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Comparative Study of the Therapeutic Effects of Topical Mometasone Furoate 0.1% Plus Tretinoin 0.05% and Topical Mometasone Furoate 0.1% Plus Eucerin in the Treatment of Vitiligo

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Background: Long-term treatments with topical corticosteroids, for diseases like vitiligo, are associated with the risk of skin atrophy.
Objectives: Recent studies suggest that administration of topical tretinoin, with a corticosteroid, diminishes skin atrophy without impacting the steroid's anti-inflammatory effects.
Patients and Methods: A placebo-controlled, paired-comparison, left-right study was conducted for a period of 6 months on topical tretinoin 0.05% and mometasone furoate 0.1% with topical mometasone furoate 0.1% and eucerin in 16 patients, diagnosed with generalized vitiligo. Clinical responses and side effects were assessed after 3 and 6 months.
Results: After 6 months treatment with topical mometasone furoate 0.1 % and tretinoin 0.05%, an excellent response was found in two (12.50%) patients, a moderate response in 13 (81.25%) and mild response in one (6.25%) patient. Two patients (12.5%) showed side effects. After 6 months treatment with topical mometasone furoate 0.1% and eucerin, an excellent response was observed in one (6.25%) patient, a moderate response in eight (50%), mild response in six (37.5 %), and no response in one (6.25%) of the patients. Eight (50%) patients had side effects. After 6 months treatment, the topical tretinoin 0.05% and mometasone furoate 0.1% had more efficacy than mometasone furoate 0.1% and eucerin (P = 0.02).
Conclusions: Combination therapy with tretinoin plus topical corticosteroids is safe and effective and provides an alternative in the treatment of patients with vitiligo.

Keywords: Vitiligo; Tretinoin; Mometasone; Therapeutic Efficacy; Safety

1. Background

Vitiligo is a common disease that affects 1% - 2% of general population. Such a disease is a pigmentary disorder due to loss of normal melanin pigment in the skin (1). Possible causes include autoimmunity, autotoxicity and neural hypotheses (2). An important challenge in dermatology is the treatment of vitiligo (3). Up to now, researchers usually employed grafting, transplantation, photochemotherapy, topical and oral immunosuppressant, topical immunomodulators and cosmetic camouflage to improve this disease (3, 4). Although topical corticosteroids are also an effective treatment, they must be used for long term, inducing side effects like cutaneous atrophy and telangiectasia (5, 6). Corticosteroids induce repigmentation in vitiligo lesions, through its anti-inflammatory effects (6).

Topical tretinoin does not reduce anti-inflammatory effects of topical corticosteroids and decreases the skin atrophy associated with their long term use (7-9).

2. Objectives

This study was hence conducted to assess the efficacy of topical corticosteroid plus topical tretinoin in vitiligo, with regard to appearance and complications, by comparing it with the effect of topical corticosteroid plus topical eucerin.

3. Patients and Methods

This clinical trial study used a placebo-controlled, paired-comparison, left-right design to compare the effect of topical mometasone furoate 0.1% plus topical tretinoin 0.05% with topical mometasone furoate 0.1% plus topical eucerin, on the healing of vitiligo lesions. This study was conducted in the dermatology clinic of Rasool-e-Akram, hospital, Iran university of medical sciences, Tehran, Iran, from December 2013 through September 2014. We enrolled patients who were between 18-50 years of age, who had gotten no treatment during the last 2 months. We excluded pregnant or lactating patients, and

