Role of the ACTH test and estimation of a safe dose for high potency steroids in vitiligo: A prospective randomized study

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ABSTRACT

**Background:** Topical corticosteroids are used as first line of therapy for vitiligo, although side effects such as adrenal insufficiency are possible. **Objectives:** To establish the role of ACTH test before, during, and after treatment with high potency topical steroids; to determine if adrenal insufficiency occurs secondary to the use of high potency topical steroids in patients with vitiligo and intact cutaneous barrier; and also to determine response to treatment and side effects. **Materials and Methods:** Forty-four adults with non-segmental vitiligo affecting 20% or less of the body surface area were included and randomized to receive topical clobetasol propionate 0.05% cream (group 1) or placebo (group 2) for 12 weeks, with a maximum dose of 50 g per week. The placebo group was crossed over after week 6 and started on clobetasol until completion of the study. Serum cortisol levels with the 1 µg ACTH test were determined at baseline and on weeks 6 and 12. **Results:** No adrenal insufficiency was detected nor statistical significance was achieved when comparing cortisol levels between and within the groups at baseline and weeks 6 and 12. Group 1 had a better response to therapy but with more side effects. **Conclusions:** Doses of 50 g or less per week of clobetasol during a period of 12 weeks are safe on adult vitiligo patients, although local side effects are possible. Repigmentation rates were incomplete with single steroid therapy, making combined therapy a better option.

Key words: Adrenal insufficiency, cortisol, topical steroids, vitiligo

INTRODUCTION

Vitiligo is the most common depigmenting disorder affecting 0.5% of the population. It occurs in half of patients before the age of 20 years and in a quarter before the age of 8 years. The two sexes are equally affected and there are no apparent differences in rates of occurrence according to skin type or race. Nonsegmental vitiligo is the most common form of disease, accounting for 85-90% of cases overall. The initial cause of nonsegmental vitiligo is still debated but appears to involve immunologic factors, oxidative stress, or a sympathetic neurogenic disturbance. Current treatment modalities aim to stimulate melanocyte proliferation or interfere with neural/inflammatory factors affecting melanocyte structure or function; however, no single treatment method has been found that is consistently effective with relatively few side effects. Topical corticosteroids are generally the first line of therapy in both children and adults with vitiligo. For generalized symmetrical types of vitiligo, topical clobetasol used over 2-6 months repigments vitiligo to some degree. Recent guidelines recommend in children and adults with recent onset of vitiligo, that single treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months. Topical corticosteroid preparations are categorized from Class I to VII according to potency determined by the vasoconstrictor assay. With the introduction of super high potency topical corticosteroids, potential for both local and systemic side effects increased. Adrenal insufficiency is a hormone deficiency syndrome attributable to primary adrenal diseases or caused by a wide variety of pituitary-hypothalamic disorders. Secondary adrenocortical insufficiency results from ACTH.
deficiency in the pituitary gland. Excessive glucocorticoid therapy is the primary cause of adrenocortical insufficiency. In general, high potency topical corticosteroids (class I) such as clobetasol propionate and halobetasol propionate can produce a reversible laboratory adrenocortical insufficiency, while lower potency corticosteroids generally do not. As little as 2 g per day of clobetasol propionate 0.05% can cause a decrease in morning cortisol after a few days only. The reactivity of hypothalamic-pituitary-adrenal (HPA) axis can be assessed with ACTH test and wherein plasma cortisol levels are measured prior to and after a bolus administration of 250 µg of synthetic α-1-24-adrenocorticotropic hormone. Some data, however, suggest that i.v. administration of 250 µg cosyntropin could be a pharmacological rather than a physiological stimulus, losing sensitivity for detecting adrenocortical failure. More sensitive and accurate, the low dose 1 µg ACTH test is as simple and safe as the standard 250 µg test. As an initial assessment of HPA function, this test has proved to be much more robust than high dose test, yet it retains all advantages of the latter (sensitivity: 93.1%, specificity: 90%, and accuracy: 90%). In a meta-analysis of 12 studies (635 subjects), a basal cortisol less than 5 µg/dl (138 nmol/l) best predicted hypothalamic-pituitary-adrenal insufficiency (HPAI), while other meta-analysis of 11 studies (589 subjects) found that values less than 16 µg/dl (440 nmol/l) at 30 min best predicted HPAI.

