Original Article
Self-control study of combination treatment of 308 nm excimer laser and calcipotriene ointment on stable psoriasis vulgaris

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Abstract: Objective: This study aims to compare the differences of clinical efficacy and safety of treatment of stable psoriasis vulgaris with calcipotriene ointment in combination with 308 nm excimer laser to 308 nm excimer laser alone. Methods: Randomized, open and self-control trial was conducted in 36 selected patients. The skin lesions from these patients with stable psoriasis vulgaris were divided into two sides along the midline of torso, one side was treated with 308 nm excimer laser, 2 times/week, at meantime Calcipotriene was applied externally, 2 times/day (treatment group); the other side was given 308 nm excimer laser alone, 2 times/week, the treatment period was 6 weeks (control group). Skin lesion area, PASI scores and cumulative doses of 308 nm excimer laser in patients with psoriasis were assessed before treatment and on weeks 2, 4 and 6 after treatment. Results: 32 of 36 patients with stable psoriasis vulgaris completed study, effective rates in two groups were better on week 6 (84.37%, 56.25%) than on week 4 (53.12%, 37.5%) and on week 2 (31.25%, 18.75%) ($P < 0.05$). Effective rate on week 6 in control group (56.25%) was lower than treatment group (84.37%) ($P < 0.05$). The two groups showed that PASI scores on weeks 2 and 4 after treatment were significantly lower than before treatments ($P < 0.05$), and PASI scores on week 6 in treatment group was significantly lower than control group ($P < 0.05$). The average cumulative laser doses in treatment group at the end of trial was 4.69 (2.03) J/cm^2, which was significantly lower than in control group 8.41 (2.42) J/cm ($P < 0.05$). Treatment efficacies in the head, folds, back, abdomen and limbs were similar and no serious adverse effects, however the number of treatment and irradiation doses in the head and folds were significantly less than in back, abdomen and limbs ($P < 0.05$). Conclusions: Treatment of psoriasis vulgaris with 308 nm excimer laser in combination with external application of Calcipotriene ointment can improve long-term treatment efficacy, decrease cumulative laser doses, and reduce adverse effects induced by laser irradiations.

Keywords: Psoriasis, vulgaris, excimer Laser, calcipotriene

Introduction

Psoriasis is a chronic, relapsing, inflammatory skin disorder, and psoriasis vulgaris accounts for 85~90% [1]. The etiology and mechanisms of the disease is not clear; it is thought currently that under certain genetic background, psychological stress, drugs, inflammation, trauma, smoke and other stimuli induce epidermal cells to react, and then activate T cells through a series of process, resulting in release of various cytokines [2, 3].

The immunological role in the pathogenesis of psoriasis is not only related to innate immune system (including keratinocytes, neutrophil gra-

nulocytes, mast cells [4], endothelial cells [5], dendritic cells and histiocytes), but also is related to acquired immune system, especial T cells [6, 7]. Activated innate immune cells produce growth factors, cytokines, and chemokines etc., the functions of acquired immune system also need those cell activations. In recent years, due to better effects in treatment of psoriasis with cyclosporine and other calcineurins, the focus on the mechanisms of psoriasis has been shifted from keratinocytes to activation of various immune cells (mainly T cells and dendritic cells [8]) and their secretory products (e.g. transforming growth factors, tumor necrosis factors, interferons, interleukins, endothelial growth factors and so on [9, 10]), and thought that

immune cells and their secretory products ultimately result in over proliferation of keratinocytes, epidermal hyperplasia, angiogenesis with vasodilation, and increase of auto-reacted T cells *in situ* [11, 12].

The quality of patients' life is severally affected because of relapses of psoriasis disorder and difficult to treat; the clinical treatment methods are numerous, however lack of clear therapeutic effects [13]. In the present study, we used a randomized, open, parallel, self-control experimental method to observe and evaluate clinical treatment efficacy and safety of 308 nm excimer laser in combination with external application of Calcipotriene in treatment of stable psoriasis vulgaris.

Subjects and methods

Subjects

Totally 36 cases were enrolled, 21 were males and 15 were females, age ranges from 20~60 years, mean was (32.56 ± 10.48) years; disease course was from 5 months~2.5 years, the average was (10.32 ± 4.61) months. Two groups of patients were comparable in gender, age, type and stage, location and size of the disease.

Inclusion criteria of cases: Age was 18~65 years; Satisfied with clinical diagnostic criteria of stable psoriasis vulgaris, skin lesion area was less than 30% of body surface area, evenly distributed skin lesions between left and right sides of the body; Obtained patients' informed consents, voluntary participation in clinical observation.

