

Efficacy of 5-Fluorouracil plus Epinephrine, Pulsed Dye Laser and Betamethasone on the Improvement of Psoriatic Plaques (A Comparative Study)

Soheila Taheri, MD
Ali Asilian, MD
Gita Faghihi, MD

Department of Dermatology, Isfahan
University of Medical Sciences, Isfahan,
Iran

Corresponding author:
Soheila Taheri, MD
Department of Dermatology,
Isfahan University of Medical Sciences
Email: s_taheri@resident.mui.ac.ir

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Abstract

Background: Many efforts are made to find new and more effective treatments for psoriasis. Intralesional 5-Fluorouracil (5-FU) +epinephrine is a cheap option which can be administered with long intervals. The effectiveness of Pulse Dye Laser (PDL) on psoriasis has been already assessed. We decided to evaluate the effectiveness of 5-FU+epinephrine and compare it to betamethasone and PDL.

Methods: A group of 22 patients with chronic stable plaque psoriasis were included. Three plaques on each patient were treated with 5-FU+epinephrine, PDL and betamethasone, respectively. Psoriasis Severity Index (PSI) scoring was applied to assess each plaque before treatment and in weeks 2, 4, 6, 12, and 24. Photos of each plaque were taken before treatment and at each treatment and follow-up session. They were finally compared and scored by a dermatologist.

Results: Decline in mean Psoriasis Severity Index (PSI) in week 6 (2 weeks after treatment) and in week 24 (the last follow-up session) was statistically significant as compared to baseline in all groups. ($P<0.001$) The highest decline in mean PSI score was in the 5-FU+epinephrine group while the lowest belonged to the PDL group (80% vs. 27%). The mean period of remission in the 5-FU+epinephrine group was significantly longer in comparison to the two other groups. ($P<0.001$) In photographic evaluation, the best response was observed in the 5-FU+epinephrine group.

Conclusion: 5-FU+epinephrine is a cheap option which can provide a rapid response and long remission. With respect to limited effectiveness, short remission and high cost; PDL dose not seem to be a preferred choice in the treatment of psoriasis. (*Iran J Dermatol* 2009;12:36-41)

Keywords: betamethasone, psoriasis, 5-Fluorouracil, pulse dye laser

Introduction

Psoriasis is a chronic disease with a histological profile including dermal vessel dilatation and tortuosity, hyperkeratosis, parakeratosis, elongation of rete ridges and infiltration of immune cells in dermis and epidermis¹.

5-Fluorouracil inhibits DNA synthesis via competitive inhibition of thymidilate synthetase^{2,3} and therefore decreases epidermal proliferation. Topical, oral and intralesional forms of 5-FU were reported to be effective^{3,4,5,6}.

If combined with epinephrine, 5-Fluorouracil (5-FU) stays longer in the lesion before it is washed out and therefore its efficacy increases³. The response rate of PDL in the treatment of psoriasis varies from 57% to 82% in previous studies⁷. PDL acts on superficial dermal vessels through selective photothermolysis^{8,9,10,11}.

In this study, we decided to evaluate the effectiveness of 5-FU and compare it to betamethasone and the newly introduced PDL (which is not experienced in our region).

Patients and Methods

A total of 22 patients with psoriasis were included in this study. Every patient had to have at least 3 chronic plaques and the involved body area was less than 20 percent. A plaque was considered chronic if it persisted for more than 2 months. The selected plaques were more or less similar in size, location and severity and were at least 3 centimeters apart from one another. Plaques on the face, scalp, thigh and gluteal region were excluded. Patients under 18, and pregnant or breast feeding mothers were not included, either. All patients had neither received systemic treatments and phototherapy during the previous 8 weeks nor topical treatments during the previous 2 weeks. None of our patients had a history of hypertrophic scar, keloid or photosensitivity. The study plan was thoroughly explained to the patients and each signed an informed consent. Three plaques were selected in each patient. The first one was treated with PDL, the second was injected with 5-FU+epinephrine and the third received topical betamethasone. The laser applied was PDL (N lite V ICN photonic Ltd, Wales, UK) with 585nm, 8-9 J/cm² fluence and 5mm spot size. Patients were treated with PDL fortnightly but not more than 3 times in the course of the therapy (week 0, 2, 4). The second plaque was injected intralesionally with 1 ml (50mg/ml) of 5-FU + 0.01 ml (0.001%) of epinephrine (maximum 100 mg 5-FU) every two weeks (week 0, 2, 4) but not more than 3 times in the course of the study. Patients were advised to use betamethasone valerate 0.1% ointment on the third plaque twice a day for 4 weeks. All therapeutic interventions finished at the end of the 4th week. Then, the patients were revisited in three sessions (week 6, 12, 24).