patients with systemic illness or psychological disorders or other dermatologic diseases. The number, size, and location of lesions, skin type and the results of follow ups were recorded in a data collection form. The lesions of contralateral sides were selected for the comparison of the two therapies. In the case of multiple lesions, we selected the ones that were preferred by patients. The assessment of vitiligo lesion was performed before beginning of treatment. The drugs were administered for a period of 6 months. When topical mometasone furoate 0.1% plus topical tretinoin 0.05% was applied to the right side, topical mometasone furoate 0.1% plus topical eucerin was applied to the left side (twice daily, with an interval of 15 - 20 minutes between each application). At the beginning of this study, hidden codes were allocated to the cases, inside closed envelopes. At the beginning of the study, the envelopes were opened, which included the detailed data about the treatment methods to be applied on the left and right sides. One fingertip unit for each drug was enough material to treat an area of skin, twice the size of an adult's hand. The patients were asked to return for examination after 3 and 6 months to check improvement or any complication. The clinical assessment of the lesions was based on observation. Clinical imaging was performed with a digital 14 megapixel Samsung camera (Samsung, Seoul, South Korea). The images taken before the study were compared with those taken after 3 and 6 months of treatment. One research blinded dermatologist examined the lesions and assessed the improvement and any side effect. To evaluate the efficacy, repigmentation of vitiligo was considered. We classified efficacy of treatment as excellent improvement (> 75% improvement in comparison with the baseline), moderate improvement (50% - 75% improvement), mild improvement (25% - 50% improvement) and without improvement (< 25% improvement in comparison with baseline). An exact P value less than 0.05 was considered to be statistically significant. Wilcoxon Signed rank test was performed for comparison of the two treatments, in months 3 and 6 of therapy. Also, this test was applied for comparing the therapeutic effects of each treatment over time. The institutional ethics committee approved this study. Verbal informed consent was obtained from the participants, after relevant explanation about the aims and process of the study. No extraordinary facilities or expenditures were directed to people, based on acceptance or decline of the enrollment in the trial. In any part of study, the participants could request to exit the performance, without any limitation or prerequisite. Besides, all the patients' information was saved carefully, to prevent undesirable leak to ensure suitable privacy for recruited people.

4. Results

We selected 21 patients who fulfilled the selection criteria of the study. Five patients were lost to follow up. The demographic details of patients were as follows: the mean ± SD age of the patients was 38.94 ± 9.63 years (range 25 - 55 years). The median duration of the disease was 12 months (range 3 - 36 months). Out of 16 patients, seven (43.75%) were male and nine patients were (56.25%) female. Seven patients (43.75%) had positive family history of vitiligo. Limbs were the most involved body location of vitiligo lesion (50%), while the trunk accounted for 37.5% and head and neck 12.5% of the patients. Fitzpatrick skin types III, IV and V were observed in four (25%), 10 (62.5%) and two (12.5%) of patients, respectively.

Table 1 shows the frequency distribution of patients with vitiligo, classified according to their improvement in comparison with baseline.

Patients treated with topical mometasone furoate 0.1% plus topical tretinoin 0.05% had no significant change in month 6, in comparison with month 3 (P = 0.12). Also, no significant change in month 6, compared to month 3, was observed in the side treated with topical mometasone furoate 0.1% plus topical eucerin (P = 0.25).

A significant difference was found between the two treatments after 3 months of therapy (P = 0.03). Also, the two treatments differed significantly after 6 months of therapy (P = 0.02), (Figure 1).

Table 1. Frequency Distribution of Patients With Vitiligo, Classified According to the Improvement in Comparison With Baseline [a]

Variables	Follow-Up Visits			
	No Improvement	Mild	Moderate	Excellent
Topical Mometasone Furoate 0.1% Plus Topical Tretinoin 0.05%				
Month 3	4 (25)	3 (18.75)	8 (50)	1 (6.25)
Month 6	1 (6.25)	6 (37.5)	8 (50)	1 (6.25)
Topical Mometasone Furoate 0.1% Plus Topical Eucerin				
Month 3	0	4 (25)	11 (68.75)	1 (6.25)
Month 6	0	1 (6.25)	13 (81.25)	2 (12.5)

[a] The values are expressed as No. (%).

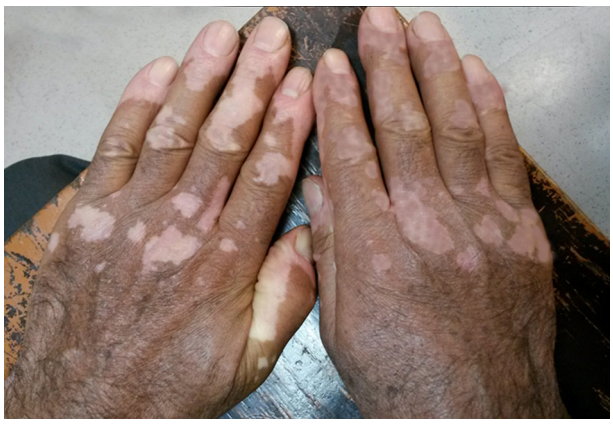

Figure 1. Comparison of the Therapeutic Effects in a Patient

We had a special case in our study, too. On the left hand of this case, after 6 months treatment with topical mometasone furoate 0.1% plus topical eucerin, no improvement was observed. However, on the right hand of this case, after 6 months treatment with topical mometasone furoate 0.1% plus topical tretinoin 0.05%, an excellent improvement was observed.