Exclusion criteria of cases: Whole skin lesion was larger than 30% of body surface area or disease condition was serious and required systematical treatment with drugs; Local skin lesion was complicated by infections of bacteria, virus or fungi; Known history of allergy to Calcipotriene or drugs with similar chemical structure; clear liver or kidney disease, parathyroid disease, abnormal blood levels of calcium, blood system diseases, autoimmune diseases, psychological or psychiatric disease, diabetes mellitus, drug abusers and alcoholism; Patients with malignant tumors or other severe diseases that could affect the accuracy of evaluation of treatment efficacy; Pregnant or lactating women; Systemic treatment, externally topical use of Calcipotriene ointment or other drugs for psoriasis 4 weeks before treatment.

Early exit criteria: Took other drugs affecting the conditions of psoriasis during the period of trial; failed compliance of medicine and follow-up on schedule; discontinued treatment due to adverse effects.

All subjects signed an informed consent form. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University.

Treatment methods

Treatment groups: Randomized, open and parallel self-control experiment was used, body surface was divided in the midline of torso in selected patients, randomized number was used to divide subjects into treatment group and control group. Treatment group had 275 pieces of skin lesions, torso 108 pieces (folds 23, abdomen 38, and back 47), upper limbs 59 pieces, lower limbs 77 pieces, and the head 31 pieces. Control group has 257 pieces of skin lesions, torso 89 pieces (folds 17, abdomen 29, and back 43), upper limbs 70 pieces, lower limbs 69 pieces, and the head 29 pieces.

Determination of minimal erythema (MED) dose: Measurement of MED was performed according to the instruction provided with the equipment, the measurement point was anterior side of forearm of patient's left upper limb [14]. The dose of MED equipment was 6 incremented circle irradiation holes with diameter of 1.0 cm, the irradiation doses were 0.05, 0.075, 0.10, 0.125, 0.150 and 0.175 J/cm^2 from holes 1~6, the vertical irradiation distance was 15.0 cm. The irradiated locations in the participants were observed at 24 hours after irradiations; the dose first inducing erythema was patient's MED.

Methods of drug administration: Treatment group were externally given Calcipotriene ointment (Bright Future Pharmaceutical Lt., Hongkong; dose: 0.005% g/g, 10 g/tube), 2 times/day, and combined with irradiation of 308 nm excimer laser (Photomedex Company, USA, xtrac-308, wavelength 308 nm), 2 times/ week, totally 6 weeks. The adjustment principle of energy after the first irradiation treatment was: used 3-fold of MED, if erythema plaque continued for 24~48 hours after treatment,

Table 1. Comparisons of number of laser irradiation and cumulative doses in different locations in two groups of patients with psoriasis vulgaris after 6 weeks of treatment

Locations	Treatment			Control		
	No. of skin lesion	No. of Irradiation	Cumulative Doses	No. of skin lesion	No. of Irradiation	Cumulative Doses
Folds	18	4.10 ± 1.24	3.03 ± 1.27	14	5.40 ± 1.61	4.26 ± 1.13
Abdomen	31	8.35 ± 2.31	6.14 ± 2.58	25	9.83 ± 2.92	7.86 ± 2.35
Back	43	9.06 ± 2.97	6.58 ± 2.14	39	10.37 ± 3.27	8.21 ± 3.62
Upper Limbs	55	8.07 ± 1.93	5.48 ± 1.93	66	9.36 ± 2.94	9.18 ± 3.13
Lower Limbs	72	7.15 ± 1.77	5.87 ± 2.06	64	9.04 ± 2.76	8.86 ± 2.49
Head	28	5.33 ± 1.69	3.26 ± 2.21	26	6.46 ± 2.07	4.74 ± 1.84

then maintained the dose for next treatment; if the duration of erythema plaque was shorter than 24 hours, then the treatment dose was increased 5%~10%; if the duration of erythema plaque lasted for 48~72 hours, then the treatment dose was decreased 0.025~0.05 J/cm^2; if the duration of erythema plaque lasted longer than 72 hours or occurrence of blisters, itching, burning and other symptoms, 3% Boric Acid solution was applied, and re-irradiated after the above symptoms were almost disappeared, and the next irradiation dose was reduced 0.05~0.10 J/cm^2 from the previous one. The control group was given 308 nm excimer laser irradiation treatments alone, 2 times/week, 6 weeks in total.