Clinical assessment

PSI (Psoriatic Severity Index) score of each plaque was measured by a dermatologist who was blinded to the study. PSI score was measured before treatment and at weeks 2, 4, 6, 12, and 24 after treatment. The PSI measurements were based on the chart below.

PSI score is the summation of erythema, induration and scale points and ranges between 0 and 12.

Photography

Digital photography (Sony, DSC200, Cyber-shot, Sony Corporation, Japan) of plaques was performed before treatment and at weeks 2, 4, 6, 12, and 24.

Table 1. Psoriasis Severity Index

| | E (Erythema) | | I (Induration) | S (Scale) |
|----------|--------------|--------------------|--------------------|----------------------|
| No sign | 0 | 0 | 0 | 0 |
| Minimal | 1 | light pink | Barely palpable | Rare scale |
| Mild | 2 | Pink or bright red | Slight elevation | Poorly defined scale |
| Moderate | 3 | Red | Moderate elevation | Defined scale |
| Sever | 4 | Dark red | Marked ridge | Heavy scale |

Photos were compared and scored by a dermatologist who was blinded to the study.

Complications

Common complications including pain, purpura, hyperpigmentation, crust and scar were assessed in all the 3 groups. VAS (Visual Analogue Scale) score was applied to assess pain in plaques treated with 5-FU+epinephrine and PDL. Patients were asked to show pain severity on a tape scaled from 0 to 10.

Remission

Clearance was defined as a clinical response of 90% - 100% or PSI score 0-2. PSI score ≥ 3 was considered as relapse. Follow-up continued until 20 weeks after the last session of therapy. During treatment and follow-up, the rest of the patients' plaques were treated with either betamethasone ointment or calcipotriol ointment. On the selected plaques, however, only emollient was applied.

The collected data was then analyzed with SPSS version 13. Comparing mean PSI score before and after treatment was performed via repeated measure analysis of variance. Changes in mean PSI among the 3 groups were compared through one-way analysis of variance. If the difference was significant, Duncan's post hoc was additionally used. Changes in photography were compared with Kruskal-Wallis. T test was applied to compare VAS score. The period of remission among the three groups was compared via analysis of variance. A P value ≤ 0.05 represented a statistically significant difference.

Table 2. Response rate evaluated by photography

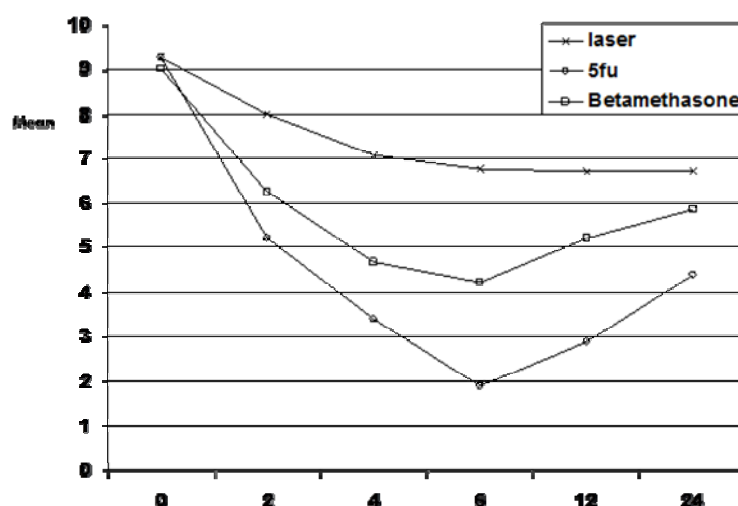
| | | |
|---|--------------------------------|---------------------|
| 0 | No response | 0-10% improvement |
| 1 | Weak response | 10-30% improvement |
| 2 | Moderate response | 30-70% improvement |
| 3 | good response | 70-90% improvement |
| 4 | Clearance (excellent response) | 90-100% improvement |

Table 3. Mean PSI score of all the study plaques

| group | week 0 | week 2 | week 4 | week 6 | Week 12 | week 24 |
|------------------|-------------|-------------|-------------|-------------|-------------|-------------|
| PDL | 9.27 ± 1.69 | 8 ± 2.04 | 7.09 ± 2.24 | 6.77 ± 2.36 | 6.72 ± 2.49 | 6.72 ± 2.49 |
| 5-FU+epinephrine | 9.27 ± 1.77 | 5.22 ± 2.3 | 3.4 ± 2.7 | 1.9 ± 2.11 | 2.9 ± 2.75 | 4.4 ± 3.29 |
| Betamethasone | 9.00 ± 1.79 | 6.27 ± 2.84 | 4.68 ± 2.74 | 4.22 ± 2.75 | 5.22 ± 2.68 | 5.86 ± 2.74 |