5. Discussion

Skin atrophy due to prolonged use of corticosteroid is a major concern. Therefore, finding an agent, which prevents skin atrophy secondary to corticosteroid use, and, at the same time, it does not interfere with the anti-inflammatory effect of corticosteroid, is a great benefit. In this study, side effects due to vitiligo treatment with topical corticosteroid, in patients who used, at the same time, topical retinoid, were significantly lower. In addition, an important finding in this study was the positive effect of topical mometasone furoate 0.1% plus topical tretinoin 0.05% on repigmentation, in patients with vitiligo.

In our study, the beneficial effects of topical mometasone furoate 0.1% plus topical tretinoin 0.05%, in comparison with topical mometasone furoate 0.1% plus topical eucerin, on repigmentation, were significant ($P = 0.02$).

We used topical mometasone furoate 0.1% plus topical tretinoin 0.05% to reduce side effects of prolonged use of topical corticosteroids and we observed improvement in the therapeutic effect on vitiligo, in four patients (25%) after 3 months and in six patients (37.5%) after 6 months.

In addition, the effect of topical mometasone furoate 0.1% plus topical tretinoin 0.05% on repigmentation occurred within 6 months. The rapid response is another benefit of this treatment.

Results were unexpected because tretinoin is a popular drug to reduce hyperpigmented lesions in photodamaged skin (1). Yoshimura et al. (10) conducted a study to investigate about this issue. They found that tretinoin does not exert any suppressing effect on melanogenesis in pigmented skin equivalents. There were no direct inhibitory effects on interactions between melanocytes, keratinocytes and fibroblasts or on paracrine actions related to melanin production (10). The effect of tretinoin on melanogenesis and its mechanism of action on the treatment of hyperpigmented lesions are not yet entirely elucidated.

Although there was a favorable report on the use of a composition of clobetasol propionate plus tretinoin on vitiligo, however, similar to the effects of tretinoin on hyperpigmented lesions, the mechanism explaining the beneficial effects of tretinoin on repigmentation of patients with vitiligo is unknown, too (11). This phenomenon may be related to the protective effect of retinoic acid on autoimmune diseases like vitiligo. Retinoic acid inhibits proliferation of T helper17 and therefore inhibits auto-immunity, which could be the cause of the positive effects of tretinoin on repigmentation (12). Retinoic acid increases expression of foxp3 and create CD 4iTreg, whereas retinoic acid does not increase expression of foxp3 on CD8+ cell. Consequently, retinoic acid causes progression in development of transforming growth factor-beta (TGF-beta) CD4 foxp3 that inhibits auto-immune diseases (13). Retinoic acid is a powerful anti-proliferative and anti-inflammatory agent and inhibits the production of Th1 cytokines. In accordance, in a research on mice, treatment with retinoic acid on systemic lupus erythematous prone NZB/WF1 mice decreased auto-immune nephritis and increased survival and, therefore, retinoic acid may represent a novel treatment approach for lupus nephritis (14). Furthermore, retinoic acid increases expression of aquaporin-3 (that is decreased in depigmented epidermis) in epidermal keratinocytes and decreases keratinocytes survival (15, 16). Multiple studies showed that tretinoin also decreases thickness of horney layer and decreases number of cell layers and, therefore, increases the absorption of other topical drugs, like topical antibiotics (17, 18).

Combination therapy with topical mometasone furoate 0.1% plus topical tretinoin 0.05% in vitiligo is safe and effective and may become a new treatment alternative in this disease. More research is necessary for detecting the mechanism responsible for the positive effect of tretinoin in patients with vitiligo. It must be noted that evaluating the pigmentation with mexameter provides a high accuracy in results. Therefore, future studies with mexameter evaluation are recommended.

