Quest Journals
Journal of Medical and Dental Science Research
Volume 8~ Issue 4 (2021) pp: 01-05
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

Clinical effects of ultra-pulsed fractional carbon dioxide laser in the treatment of different types of onychomycosis

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ABSTRACT:
Objective: *To evaluate the clinical efficacy and safety of ultra-pulsed fractional carbon dioxide laser in the treatment of onychomycosis.*
Methods: *The onychomycosis patients from January 2017 to December 2020 were treated with ultra-pulsed fractional carbon dioxide laser once a week for 4 weeks, and then once every 2 weeks for 4 times, for a total course of 3 months. The clinical efficacy, mycological examination results and adverse reactions were recorded, and the clinical effective rate and fungal clearance rate were calculated.*
Results: *In total, 156 onychomycotic nails were treated, including 78 cases of distal and lateral subungual onychomycosis (DLSO), 42 superficial white onychomycosis (SWO), 28 proximal subungual onychomycosis (PSO) and 8 total dystrophic onychomycosis (TDO). The clinical effective rate was 87.18% and the fungal clearance rate was 71.80% six months after the treatment. The effective rates were 92.30% and 85.71% in the scoring clinical index of onychomycosis (SCIO) <12 group and ≥ 12 group, respectively. No serious adverse reactions occurred.*
Conclusions: *Ultra-pulsed fractional carbon dioxide laser is a safe and effective treatment for onychomycosis and is worthy of clinical application.*
KEYWORDS: *ultra-pulsed fractional carbon dioxide laser; onychomycosis; scoring clinical index of onychomycosis (SCIO); therapy.*

Received 20 Mar, 2021; Revised: 02 Apr, 2021; Accepted 04 Apr, 2021

I. INTRODUCTION

Onychomycosis, a common chronic infectious disease, is difficult to cure and easy to relapse. It is generally divided into four types, distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO) and total dystrophic onychomycosis (TDO)[1]. Traditional therapeutic options for the treatment include topical and systemic antifungal agents. These treatments have certain efficacy, but there are still limitations. Certain patients cannot tolerate the systemic drugs and the topical antifungals are sometimes ineffective. With the continuous progress of laser technology, the laser treatment for onychomycosis has also been explored, in which the long-pulsed neodymium: yttrium-aluminium-garnet (Nd:YAG) 1064nm laser is the most studied, while there is few research on the ultra-pulsed fractional carbon dioxide (CO_2) laser for the treatment of onychomycosis. The exploration of more safe and effective treatments for onychomycosis is still the hot spot. In our study, we used the ultra-pulsed fractional CO_2 laser to treat patients with onychomycosis and explored the efficacy and safety of the laser therapy for onychomycosis.

II. PATIENTS AND METHODS

2.1 Patients

The study enrolled a total of 98 patients with onychomycosis treated in the Dermatology Department of the Fourth Hospital of Hebei Medical University from January 2017 to December 2020, including 40 males and

58 females, aged from 25 to 60 years. The total number of affected nails was 184. The duration of onychomycosis ranged from 3 months to 10 years, with an average of (2.82 ± 1.02) years. Inclusion criteria: (1) Age between 18 and 75 years old, no gender limitation; (2) The diagnosis of onychomycosis by fungal microscopic examination (KOH) and/or fungal culture; (3) Clinical symptoms and manifestations of onychomycosis; (4) No topical antifungal agents were used within 1 month, and no oral antifungal agents were used within 3 months. Exclusion criteria: (1) Patients using systemic or topical antifungal agents during treatment; (2) Patients with severe cardiovascular, respiratory, hematological diseases or other serious organic diseases; (3) Patients who cannot tolerate laser treatment due to their own reasons; (4) Patients who discontinued the treatment due to their own reasons; (5) Pregnant and lactating women; (6) Severe adverse reactions or discontinuance of treatment due to other reasons. The contents of the test in detail were explained to all patients before enrollment and a written informed consen.t was obtained from all patients.

The 98 patients included were divided into group A and group B according to scoring clinical index of onychomycosis (SCIO) from Sergeev et al[2] with SCIO<12 in group A and ≥ 12 in group B.

