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Progress in Laser Treatment of Primary Cutaneous Amyloidosis

Shuang Wang, Jin Gong*

Department of Dermatology, Jingzhou First People's Hospital Affiliated with Yangtze University, Jingzhou, China
Email: *790917@qq.com

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Abstract

Primary cutaneous amyloidosis is a chronic disease characterized by amyloid protein deposition in normal skin. It not only affects skin appearance but also causes persistent itching, significantly impacting patients' quality of life. Treatment options for this condition are diverse, encompassing pharmaceutical, physical, and surgical approaches. Currently, no standard treatment protocol exists, with choices often based on individual patient characteristics and physician experience. Laser technology, valued for its precision, minimally invasive nature, and safety profile, has gained increasing application in treating this condition, yielding notable efficacy and attracting widespread attention. This paper aims to provide a comprehensive review of the current status and future prospects of laser applications in the treatment of primary cutaneous amyloidosis.

Keywords

Primary Cutaneous Amyloidosis, Laser Treatment

1. Introduction

Primary cutaneous amyloidosis (PCA) refers to a type of disease in which amyloid protein is deposited in the normal skin and manifests only as skin damage without other organ involvement [1]. The etiology of PCA is still unclear, but it is believed to be related to genetics, long-term friction, viruses (such as Epstein-Barr virus), and environmental factors [2]. The most common subtypes of primary cutaneous amyloidosis are licyoid cutaneous amyloidosis (LA) and macular amyloidosis (MA). Both types of amyloid fibrils are denatured keratins, and their pathological features are similar, with amyloid deposits confined to the dermal papilla. LA usually occurs in the anterior tibia of both legs and is characterized by multiple hem-

*Corresponding author.

ispherical light red or brown papules. MA usually occurs in the interscapular region of middle-aged and older women, and can also involve the trunk and limbs. Ma is typically manifested as reticular or corrugated punctate brown or gray pigmented spots. Other rare types include nodular amyloidosis (NA), which is characterized by smooth reddish or brownish solid nodules or plaques, with amyloid deposits in the entire dermis and subcutaneous adipose tissue.

At present, there is no complete and effective treatment for this disease. Common treatment methods include topical drugs (glucocorticoids, retinoids, calcineurin inhibitors, etc.), oral administration (antihistamines, retinoids, immunosuppressants, etc.), physical therapy (laser, fire needling, phototherapy, etc.), and even surgery. Recently, oral Janus kinase inhibitors and subcutaneous injection of dupilumab have also been reported for the treatment of PCA [3]. With the wide application of laser technology in dermatology, laser therapy and even laser combined with topical drug therapy are increasingly used in PCA patients. This article reviews the current status and future prospects of laser therapy in the treatment of PCA.

2. Types and Efficacy of Laser Therapy for PCA

Laser technology has the characteristics of non-invasive or minimally invasive, quick recovery, safe and effective, and has become a common treatment method in dermatology. Using its selective photothermal effect, it can accurately target amyloid deposition in the lesion area, destroy its structure and promote metabolic clearance, while minimizing damage to the surrounding normal skin as much as possible. The longer the wavelength of the laser, the deeper the penetration. The 532 nm wavelength laser can penetrate the papillary layer of the dermis, and the 1064 nm wavelength laser can reach the deep dermis. At present, the lasers reported to be used in PCA patients mainly include carbon dioxide (CO_2) laser, neodymium doped yttrium aluminum garnet (Nd:YAG) laser, Erbium-doped yttrium aluminum garnet (Er-YAG) laser, pulsed dye laser (PDL), yttrium/erbium fiber laser, etc. [4].

2.1. CO_2 Laser

CO_2 laser is the most widely used laser in clinical practice. It is a gas molecular laser, which is divided into target color base by water in tissue. It can be efficiently absorbed by the water in the skin tissue, resulting in local thermal effect, leading to vaporization and carbonization of the diseased tissue. This process not only directly removes amyloid deposited in the dermis, but also improves the appearance and function of skin lesions by stimulating the regeneration of collagen and the remodeling of skin structure.

Norisugi *et al.* [5] used CO_2 laser to treat 2 male patients with LA twice a month. The treatment parameters were power 10 - 15 W, pulse width 0.12 s, and 5 mm spot. The papules on the lower leg of the two patients gradually became flat at the sixth and tenth months, respectively, and the VAS pruritus intensity scores decreased by 70 points. No adverse reactions were observed. Korbi *et al.* [6] reported

that a male patient with LA who had been unresponsive to long-term corticosteroid and emollient therapy achieved cure after four sessions of fractional carbon dioxide laser (energy density: 5 to 8 J/cm^2, 8 mm spot, stacked twice) without adverse effects. Howard Chu *et al.* [7] reported that three patients with LA and concomitant atopic dermatitis achieved satisfactory therapeutic results after receiving fractional CO_2 laser treatment (energy density: 5 to 8 J/cm^2, 8 mm spot, 2 times per month). The side effect was mild pain. During the follow-up of more than 1 year, one patient had recurrence.

