immunosuppressive effects by inducing T-lymphocyte apoptosis and immunomodulatory effects, too **(23)**.

A single 308-nm UVB dose reduced the number of pathogenic memory/effector T cells infiltrating psoriatic lesional epidermis and dermis, and, consistent with apoptosis induction, caspase activation increased in lesional T cells after treatment. Another interesting finding is the preferential induction of endothelin-1 in a human epidermal equivalent model by narrowband ultraviolet B light sources. This molecule is associated with UVB-induced migration of melanocytes and stimulates DNA synthesis in melanocytes **(23)**.

- **Advantages of excimer laser**

The advantages of monochromatic excimer laser over phototherapies of other kinds have been depicted as lower UV dose exposure, shorter course of therapy and for the most part, the possibility of being directed at distinct sites of skin rather than compromising the adjacent normal skin. Excimer lasers have minimal absorption depth in tissue, which means they allow removing microscopic layers of tissues, causing minimum damage to the surrounding area **(24)**.

- **Disadvantages of excimer laser**

Some patients had a feeling of some pain during irradiation, but it is tolerable and disappears within a day **(25)**.

Complications of laser treatment

The reported incidence of complications following laser use for the treatment of onychomycosis is low, substantiating its role as a treatment modality for this condition. Side effects, however, may include **(15)**:

- Pain, heat or tingling.
- Temporary darkening under the nail.

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