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Original Research Article

Comparative therapeutic evaluation of 308 nm monochromatic excimer light in combination with calcipotriol ointment vs 308 nm monochromatic excimer light alone in palmoplantar psoriasis

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ABSTRACT

Background: Palmoplantar psoriasis is difficult to treat and often recalcitrant to traditional treatment modalities like topical steroids, anthralin, calcipotriol, methotrexate, cyclosporine, NB-UVB and PUVA. This study was aimed to compare efficacy of 308 nm monochromatic excimer light (MEL) in combination with calcipotriol ointment to 308 nm MEL alone in treatment of palmoplantar psoriasis.
Methods: This self-control study was conducted in 30 patients of palmoplantar psoriasis. Right side was treated with 308 nm MEL, 2 times/week, at meantime calcipotriol ointment was applied externally, 2 times/day (treatment group); the left side was treated with 308 nm MEL alone, 2 times/week (control group). Erythema, scaling, induration and fissuring (ESIF) score and cumulative doses of 308 nm MEL were assessed before treatment and on weeks 2, 4 and 6 after initiation of treatment.
Results: All 30 patients completed the treatment. ESIF scores on week 2, week 4, and week 6 in treatment group were significantly lower than control group ($p<0.01$). The average cumulative MEL dose in treatment group at the end of trial was 8.12±1.72 J/cm^2, which was significantly lower than in control group 12.76±1.92 J/cm^2 ($p<0.01$).
Conclusions: Treatment of palmoplantar psoriasis with 308 nm MEL in combination with external application of calcipotriol ointment can improve long-term treatment efficacy, decrease cumulative doses, and adverse effects induced by MEL irradiations.

Keywords: Palmoplantar psoriasis, Monochromatic excimer light, Calcipotriol

INTRODUCTION

Palmoplantar psoriasis is a chronic disabling condition characterized by erythematous scaly plaques of the palms and soles, often associated with pain, erythema, and fissuring. Palmoplantar psoriasis accounts for 3–4% of all psoriasis cases, produces significant functional and social disability.[1] Although palmoplantar psoriasis appears to be a distinct entity in terms of epidemiology and pathophysiology, it might be associated with other forms of psoriasis. This condition poses a unique therapeutic challenge in that it is refractory to many therapies currently approved for the management of psoriasis. Different treatment options are available such as potent topical steroids, topical tar or anthralin, calcipotriol, topical retinoids, phototherapy, and systemic modalities like methotrexate, cyclosporine, retinoids and biologics. However, they all have limitations in terms of efficacy or side effect profile.

The 308-nanometer (nm) monochromatic excimer light lamp (MEL), a handheld device, uses a xenon chloride (XeCl) gas mixture to generate an ultraviolet laser light source of UVB radiation than can concentrate energy solely on a psoriasis plaque and avoid damage to surrounding healthy skin. The 'excimer' is an excited dimer, a molecule formed by the combination of two atoms: a noble gas xenon and chloride. The excitation of the molecule emits an ultraviolet photon at 308 nm. Advantages of the excimer laser over other forms of phototherapy include healthy skin surrounding the areas of psoriasis are not exposed to radiation; a higher dose of radiation can be used to induce a visible reaction in the psoriatic plaque.

Campolmi et al observed an improvement ranging from 75% to 100% after 6 weeks of treatment with 308nm monochromatic excimer light in 11 patients with palmoplantar psoriasis and no relapse at 16-week follow-up.[2] Al-Mutairi and Al-Haddad concluded that 308-nm excimer laser is an effective, safe, easy, and relatively quicker method for the treatment of psoriasis at difficult to treat sites, with good results in a somewhat short time.[3]

A study by Feldman et al concluded that the excimer laser is more advantageous than conventional photo-chemotherapy because it requires fewer visits, spares the surrounding psoriasis free skin, has minimal side effects and appears to be safe and effective for the treatment of psoriasis.[4] Bianchi et al in their study observed that psoriatic skin after monochromatic excimer light therapy is associated with significant T cell depletion and alterations of apoptosis related molecules accompanied by a decreased proliferation index and clinical remission.[5]