Table 4. Comparison at mean PSI score among the three groups (P value)

| Paired groups | week 0 | week 6 | week 4 | week 6 | week 12 | week 24 |
|---------------|--------|--------|--------|--------|---------|---------|
| PDL vs Beta | 0.6 | 0.02 | 0.003 | 0.001 | 0.06 | 0.32 |
| 5-FU vs Beta | 0.6 | 0.16 | 0.1 | 0.002 | 0.005 | 0.1 |
| PDL vs 5-FU | 1 | <0.001 | <0.001 | <0.001 | <0.001 | 0.009 |

**Figure 1:** The evaluation of mean PSI score in 3 groups

Results

Table 3 and 4 and figure 1 show the results.

PSI scores

In the 5-FU+epinephrine group, there was a significant difference between mean baseline PSI and mean PSI at weeks 6 and 24 with a reduction of 80 percent at week 6 ($P<0.001$). Except for weeks 6 and 12 ($P=0.1$), difference of mean PSI in all other weeks proved to be significant. In the PDL group, the mean value of baseline PSI score was significantly different from PSI mean at the sixth week ($P<0.001$) with a reduction of 27%. Similarly, PSI mean at the week 24 showed a significant difference with baseline PSI mean ($P<0.001$). On the contrary, mean PSI at weeks 2, 4, 6, 12, and 24 did not show any significant differences with each other. In the betamethasone group, the difference

between mean PSI at weeks 6 and 24 with mean baseline PSI was significant with a reduction of 53% at week 6. However, mean PSI was not significantly different between weeks 4, 6, 12 and 24. The difference of mean PSI between PDL and betamethasone groups was shown to be significant in all weeks except for week 24. Although the difference between mean PSI of 5-FU+epinephrine and betamethasone groups was not significant at weeks 2 and 4, it was significant at weeks 6, 12 and 24. The difference of mean PSI between 5-FU+epinephrine and PDL groups was significant in all weeks ($P<0.001$).

Remission

The mean period of remission in the 5-FU+epinephrine group was 9 ± 7.9 weeks. This

showed a significant difference with the other two groups. ($P<0.001$)

The mean remission period in the PDL and betamethasone groups were 0.7 ± 2.6 and 2.7 ± 6.5 weeks, respectively. In the PDL group, 3 cases of clearance were recorded and two of them remained in remission until week 24. In the 5-FU group, there were 17 cases in remission and 8 of them stayed in remission until week 24. There were 5 cases in remission in the betamethasone group and two of them remained in remission until week 24.

Complications

In the PDL group, there were 4 cases with purpura and 3 with severe itching. In the 5-FU + epinephrine group, 3 patients reported severe itching following injection, crust formation happened in 2 patients and 17 cases developed hyperpigmentation. It disappeared in all but one within a period of 4-6 weeks. Pain assessment was made using VAS scoring system. The mean pain VAS score was 5.4 ± 3 and 7 ± 2.7 in the PDL and the 5-FU+epinephrine groups, respectively. This difference was statistically significant ($P=0.01$). The serum 5-FU level was not measured.

Photography

Photos of all lesions were taken in every visit. The clinical response was then evaluated by a dermatologist blinded to the study. Using Kruskal-Wallis test, it was shown that the clinical response was significantly different among the three groups ($P<0.001$). The best clinical response came from the 5-FU+epinephrine group with a good response rate of 61% and an excellent response rate of 33.3%. In the PDL group, however, a good response rate of 11.1% and an excellent response rate of 5.6% were reported. In the betamethasone group, the rate of good and excellent response was 22%.

Discussion

In our study in the group treated with intralesional injection of 5-FU+epinephrine, there was a significant difference between mean baseline PSI score and mean PSI score at weeks 6 and 24 which indicated the efficacy of 5-FU therapy. This finding is corroborated by Pearlman et al.⁵, that showed significant clearance of psoriatic plaques in contrast to the control group treated with intralesional 5-FU. The within group comparison of mean PSI score in 5-FU+ epinephrine group showed a significant difference between all weeks except for the borderline difference between weeks 6 and

12 ($P=0.1$); which is probably due to the high rate of recurrence in this period. The mean period of remission in this group was 9 ± 7.9 weeks, which was significantly longer than remission in PDL and betamethasone groups ($p<0.001$). In the 5-FU + epinephrine group, there were 17 cases of remission but 8 of them stayed in remission until week 24 which showed a longer remission in comparison with the study by Pearlman.