Objectives

To determine if adrenocortical insufficiency occurs secondary to the use of class I (high potency) topical steroids in patients with vitiligo and intact cutaneous barrier; to establish the role of measuring plasma cortisol levels by performing the ACTH test before, during, and after treatment with high potency topical steroids; and finally to determine other side effects and response to treatment.

MATERIALS AND METHODS

This was a prospective, randomized, double-blinded and single crossover study in which patients of 18-years or older with localized or disseminated vitiligo and with an affected body surface area of 20% or less were included. We excluded patients with segmental vitiligo, those with history use of steroids or any other medications within the past year that could interfere with steroid or cortisol metabolism, metabolic or autoimmune diseases, adrenal insufficiency, HIV, psychiatric disorders, pregnancy, lactation, granulomatous diseases, neoplasms, and panhypopituitarism. We also considered the stability of vitiligo as 1 year with no changes. After the screening visit, where a complete physical exam and determination of the affected body surface area (1 hand with fingers by the palmar side = 1% body surface area) were performed, informed consent was signed, and then the 1 µg ACTH test was performed before starting treatment and again on weeks 6 and 12. For this test, a disposable 21G infusion kit (Terumo Corporation, Tokyo Ind) was used to draw venous blood samples and also to infuse synthetic 1-24 ACTH (Cortrosyn, Amphastar). On each test, blood samples were obtained before (basal) and after 30 min of the infusion of ACTH. Commercial electrochemiluminescence kits (Elecsys 2010, Roche Hitachi) were used to determine plasma cortisol levels. All samples were processed by duplicate, with intra- and inter-assay coefficients of variation determined for low, mid, and high values up to the moment when measures were performed. After having results from the screening visit and if normal, patients were randomized and assigned into group 1 (clobetasol propionate 0.05% cream during 12 weeks) or group 2 (placebo during 6 weeks and then clobetasol propionate 0.05% cream during 6 weeks). Treatment was manufactured and prepared into plastic jars that contained 50 g of steroid or placebo. Patients were instructed to apply the treatment once a day with fingertip unit only for vitiligo areas of the neck, trunk, and extremities; and once a day, on an on-and-off weekly basis on the face, axilla, genital area, and groins during 12 weeks, with a maximum of one jar (50 g) per week. After week 6, patients from group 2 were crossed over to start treatment with clobetasol propionate 0.05% cream for the remaining 6 weeks. All patients were appointed for medical follow-up every three weeks until the completion of the study (week 12); where complete physical exam, determination of the affected body surface area in percentage, follow-up pictures, adverse effects, and amount of treatment used per week were recorded. An analytic weight was used to calculate the amount of grams used per week, that is, by weighing all the used returned jars. The amount of cream leftovers then was substracted from the original weight on every jar. Adrenocortical insufficiency was considered for any baseline cortisol level less than 5 µg/dl or less than 16 µg/dl after the 30 min i.v. infusion of 1 µg ACTH. Response to treatment was evaluated by percentage of repigmentation achieved at week 12 (or the last follow-up visit) from baseline as follows: Worsening of the affected body surface area, no repigmentation, mild repigmentation (<25%), moderate repigmentation (25-50%), good repigmentation (51-75%), and very good repigmentation (>75%). Response to treatment was considered if 25% or more repigmentation of the total affected body surface area was achieved. All data was stored and analyzed with SPSS Statistics program (V.17). Analysis of Variance (ANOVA) was performed to compare intragroup cortisol levels at different time points: Baseline, weeks 6, and 12 in both groups. The Mann-Whitney test was also performed for non-normally distributed continuous data at baseline, weeks 6, and 12 in order to compare intergroup cortisol levels. Chi-square test was used for categorical variables and to determine response to treatment. All P values equal to or less than 0.05 were considered statistically significant. This study was approved and based in accordance with the ethical standards of our institution’s Ethical and Investigation Committee on Human experimentation and with the Declaration of Helsinki (1975), as revised in 2000.
RESULTS