Calcipotriol (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 calcipotriol showed reduced number of chemokines, neutrophils and T lymphocytes, and lessened epidermal and dermal inflammations, indicating that this drug has roles in immune inhibition and direct anti-inflammations.[6]

Tang et al studied combination treatment of 308 nm excimer laser and calcipotriene ointment on stable psoriasis vulgaris. They concluded that 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.[7]

However, there are no studies reported on efficacy of monochromatic excimer light combined with calcipotriol ointment in palmoplantar psoriasis in Indian patients. The aim of our study is to compare the clinical efficacy of combination of calcipotriol ointment with 308 nm MEL to 308 nm MEL alone in palmoplantar psoriasis.

METHODS

This self-control study was carried out in Department of Dermatology, Venereology and Leprosy of Smt. Kashibai Navale Medical College, Pune from July 2017 to June 2018.

Inclusion criteria

Inclusion criteria were patients above 18 years of age, diagnosed to have palmoplantar psoriasis on clinical features and skin biopsy; patients who have stable lesions covering more than 30% of palms and/or soles but not covering more than 5% of other body areas; patient with evenly distributed skin lesions between left and right sides; patient who are willing to give informed consent.

Exclusion criteria

Exclusion criteria were patients, who were taking systemic medication and phototherapy for less than 8 weeks or applying topical treatment within past 4 weeks for psoriasis; patient with history of skin cancer or photosensitivity related disorders; patient with history of allergy to calcipotriol or drugs with similar chemical structure, patients with hypercalcemia, pregnant or lactating women.

After taking informed written consent, patients were enrolled in the study. All patients underwent detailed clinical examination, blood investigations and skin biopsy. Prior to the treatment the minimal erythematous dose (MED) was determined on healthy and unexposed skin on anterior side of left forearm. A dosage thrice of MED was used on affected skin. Lesions were irradiated protecting the surrounding skin and petrolatum ointment was applied on the scaly patches prior to irradiation to minimize light reflections.

Each treatment was tailored to the individual patient's response from the previous session. If there was no response or minimal erythema, the dose was increased by 30%. If there was moderate erythema, the dose was increased by 20%, and if significant erythema, the dose was increased by 10% until the patient could not tolerate further increases. For severe reactions or blistering, the dose was decreased by 20%.

Methods of drug administration

The skin lesions from these patients were divided into two sides, right and left. Right side was treated with externally given calcipotriol ointment (dose: 0.005% w/w, 20 g/tube), 2 times/day, and combined with irradiation of 308 nm MEL (Quantel Derma Company, Germany), 2 times/week, totally 6 weeks. The left side was treated with 308 nm MEL irradiation treatment alone, 2 times/week, 6 weeks. The 308 nm MEL produces a power density of 50 mw/cm^2 and beam diameter 40×40 mm.

Table 1: ESFI score.

Score	Erythema	Scaling	Fissuring	Induration
0	None	None	None	None
1	Barely perceptible	Minute, powdery	Mild	Mild
2	Dull red	Thin flakes	Moderate	Moderate
3	Deep/ dark red	Thick scales	Severe	Severe

ESFI= erythema, scaling, fissures and induration.

Assessment standards of treatment efficacy

The lesions were assessed for the degree of erythema, scaling, induration and fissuring (ESIF) and were scored on a severity scale of 0-3 (Table 1). The most severe condition was given 12 points. Percentage of overall improvement was calculated by decreased index of ESIF score of skin lesion = (pre-treatment ESIF score – post treatment ESIF score)/pre-treatment ESIF score which was categorized as follows:

Recovery: >75% decreased index of ESIF score
Effective: 51-75% decreased index of ESIF score
Improved: 26-50% decreased index of ESIF score
Invalid: <25% decreased index of ESIF score

The efficiency was calculated by recovery plus effective. Clinical evaluation was carried out at 2 weeks, 4 weeks and 6 weeks of treatment.