Fawzi *et al.* [8] compared 24 PCA patients (16 MA and 8 LA) with 24 healthy controls. Each PCA patient underwent four fractional CO_2 laser treatments (power 15 W, pitch 500 μm, dwell time 500 μs, penetration depth 90 μm, and coverage of the treatment area 13.3%) at 4-week intervals. After treatment, the pigmentation, lesion thickness and pruritus of the patients were all improved, and the IL-31 and IL-31R levels in the lesion tissue were also significantly decreased compared with those before treatment. IL-31 can participate in the formation of pruritus by up-regulating neuronal excitability, and can also recruit a variety of cytokines to promote inflammation by activating JAK/STAT, PI3K/AKT and other signaling pathways [9]. The reduction of IL-31 and its receptor seems to be one of the mechanisms of fractional CO_2 laser in improving pruritus in PCA patients.

Esmat *et al.* [10] explored the efficacy of fractional CO_2 laser in different modalities for the treatment of PCA. The lesions of 25 PCA patients (16 cases of MA and 9 cases of LA) were divided into two zones. The superficial ablation mode (power 15 W, pitch 500 μm, dwell time 500 μs, overlay 1, penetration depth 90 μm, coverage 13.3%) and deep rejuvenation mode (power 25 W, pitch 900 μm, overlay 1) were used respectively. Interval time 800 μs, superposition 3, penetration depth 180 μm, coverage 6.2%). After four treatments with an interval of 4 weeks, both modalities significantly improved the pigmentation and thickness of skin lesions, reduced pruritus, and significantly reduced amyloid deposition. However, in the superficial ablation mode, the pigmentation was improved more obviously, and the deep rejuvenation mode made the pain of the patients more prominent, and there were 2 patients with pixellation. The superficial mode with better tolerance is more worthy of recommendation.

Lesiak *et al.* [11] successfully treated a 60-year-old NA patient with CO_2 laser (energy density 10 J/cm^2, 3 - 6 mm spot, power 15 - 18 W). Atrophic scars were found in the laser treated area after 8 weeks, and no recurrence was found during the follow-up of 12 months.

2.2. Neodymium-Doped Yttrium Aluminum Garnet (Nd:YAG) Laser

Nd: YAG laser can release 1064 nm wavelength of near-infrared light, the target color is melanosomes, and can obtain high-intensity short pulses through Q-switched technology. At present, Q-switched laser has been developed to the pi-

cosecond stage. Nd: YAG laser can also be doubled to 532 nm for the treatment of superficial lesions. In recent years, the application of Nd:YAG laser in dermatology has been gradually expanded.

Lueangarun *et al.* [12] used 1064 nm Nd: YAG picosecond laser (energy density 1.8 - 2.2 J/cm^2, 6 mm spot, frequency 6 Hz) to treat two patients with LA. After 5 courses of treatment with an interval of 4 weeks, the appearance of skin lesions and pruritus of the two patients was effectively improved. Ostovari *et al.* [13] used Q-switched Nd: YAG laser in 20 women with MA to compare the effect of 532 nm and 1064 nm wavelengths on reducing MA pigmentation. The treatment parameters were 3 mm spot, and the energy density was 4.5 J/cm^2 and 14 J/cm^2, respectively. At 8 weeks after the end of the treatment, the MA color was effectively improved, and the 532 nm laser was more effective. However, patients in the 532 nm laser treatment area experienced more pain during the treatment. No adverse reactions such as scar formation, hypopigmentation, or postinflammatory hyperpigmentation were observed during the 6-week visit after treatment. Nilforoushzadeh *et al.* [14]enrolled 39 women with MA and compared Q-switched 1064 nm Nd: YAG laser (energy density 700 J/cm^2, 900 J/cm^2 and 1100 J/cm^2, pulse frequency 10 Hz, 5 mm spot, pulse duration 5 - 10 ns) combined with 2940 nm Er: Treatment efficacy between YAG laser (energy density 500 J/cm^2, pulse frequency 10 Hz, 5 mm spot, pulse duration of 5 - 10 ns) and QS 1064 nm Nd: YAG laser alone. After 4 courses of treatment with an interval of 4 weeks, the results showed that both types of laser treatments were effective in the treatment of MA, and the combined laser treatment had a more significant reduction in melanin index and higher patient satisfaction. Side effects were only manifested as transient slight burning sensation and skin desquamation after treatment.

2.3. Erbium-Doped Yttrium Aluminum Garnet (Er-YAG) Laser

The Er:YAG laser outputs mid-infrared light with a wavelength of 2940 nm, which has a precise tissue vaporization ability and a controlled penetration depth (about 1 - 3 μm), and is suitable for the treatment of skin diseases.