Assessment standards of treatment efficacy: The scoring system of psoriasis area and severity index (PASI) of skin lesion was used to evaluate the severity of skin lesion [15]. A: area of skin lesion: observation and record cumulative skin lesion areas in different body regions [the head (h), torso (t), upper limbs (u), lower limbs (l)], assigned scores were 1~6 according to the size of area; B: severity of clinical appearance: elective erythema (E), invasion (I), scaling (S) 3 indexes, each item was scored according to the degree of severity, score was 0~4. Patients' symptoms, signs and adverse effects were assessed when they entered the group as baseline and each follow-up. PASI score = 0.1*h (E+I+S)*Ah+0.2*u(E+I+S)*Au+0.3*t(E+I+S)*At+0.4*l(E+I+S)*Al. Decreased index of PASI score of skin lesion = (pre-treatment PASI score - post-treatment PASI score)/pre-treatment PASI score.

> 95% decreased index of PASI score was considered as recovery; 61%~95% decreased index of PASI score was considered as effective; 20%~60% decreased index of PASI score was considered as improved, less than 20% decreased index of PASI score was considered as invalid. The efficiency was calculated by recovery plus effective.

Safety evaluation: Selected cases was conducted for safety evaluation of clinical adverse effects that occured during the process of drug treatment, including erythema, skin atrophy, telangiectasia, pigmentation change, folliculitis and so on, patients with occurrence of severe reaction and withdraw of observation were considered invalid. The two groups were followed up at weeks 2, 4 and 6, and were compared the differences in the incidences of adverse events.

Statistical analysis

Experimental data was analyzed with SPSS 13.0 statistical software, measurement data were represented as x ± s, paired data before and after treatment were analyzed by analysis of variance, recovery rates of two groups and total effective rate were analyzed by analysis of variance, p < 0.05 is considered as statistical significance.

Results

MED measurement, cumulative doses and PASI scores

Among the selected 36 cases, 8 cases had MED of 0.1 J/cm^2, 13 cases of 0.15 J/cm^2, 10 cases of 0.2 J/cm^2, 3 cases of 0.25 J/cm^2, and 2 cases of 0.3 J/cm^2. The average cumulative dose of 308 nm excimer laser in treatment group was 4.69 ± 2.03 J/cm^2, which was significantly lower than the control group 8.41 ± 2.42 J/cm (P < 0.05). 4 cases were lost at the end of the course of treatment, 3 subjects could not be followed up, 1 case withdrew, and all the oth-

Table 2. PASI comparison (x ± s) between pre-treatment and post-treatment in two groups of patients with psoriasis vulgaris

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Treatment	12.05 ± 2.03	7.93 ± 3.27	4.96 ± 2.48	1.82 ± 0.74▲,*
Control	11.47 ± 1.87	9.08 ± 2.13	6.73 ± 1.61	5.08 ± 1.65

Note: ▲compared to pre-treatment, $P < 0.05$; *compared to control group, $P < 0.05$.

er patients completed the treatment. On week 6 of treatment, effective treatment was observed in the head, folds, back, abdomen and limbs, however the number of treatment and the doses of irradiation in the head and folds were significantly less than those in torso, abdomen and limbs (F = 10.52, 5.82, $P < 0.05$) (**Table 1**).

Comparison of PASI scores before treatment between treatment group and control group, the difference was not statistically significant ($P > 0.05$). The two groups showed significant decreases in PASI scores on week 2 and week 4 compared to that before treatment ($P < 0.05$), however comparison between the two groups was not statistically significant ($P > 0.05$). PASI score on week 6 in treatment group was significantly lower than control group, the difference reached statistically significant ($P < 0.05$) (**Table 2**).

Comparison of clinical efficacy

Treatment and control groups showed remarkable improvement in erythema, scaling, infiltration hypertrophy, pruritus and area of skin lesions compared to pre-treatment, and treatment efficacy continued to increase with prolonged therapeutic course, the efficacies on week 6 of treatment (84.37%, 56.25%) were markedly better than those on week 4 (53.12%, 37.5%) and week 2 (31.25%, 18.75%), the differences were statistically significant (x_2 = 9.46, 11.24, 8.66, 9.73, $P < 0.05$). The efficacy on week 6 in control group (56.25%) was significantly lower than treatment group (84.37%), the difference was statistically different (X_2 = 7.34, $P < 0.05$) (**Table 3**).