Safety evaluation: Selected cases were conducted for safety evaluation of clinical adverse effects that occurred during the process of drug treatment, including erythema, skin atrophy, telangiectasia, pigmentation change, folliculitis.

Statistical analysis was performed using paired "t" test to compare mean ESIF score and cumulative dose of MEL in two groups, $p<0.01$ was considered as statistically significant.

RESULTS

MED measurement, cumulative doses and ESFI scores

Among the selected 30 cases, 4 cases had MED of 0.15 J/cm^2, 6 cases of 0.20 J/cm^2, 3 cases of 0.25 J/cm^2, 10 cases of 0.30 J/cm^2, and 7 cases of 0.35 J/cm^2. The average cumulative dose of 308 nm monochromatic excimer light in treatment group was 8.12±1.72 J/cm^2, which was significantly lower than the control group 12.76±1.92 J/cm^2 ($p<0.01$). Treatment group required less number of mean irradiation than control group (Table 2).

Table 2: Comparisons of number of MEL irradiation and cumulative doses in two groups of patients after 6 weeks of treatment.

	Treatment group	Control group
No of MEL irradiation (mean)	10	12
Cumulative doses (mean) P value=0.000007	8.12±1.72 J/cm^2	12.76±1.92 J/cm^2

Table 3: ESFI score (mean±SD) comparison between pre-treatment and post-treatment in two groups of patients with palmoplantar psoriasis.

Group	Pre-treatment	2 weeks	4 weeks	6 weeks
Treatment	10.06±1.18	7.25±1.62	4.12±1.04	1.34±0.32
Control	10.50±1.21	8.31±1.34	6.24±1.13	3.8±0.74
P value	0.159	0.007	0.0001	0.0001

The difference in ESFI score before treatment, between treatment and control group, was not statistically significant ($p>0.01$). The two groups showed decrease in ESFI scores on week 2, week 4 and week 6 compared to before treatment. ESFI score on week 2, week 4 and week 6 in treatment group was significantly lower than control group ($p<0.01$) (Table 3).

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. Treatment efficacy continued to increase with prolonged therapeutic course, the efficacies on week 6 of treatment (93.33%, 66.66%) were markedly better than those on week 4 (63.12%, 40%) and week 2 (30%, 16.66%) (Table 4).

Table 4: Comparison of clinical efficacy in two groups.

	Group	Case (n)	Recovery	Effective	Improved	Invalid	Efficacy (%)
2 weeks	Treatment	30	3	6	17	4	30
	Control	30	0	5	15	10	16.66
4 weeks	Treatment	30	8	11	9	2	63.33
	Control	30	4	8	11	7	40
6 weeks	Treatment	30	16	12	2	0	93.33
	Control	30	8	12	6	4	66.66

Efficacy= Recovery plus Effective.

Adverse effects: 7 of 30 patients showed adverse effects during the study. Among those, 4 cases showed local mild pain, 3 cases were manifested with erythema, burning sensation with pruritus at the irradiated areas, however they got better after topical application of cold pad. All the 7 patients had mild pigmentation.

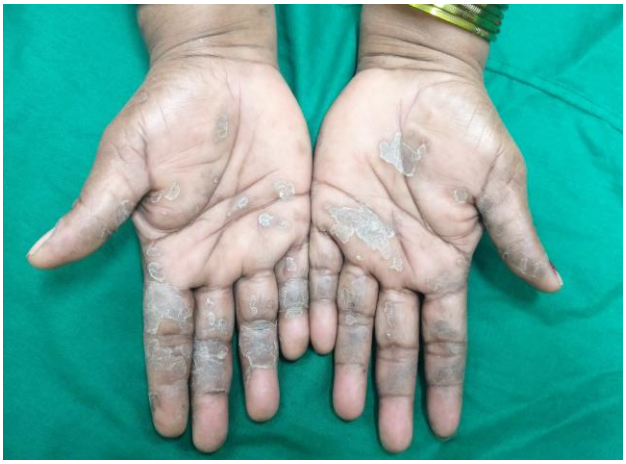

Figure 1: Before treatment.