2.2 Treatment protocol

Disinfect the infected nails with benzalkonium chloride solution and remove the thickened or discolored nails as more as possible by dermabrasion prior to treatment. The infected nails were irradiated with transverse and longitudinal laser beam using ultra-pulsed fractional CO_2 laser (Lumenis Inc. USA), and six passes were given at the same nail for one treatment. The patients was treated once a week for 4 weeks, and then once every 2 weeks for 8 weeks, altogether 8 sessions of laser therapy with a total course of 3 months. The parameters were adjusted according to the tolerance of patients during treatments, and the adverse reactions, solutions and remissions were recorded during and after each treatment. The efficacy was assessed after treatment, and at 3 and 6 months after treatment.

2.3 Efficacy evaluation

Treatment efficacy was analyzed in four grades as follows: complete response (normal-appearing nail > 90%, smooth and shiny nail plate); significant response (75-90% normal-appearing nail); moderate response (40-75% normal-appearing nail); no response (normal-appearing nail < 40%). Total effective rate = complete response rate + significant response rate. Mycological examination: direct fungal microscopic examination (KOH) and fungal culture. Mycological clearance criteria: fungal microscopic examination and fungal culture were both negative. The mycological clearance rate was calculated.

2.4 Statistical analysis

Data were analyzed by χ^2 test with SPSS 13.0 software (IBM Corp.), and *P*-value of less than .05 was considered to be statistically significant.

III. RESULTS

3.1 Clinical results

Among the 98 patients enrolled, 86 patients completed the treatment and follow-up, and 12 patients discontinued the treatment due to various reasons. A total of 156 infected nails were treated, including 78 DLSO (50.00%), 8 TDO (5.13%), 42 SWO (26.92%), and 28 PSO (17.95%).

3.2 Clinical efficacy

3.2.1 Total clinical efficacy evaluation

The total effective rate was 53.85% after treatment, 79.49% at 3 months of follow-up, and 87.18% at 6 months of follow-up, respectively. There was a significant difference between the effective rate after treatment and the rate at 3 months of follow-up (χ^2= 23.08, $P < 0.05$), and there was also a significant difference between the rate after treatment and the rate at 6 months of follow-up (χ^2= 42.52, $P < 0.05$). There was no significant difference between the effective rate at 3 months of follow-up and at 6 months of follow-up (χ^2= 3.51, $P > 0.05$). See Table 1 for details.

Table 1. Comparison of clinical efficacy between after treatment, at 3 months of follow-up and at 6 months of follow-up [n (%)]

Group	Nails	Complete response	Significant response	Moderate response	No response	Total effective rate
After treatment	156	40(25.64)	44(28.21)	48(30.77)	24(15.38)	84(53.85)*
At 3 mo of follow-up	156	72(46.15)	52(33.33)	20(12.82)	12(7.69)	124(79.49)
At 6 mo of follow-up	156	83(53.21)	53(33.97)	14(8.97)	6(3.85)	136(87.18)

*Compared with the rate at 3 months of follow-up and 6 months of follow-up, $P<0.05$.

3.2.2 Comparative evaluation between different types of onychomycosis

After the treatment, 3 months after the treatment and 6 months after the treatment, the total effective rates of SWO were 59.52%, 88.10% and 92.86%, respectively, and the total effective rates of DLSO were 60.26%, 82.05% and 92.31%, respectively, and the total effective rates of PSO were 39.29%, 78.57% and 85.71%, respectively. The total effective rates of TDO were 12.50%. There was no significant difference between DLSO, SWO and PSO three groups regarding effective rates, respectively ($P > 0.05$), while there are significant differences between these three groups and TDO group respectively ($P < 0.05$). See Table 2 for details.

Table 2. Comparison of clinical efficacy between different types of onychomycosis [n (%)]

Group	Nails	After treatment	At 3 mo of follow-up	At 6 mo of follow-up
DLSO	78	47(60.26)*	64(82.05)*	72(92.31)*
SWO	42	25(59.52)	37(88.10)	39(92.86)
PSO	28	11(39.29)	22(78.57)	24(85.71)
TDO	8	1(12.50)**	1(12.50)**	1(12.50)**

*Compared with SWO, PSO groups, $P > 0.05$, respectively
**Compared with DLSO, SWO, PSO groups, $P < 0.05$, respectively

3.2.3 Comparative evaluation between different SCIO groups

At the end of the treatment, 3 months after treatment and 6 months after treatment, the total effective rate of group A was higher than that of group B, but there was no statistical significance ($P>0.05$). See Table 3 for details.