There were two concerns with the 5-FU +epinephrine group. The first was the severe pain accompanied by 5-FU+epinephrine injection. The pain with 5-FU+epinephrine was significantly more than that with PDL. Similarly in previous studies, 5-FU injection pain was regarded as an adverse effect⁵. However, the pain was felt during injection and gradually disappeared within 1-2 hours. The second concern was the high rate of pigmentation which can simply be justified by the high Fitzpatrick skin type (type III, IV) of our patients. Development of hyperpigmentation, however, limits its use in the face.

The effectiveness of PDL in the treatment of psoriasis has been already proved in previous studies, however, long remission was hardly ever reported in these studies. In our study, mean PSI score at weeks 6 and 24 showed a significant difference with baseline values in the PDL group. This fact suggests that PDL could decline PSI score which is quite similar to most previous studies^{1,12,13,14,15,16}. According to our results, the mean PSI score between weeks 2, 4, 6, 12, 24 were not significantly different. This means that PDL was most effective in the first 2 sessions which is contrary to the idea that increasing the frequency of PDL would proportionately increase its efficacy or that PDL could have delayed effectiveness⁷. Significant complications were not found in the PDL group. Evaluation of the patients' pain with VAS score showed a mean of 5.4 ± 3 which was lower compared to Erceg study¹⁶. Similar to Erceg et al. we found no relationship between pain and the treatment outcome. We could not find a decline in laser-induced pain after successive treatment sessions in contrast to Erceg et al.

Ilkanar et al,¹⁷ found that the size of psoriatic plaques increased after PDL while there was no change in the size of lesions treated with clobetasol propionate. They concluded that PDL could have possibly caused koebnerization. Three of our patients also had an increase in PSI score following PDL which could possibly be justified by koebnerization.

Hern et al. in two studies ^{10,18} concluded that vascular disorders in psoriasis can even affect deeper feeding vessels in the reticular dermis. This could challenge the effect of PDL on psoriasis since in many studies, the effect of PDL was shown to be confined to superficial capillaries.

In the group treated with betamethasone, the difference between mean baseline PSI score and mean PSI scores at weeks 6 and 24 were significant which clearly demonstrated the effectiveness of betamethasone. However, the difference of mean PSI scores between weeks 4, 6, 12 and 24 were not significant which denoted early relapse after cessation of treatment.

Our results showed that PDL was less effective in comparison with betamethasone and lack of difference in mean PSI score between these two groups at week 24 could be possibly due to the relapse of the betamethasone treated lesions.

In a study by Ilkanar et al,¹⁷ topical steroid (clobetasol) was proved to be more effective than PDL. On the contrary, PDL was introduced to be more effective than topical steroid in some other studies. For instance, Zelickson et al¹⁹, found that PDL more effective than triamcinolone ointment; however, triamcinolone is a low potent topical steroid. In the study by Erceg et al,¹⁶ PDL caused a significant decrease in psoriatic severity scale when compared to calcipotriol/betamethasone. Lack of accordance in the results of various studies may be attributed to differences in Fitzpatrick skin type of patients or the differences in PDL fluences. PDL seems to be less effective in darker skins which are more common in our region ²⁰⁻²³. Taibjee et al ⁷, also found that patients with higher skin type showed a lower response to PDL.

In our study, PDL was constantly less effective than 5-FU+ epinephrine. Intralesional 5-FU+ epinephrine and betamethasone were both effective and were not significantly different at weeks 2 and 4 but they were significantly different at weeks 6, 12 and 24 suggesting that in the long term, 5-FU+epinephrine could be more effective than betamethasone. In fact, it provided a longer remission.

The photographic evaluations confirmed PSI score findings between the groups with the best response achieved in the 5-FU+epinephrine group.

The longer effect of intralesional 5-FU+epinephrine than a potent topical steroid along with its lower cost compared to PDL makes it more preferable in the treatment of psoriasis and the patient does not need to repeatedly use ointments or creams. However, the severe pain of injection

besides hyperpigmentation at the site of injection and dose limitation in every injection confines its administration to resistant plaques of extremities and trunk ²⁴. It specially showed a considerable effect in the improvement of resistant palmar-plantar lesions. However, injection in such areas is much more painful than in other body sites. Most of our patients were satisfied with the outcome of 5-FU injection and frequently asked if it could be used to treat other plaques on their body. Regarding its low effectiveness, short remissions and high cost, PDL dose not seem to be an effective choice in psoriasis.

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