Adverse effects

6 of 32 patients showed adverse effects during the study. Among those, 3 cases showed local mild pain, 2 cases were manifested with erythema, burning sensation with pruritus at the irradiated areas, however they got better after topical application of cold pad, the other case showed blisters in the irradiated area and was stopped irradiation treatment. The patient got better after aspirating the blisters and covered with wet pad. All the 6 patients had mild pigmentation, but did not affect the observation of efficacy of treatment.

Discussion

The characteristics of psoriasis are epidermal hypertrophy, abnormal differentiation of keratinocytes and inflammation; T cells play an important role in the pathogenesis of psoriasis. 308 nm excimer laser exerts therapeutic role in treating psoriasis by inducing T cell apoptosis and by inhibiting generation of cytokines [16]. Its excitation wavelength is similar to ultraviolet lights, it is XeCl excimer light. Comparing to NB-UVB, 308 nm excimer light can selectively act on skin lesions with stronger targeting ability, and only act on irradiated area but no effect on un-irradiated normal skin, few adverse effects, is suitable for all region treatment in the whole body [17, 18]. However, long-term use of 308 nm excimer laser can cause DNA mutation, activation of oncogenes, local T cells apoptosis, decreased activity of NK cells, and consequently leading to decrease in immune surveillance function in organism, the occurrence of skin cancer, e.g. squamous cell carcinoma and melanoma [19].

Treatment of psoriasis with 308 nm excimer light in combination with external application of drugs can improve therapeutic efficacy and reduce accumulation of ultraviolet lights, thereby reducing risk of carcinogenesis [20]. Calcipotriene (0.005%) is a synthetic analog of vitamin D3 and can bind to keratin to form vitamin D3 receptors on cell membrane. It can effectively inhibit proliferation of keratinocytes and induce cell differentiation through regulating gene activities within cell. Patients externally treated with calcipotriene showed reduced number of chemokine neutrophils and T lymphocytes, and lessened epidermal and dermal inflammations, indicating that this drug has roles in immune inhibition and direct anti-inflammations [21].

In the present study, the left and right sides of patient's own were compared to assess the treatment efficacy and the safety of 308 nm

Table 3. Comparison of clinical efficacy in two groups

Group	Case (n)	2 weeks					4 weeks					6 weeks				
		Recovery	Effective	Improved	Invalid	Efficacy (%)	Recovery	Effective	Improved	Invalid	Efficacy (%)	Recovery	Effective	Improved	Invalid	Efficacy (%)
Treatment	32	3	7	18	4	31.25	7	10	14	1	53.12	14	13	5	0	84.37
Control	32	0	6	16	10	18.75	4	8	13	7	37.50	8	10	10	4	56.25

excimer light in combination with calcipotriene ointment during treatment of stable psoriasis vulgaris, so the statistical errors can be excluded due to gender, age, stages of disease, location of drug application and other individual differences. The present study showed that PASI scores were significantly decreased in 308 nm excimer light in combination with calcipotriene ointment group and 308 nm excimer light alone group compared to those before treatment ($P <$ 0.05), the effective rates were 31.25% and 18.75%, respectively, suggesting that treatment of psoriasis vulgaris with 308 nm excimer light had quick onset, short treatment course, and remarkable effect. The decreased cumulative PASI scores and treatment efficacy on week 2 and week 4 after treatment were not statistically significant between the two groups ($P > 0.05$), which might be associated to slow onset of calcipotriene, however it showed that the cumulative PASI score after 6 weeks was 1.82 ± 0.74, which is significantly lower than the control group 5.08 ± 1.65 ($P < 0.05$), suggesting that application of 308 nm excimer light in combination with calcipotriene ointment can inhibit inflammatory responses of keratinocytes for relative long time, and consequently can maintain stable period for a relative long time. Furthermore, the average cumulative laser dose at the end of trial in the treatment group (4.69 ± 2.03 J/cm^2) was significantly less than the control group (8.41 ± 2.42 J/cm, $P <$ 0.05), indicating that combination of the two drugs can reduce the accumulation of laser doses, prolong remission, improve the quality of life of patients.

This study showed that recent adverse effects induced by 308 nm excimer laser were mainly mild pain, erythema, pruritus and blisters, but strictly measure MED before treatment, then conduct irradiation treatment according to different MED values at different regions [22], and carefully observe and record to minimize the occurrence of these adverse events, if it occurs and treats it promptly, it will not affect the efficacy, but the long-term efficacy and adverse effects still needs further clinical observations.

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Disclosure of conflict of interest

None.

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