Table 3. Comparison of clinical efficacy between different SCIO groups [n (%)]

Group	Nails	After treatment	At 3 mo of follow-up	At 6 mo of follow-up
A	65	40(61.54)*	54(83.08)*	60(92.30)*
B	91	44(48.35)	70（76.92）	78(85.71)

*Compared with group B, $P>0.05$

3.3 Mycological clearance rate

At the end of the treatment, 3 months after treatment and 6 months after treatment, there was a significant difference between the mycological clearance rate after treatment and the rate at 3 months of follow-up (χ^2= 4.71, P = 0.03), and there was also a significant difference between the rate after treatment and the rate at 6 months of follow-up (χ^2= 14.7, $P < 0.01$). There was no significant difference between the rate at 3 months of follow-up and at 6 months of follow-up (χ^2= 2.86, $P > 0.05$). See Table 4 for details.

Table 4. Comparison of mycological clearance rates between after treatment, at 3 months of follow-up and at 6 months of follow-up [n (%)]

	Nails	Clearance	No clearance
After treatment	156	79(50.64)*	77(49.36)
At 3 mo of follow-up	156	98(62.82)**	58(37.18)
At 6 mo of follow-up	156	112(71.79)	44(28.21)

*Compared with the rate at 3 months of follow-up and 6 months of follow-up, $P<0.05$, respectively.
**Compared with the rate at 6 months of follow-up, $P>0.05$.

3.4 Adverse reactions

All patients felt burning and pain during the treatment, but all relieved spontaneously after treatment or after ice compress. No bleeding under the nails, infection or other adverse reactions.

IV. DISCUSSION

Antifungal drugs have been the mainstay of therapy for many years, however, it is limited by low efficacy because of subtherapeutic concentrations reaching the nail bed. Although the treatment efficacy for onychomycosis has improved in recent years with various combination therapies and the introduction of new oral and topical agents, relapse and reinfection rates remain high (16%-18% of cured patients)[3]. Particularly for those who cannot tolerate medication, such as patients with hepatic or renal dysfunction, of advanced age, and in use of multiple medication that limits the use of antifungal agents, non-pharmacological treatment of onychomycosis could be a better option. In recent years, laser therapy has been applied in the treatment of onychomycosis for the advantages of simple operation and mild adverse reactions. The laser systems that have been studied include CO_2 laser, Nd: YAG 1064nm laser, semiconductor laser, Erbium laser and laser-related photodynamic therapy.

Laser therapy can be used alone in the treatment of onychomycosis or can be combined with oral or topical antifungal agents, as a supplementary role. Wang et al[4] reported the efficacy of long pulse Nd: YAG 1064nm laser in the treatment of DLSO without affecting nail matrix. The study enrolled 30 patients with a total of 58 infected nails, including 22 affecting nail matrix, all of which were DLSO type. All of the infected nails were given laser treatment for 12 weeks. The results showed that after treatment and at six months of follow-up, the clinical effective rate and mycological clearance rate of the infected nails without affecting nail matrix were better than those involved nail matrix, respectively. The difference was statistically significant ($P<0.001$). A retrospective study conducted by Rovers et al[5] reported the limitations of 1064 nm Nd: YAG laser in the treatment of onychomycosis. The cure rate of onychomycosis treated with the laser was only 12.4%, which was far from being comparable with the rate of oral terbinafine (76%) or itraconazole (63%) as the first-line treatment. However, it is still applicable to certain patients who have failed to respond to conventional treatments or are contraindicated to oral antifungal agents. CO_2 laser is one of the earliest laser therapies used in the treatment of onychomycosis. The traditional CO_2 laser can directly vaporize and decompose the tissue by burning and drilling, so as to kill fungi. However, this method has the disadvantages of cumbersome operation and great harm to patients, so it is difficult to be popularized. The new ultra-pulsed fractional CO_2 laser has the advantages of more uniform drilling, simple operation and mild adverse reactions, which is more likely to be widely used in clinical practice.