Fawzy *et al.* [15] treated 10 patients with MA and LA with 2940 nmEr: YAG laser. After 4 treatments with an interval of 4 weeks, the degree and histology of pigmentation, corrugations, lichification, and pruritus were greatly improved, and only 1 patient relapsed at the three-month follow-up after the end of the treatment. Nahidi *et al.* [16] treated 15 MA patients with 1540 nm fractional Er: YAG laser (15 nm spot, energy 8 - 15 mJ/MB, pulse duration 15 ms). The skin lesions were significantly improved during the follow-up period of 3 months, and the side effects were erythema and edema. Anitha *et al.* [17] reported a case of LA in a patient who received fractional 2940 nmEr:YAG laser (9 mm spot, 1400 mJ energy, stacking 6 - 8 times) for 6 sessions at 3-week intervals with significant improvement in skin lesions, and no recurrence was observed during the subsequent 6-month follow-up. Only mild erythema, edema and desquamation were observed during the treatment.

2.4. Pulsed Dye Laser (PDL)

PDL target color is oxyhemoglobin, has multiple wavelengths, and is often used to treat vascular skin diseases. Barsky *et al.* [18] used 595 nmPDL (a 10-mm spot with an energy density of 7.5 J per cm^2) to treat a patient with refractory MA. After a total of three treatments with an interval of 2 weeks, amyloid accumulation was successfully reduced and skin pigmentation was improved. Sawamura *et al.* [19] reported a patient with LA who was treated with 585 nm PDL (7 mm spot, energy density 5.5 - 6.0 J/cm^2, pulse width 0.45 ms). After two treatments, the patient's skin lesions and pruritus were improved, and there was no recurrence during the follow-up of 15 months. In the study by Alster and Manaloto [20], a patient with NA was treated with 585 nmPDL (10 mm spot, energy density 5.25 J/cm^2), and the histopathology and clinical appearance of the skin lesions improved after four treatments.

2.5. Yttrium/Erbium Fiber Laser

Panchaprateep *et al.* [21] treated 10 patients with LA using a 1550 nm yttrium/erbium fiber laser with an energy density of 30 mJ/cm^2. After 3 treatments with an interval of 4 weeks, the appearance, pruritus, and histology of the rash were effectively improved.

3. Advantages and Safety of Laser Therapy Combined with Topical Drugs

The innovation of laser technology in the treatment of PCA is not only reflected in its therapeutic effect, but also in its synergistic effect with other treatment methods to form a diversified treatment plan. Laser combined with drug encapsulation, topical glucocorticoid or retinoic acid ointment, etc., has shown significant synergistic effects. This diversified treatment strategy not only reduces the limitations of single treatment, but also improves the effectiveness of treatment, providing a more personalized and comprehensive treatment plan for PCA patients.

Sobhi *et al.* [22] included 10 patients with MA in the study and divided their rash into three areas, all of which were treated with fractional CO_2 laser four times with an interval of 4 weeks (power 18 W, pitch 800 μm, dwell time 600 μs, superimposed 3 times). Zone 2 was treated with topical steroids, and zone 3 was treated with topical vitamin C. The appearance of the rash improved in each of the last three regions, with a significant histological reduction in the amount of amyloid in each region, with the most significant reduction in region 2. Gao Qiong *et al.* [23] selected 40 patients with anterior tibial skin amyloidosis to compare the efficacy of fractional laser combined with retinoic acid ointment and retinoic acid ointment alone, and the results showed that the former had a higher effective rate. Su *et al.* [24] conducted a study on 30 patients with LA. 15 patients in the control group were treated with compound flumetasone ointment encapsulation, and 15 patients in the treatment group were treated with CO_2 fractional laser (energy range 80 - 90 mJ/pulse, dot spacing 0.3 - 0.6 mm) combined with compound

flumetasone ointment encapsulation. The results showed that the treatment group was superior to the control group in the regression of skin lesions and improvement of pruritus.

4. Summary

Laser treatment of PCA, on the one hand, can directly remove amyloid deposited in the superficial dermis, on the other hand, through the combination of topical drug treatment, it can promote the absorption of drugs and improve the efficiency of drug treatment. A review of all the current studies, both case reports and clinical controlled trials, has shown promising results. Side effects were only mild or temporary. In all studies, the most common was fractional CO_2 laser, which in combination with topical hormones or retinoids showed superiority over either laser or drug alone. However, we noticed the lack of consistent implementation methods and standardized objective evaluation methods in most studies. We still need more large sample, multi-center clinical randomized controlled trials to provide more adequate evidence-based medical evidence for the efficacy and safety of laser treatment of PCA. The differences in the efficacy of different types of lasers and the influence of key parameters such as laser power, pulse width and treatment interval on the efficacy of PCA need to be further explored by more RCTS in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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