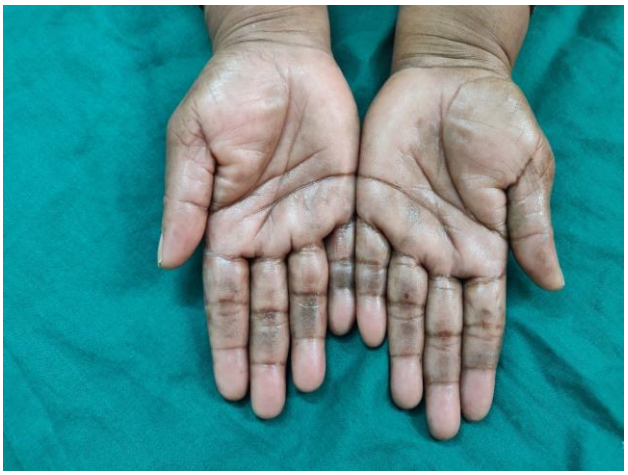

Figure 2: After treatment at 6 weeks.

DISCUSSION

Palmoplantar psoriasis is a chronic disease which is commonly characterized by frequent exacerbations, difficulty in its management and resistance to therapy. Topical corticosteroids and phototherapy are the most widely used therapeutic modalities for this subtype of psoriasis. In cases with palmoplantar psoriasis, which could hardly be clinically differentiated from chronic eczema, even systemic corticosteroids are used. These medications are harmful for the course of psoriasis, since severe exacerbations and complications of the disease may occur after withdrawal of these drugs. Therefore an effective, steroid-free therapeutic modality is needed for management of the palmoplantar psoriasis.

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 MEL exerts therapeutic role in treating psoriasis by inducing T cell apoptosis and by inhibiting generation of cytokines.[8] Comparing to NB-UVB, 308 nm MEL can selectively act on skin lesions with stronger targeting ability, only act on irradiated area but no effect on un-irradiated normal skin and few adverse effects is suitable for all region treatment in the whole body.[9]

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 and the occurrence of skin cancer, e.g. squamous cell carcinoma and melanoma.[10]

Calcipotriol (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 calcipotriol showed reduced number of chemokines, neutrophils, T lymphocytes, and lessened epidermal and dermal inflammations, indicating that this drug has roles in immune inhibition and direct ant inflammations.[11]

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 MEL in combination with calcipotriol ointment during treatment of palmoplantar psoriasis, 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 ESFI scores were significantly decreased in 308 nm MEL in combination with calcipotriol ointment group and 308 nm MEL alone group compared to those before treatment ($p<0.01$). The effective rates in treatment and control group at 2, 4 and 6 weeks were (30%, 16.66%), (63.33%, 40%), (93.33%, 66.66%) respectively, suggesting that treatment of palmoplantar psoriasis with 308 nm MEL had quick onset, short treatment course, and remarkable effect. The decreased cumulative ESFI scores in treatment group after 6 weeks was 1.34±0.32, which was significantly lower than the control group 3.8±0.74 ($p<0.01$). This suggests that application of 308 nm excimer light in combination with calcipotriol 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 MEL dose at the end of trial in the treatment group (8.12±1.72 J/cm^2) was significantly less than the control group (12.76±1.92 J/cm^2, $p<0.01$)), which indicates that combination of the two drugs can reduce the accumulation of MEL doses, prolong remission, improve the quality of life of patients.

Our study findings are in concordance with earlier study which showed that adverse effects induced by 308 nm MEL were mainly mild pain, erythema, pruritus which can be minimised by strictly measuring MED before treatment and then conducting irradiation treatment according to response to MED.[12] However, blisters were not observed in our patients.

In present study, we observed that, treatment of palmoplantar psoriasis with 308 nm MEL in combination with external application of calcipotriol ointment can improve long-term treatment efficacy, decrease cumulative doses, and adverse effects induced by MEL irradiations. However in our study, follow up was done at 6 weeks only hence further clinical studies are required to determine long-term treatment efficacy and adverse effects.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee Smt. Kashibai Navale Medical College, Pune, Maharashtra

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