Our study showed that the ultra-pulsed fractional CO_2 laser is safe and effective in the treatment of onychomycosis. The results showed that the effective rate was 53.85% after treatment, 79.49% at 3 months of follow-up, and 87.18% at 6 months of follow-up, respectively. And the effective rate after the treatment was significantly different from the rate at 3 months of follow-up and 6 months of follow-up respectively. The effective rates were analyzed respectively according to the different types of onychomycosis. We found that the SWO had the highest effective rate, followed by DLSO, PSO, while TDO had the lowest effective rate of 12.50%, indicating that the ultra-pulsed fractional CO_2 laser might have a better treatment effect on SWO and DLSO. We speculate that the poor efficacy of TDO is related to the insufficient laser penetrating the nail, which leads to the failure to completely kill the fungi in the nail plates. SWO and DLSO lesions are relatively shallow in depth and small in size, so the fractional CO_2 laser has a better effect. In addition, the mycological clearance rates at the end of the treatment, 3 months after treatment and 6 months after treatment were 50.6%, 62.8%, 71.8%, respectively. The mycological clearance rate increased gradually over time, and there was significant differences between the mycological clearance rate after treatment and the rate at 3 months of follow-up and 6 months of follow-up respectively. The results indicated that the ultra-pulsed fractional CO_2 laser can kill fungi, possibly due to the local temperature rise caused by laser treatment. A randomized controlled trial by Tatawy et al[6] also showed that the efficacy of fractional CO_2 laser in treating onychomycosis was close to that of laser

combined with topical antifungal, and was superior to topical antifungal alone. In this trial, 30 patients with onychomycosis were randomly divided into laser group, topical treatment group and combination group. In laser group, the affected nails were treated with fractional CO_2 laser 6 times a month for 6 months. In topical treatment group, the affected nails were treated with topical tioconazole 28% solution twice per day for 6 months. In combination group, the affected nails were treated with both topical tioconazole 28% solution and fractional CO_2 laser at the same frequency and duration as the previous two groups. Three months after the treatment, the clinical improvement, patient satisfaction and mycological clearance rate of the combination group were all higher than those of the laser group, but the differences were not statistically significant (*P* values were 1, 0.79, 0.628, all less than 0.05). The clinical improvement (*P*=0.036, *P*=0.024) and patient satisfaction (*P*=0.046, *P*=0.003) in the laser group and the combination group were significantly better than those in the topical treatment group. Quan et al[7] treated 35 patients with onychomycosis with a combination of fractional laser and topical antifungal agents in a study. The results showed that after the fourth treatment, the effective rate was 54.29% and the mycological clearance rate was 74.29%. Three months after the treatment, the effective rate was 82.89%, and the mycological clearance rate was 88.57%. The differences in results may be related to the treatment period, frequency, laser parameters and the combination of drugs.

In our study, the treatment of onychomycosis with ultra-pulsed fractional CO_2 laser proved clinical efficacy, which may be related to the following mechanisms. After fractional laser irradiation, the temperature of infected nails can reach 80℃ in an instant, while the highest temperature that eukaryotic fungi can withstand is only 42.5℃. When the heat generated by the laser penetrates the whole nail plate, the fungal tissue at the infected nail will undergo thermal decomposition effect and protein denaturation, which could destroy the cell wall, thus killing the fungi at the lesion[8]. Carney et al. reported that grinding the infected nail before treatment to a thickness of less than 2mm facilitates laser penetration of the nail[9]. If more than 50% of the nail are affected, nail malnutrition or nail matrix invasion may adversely affect the prognosis of laser therapy. Most studies showed that laser treatments for onychomycosis need to be repeated at least four times. It is also believed that altering the frequency and total course of laser treatment can improve the cure rate and clinical efficacy of onychomycosis[10].

It is safe and effective to treat onychomycosis with ultra pulse CO2 lattice laser. There is no destruction and injury of nail bed and no subungual hemorrhage. However, whether it is effective for onychomycosis caused by different strains of infection needs further research and exploration, in order to develop the best treatment for patients, which has been widely promoted in clinical.

V. CONCLUSION

Ultra-pulsed fractional CO_2 laser is safe and effective in the treatment of onychomycosis, and there is no injury or damage to nail bed and no subungual hemorrhage. However, whether it is effective for onychomycosis caused by infection of different strains needs further research and exploration, in order to develop the best treatment protocol for patients, and be widely promoted in clinical practice.

Funding

This work was supported by the S&T Program of Hebei (No.17277755D).

Conflict of interest

The authors declare that they have no conflict of interest.

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