References

1. Goldfarb MT, Ellis CN, Voorhees JJ. Topical tretinoin: its use in daily practice to reverse photoageing. *Br J Dermatol.* 1990;**122 Suppl 35**:87–91.
2. Gilchrest BA. Retinoids and photodamage. *Br J Dermatol.* 1992;**127 Suppl 41**:14–20.
3. Koster W, Wiskemann A. [Phototherapy with UV-B in vitiligo]. *Z Hautkr.* 1990;**65**(11):1022–4.
4. Xu AE, Zhang DM, Wei XD, Huang B, Lu LJ. Efficacy and safety of tarcrolimus cream 0.1% in the treatment of vitiligo. *Int J Dermatol.* 2009;**48**(1):86–90.
5. Griffiths CE, Russman AN, Majmudar G, Singer RS, Hamilton

TA, Voorhees JJ. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med.* 1993;**329**(8):530–5.
6. Kwon HB, Choi Y, Kim HJ, Lee AY. The therapeutic effects of a topical tretinoin and corticosteroid combination for vitiligo: a placebo-controlled, paired-comparison, left-right study. *J Drugs Dermatol.* 2013;**12**(4):e63–7.
7. Lesnik RH, Mezick JA, Capetola R, Kligman LH. Topical all-trans-retinoic acid prevents corticosteroid-induced skin atrophy without abrogating the anti-inflammatory effect. *J Am Acad Dermatol.* 1989;**21**(2 Pt 1):186–90.
8. De Lacharriere O, Escoffier C, Gracia AM, Teillac D, Saint Leger D, Berrebi C, et al. Reversal effects of topical retinoic acid on the skin of kidney transplant recipients under systemic corticotherapy. *J Invest Dermatol.* 1990;**95**(5):516–22.
9. Kligman LH, Schwartz E, Lesnik RH, Mezick JA. Topical tretinoin prevents corticosteroid-induced atrophy without lessening the anti-inflammatory effect. *Curr Probl Dermatol.* 1993;**21**:79–88.
10. Yoshimura K, Tsukamoto K, Okazaki M, Virador VM, Lei TC, Suzuki Y, et al. Effects of all-trans retinoic acid on melanogenesis in pigmented skin equivalents and monolayer culture of melanocytes. *J Dermatol Sci.* 2001;**27 Suppl 1**:S68–75.
11. Parsad D, Saini R, Juneja A. Combination of clobetasol and tretinoin in vitiligo -letter. *Int J Dermatol.* 2000;**39**(8):639–40.
12. Xiao S, Jin H, Korn T, Liu SM, Oukka M, Lim B, et al. Retinoic acid increases Foxp3+ regulatory T cells and inhibits development of Th17 cells by enhancing TGF-beta-driven Smad3 signaling and inhibiting IL-6 and IL-23 receptor expression. *J Immunol.* 2008;**181**(4):2277–84.
13. Ma J, Liu Y, Li Y, Gu J, Liu J, Tang J, et al. Differential role of all-trans retinoic acid in promoting the development of CD4+ and CD8+ regulatory T cells. *J Leukoc Biol.* 2014;**95**(2):275–83.
14. Kinoshita K, Yoo BS, Nozaki Y, Sugiyama M, Ikoma S, Ohno M, et al. Retinoic acid reduces autoimmune renal injury and increases survival in NZB/W F1 mice. *J Immunol.* 2003;**170**(11):5793–8.
15. Bellemere G, Von Stetten O, Oddos T. Retinoic acid increases aquaporin 3 expression in normal human skin. *J Invest Dermatol.* 2008;**128**(3):542–8.
16. Cao C, Wan S, Jiang Q, Amaral A, Lu S, Hu G, et al. All-trans retinoic acid attenuates ultraviolet radiation-induced down-regulation of aquaporin-3 and water permeability in human keratinocytes. *J Cell Physiol.* 2008;**215**(2):506–16.
17. Hguyen QH, Kim YA, Schwartz RA. Management of acne vulgaris . *Am Fam Physician.* 1994;**50**(1):89.
18. Kubbak R, Bajaj AK, Thappa DM. Topical Retinoids. *Indian J Dermatol Venerol Leprol.* 2009;**75**(NUM S1):28–30.