A total of 22 males and 22 females (N = 44) were included. In each group, there were 11 males and females, respectively. Mean ages for group 1 and 2 were 35.05 (range: 18-59 years) and 35.62 (range: 18-57 years), respectively. In both groups, unstable vitiligo predominated, 16 in group 1 and 18 in group 2. The mean affected body surface area was 8.5% (range: 1-18) for group 1 and 7.64 (range: 1-20) for group 2. Mean weekly dose in both groups were similar, 23.38 g in group 1 and 24.92 g in group 2 [Table 1]. One patient from each group voluntarily retired from the study at week 9.

After determining cortisol levels and comparing the intergroup values, basal and 30 min cortisol levels were higher in group 1 except at week 12. The statistical analysis between both groups at week 0 (P = 0.078), week 6 (P = 0.542), and week 12 (P = 0.91) was not significant. The intragroup values in group 1 showed progressive decreasing cortisol levels from week 0 (basal = 18.59, 30 min = 27.25) to week 6 (basal = 15.82, 30 min = 24.83) and week 12 (basal = 15.51, 30 min = 24.62), respectively; while also decrease in cortisol levels occurred in group 2 but only from week 0 (basal = 15.79, 30 min = 25.44) to week 6 (basal = 14.89, 30-min = 23.65), but not on 12 week (basal = 15.82, 30-min = 26.72) where surprisingly cortisol reached its top level. The statistical analyses in both groups for basal and 30-min cortisol levels were also not significant [Tables 2 and 3]. None of the 44 patients enrolled in the study fulfilled the criteria for adrenocortical insufficiency, including two patients that retired at week 9.

After examining treatment response or failure, our data demonstrated that there were more patients who responded to treatment in group 1 than in group 2 (7 vs 1, respectively). By the same way, there were more treatment failures in group 2 than in group 1 (21 vs 15, respectively). The statistical analysis between both groups was significant (P = 0.019) [Table 4].

A total of 57 adverse effects were present in 28 patients (63.63%), being most from group 1 (36). The most frequent were pruritus, acne, and xerosis. It is important to emphasize that five cases of acne, two of contact dermatitis, and one of folliculitis developed in group 2 after being crossed over and started on clobetasol. Only three patients developed telangiectasias and one cutaneous atrophy, all in group 1. For statistical analysis and comparison of adverse effects between groups, patients form group 2 were further subdivided into side effects that occurred during weeks 0-6 (placebo) and during weeks 7-12 (clobetasol). The only statistical significant adverse effects found were acne (P = 0.035), telangiectasias (P = 0.043), and xerosis (P < 0.001) [Table 5].

DISCUSSION

The first reports about adverse effects of topical corticosteroids became available in 1955 after the use of fludrocortisone. Less commonly; local hypertrichosis,
hypopigmentation, glaucoma, and allergic contact dermatitis occurred.\cite{21} The potential systemic side effects of their use include diabetes, hypertension, and HPA axis suppression.\cite{9} Allenby et al.,\cite{22} reported adrenal suppression in as many as 64% of adult patients with lichen planus, atopic dermatitis, and psoriasis (altered skin barrier) when using 50 g or more of potent class I topical corticosteroids (clobetasol propionate) for greater than 2 weeks. On the contrary, similar serum cortisol levels were achieved in both patients with lichen planus (altered skin barrier) and healthy volunteers treated for 3 weeks with 500 mg of a 0.05% fluocinonide gel (class II) three times a day for 3 weeks.\cite{12} Additionally, Wester et al.,\cite{23} found no significant difference in the percentage of hydrocortisone (class VII) absorbed in psoriatic human skin, as compared with healthy skin. This can be explained by the different steroid potency and vehicles used, and also because of higher doses and altered cutaneous barrier in most of these studies, as compared with our study where a strict maximum dose of 50 g per week and intact cutaneous barrier were considered. These seem reasonable explanations for the results found in our study where no adrenocortical alterations were found for up to 12 weeks while on steroid treatment, and the importance of the ACTH test. We also consider that further studies are needed if the dose of 50 g per week is going to be used for longer than 12 weeks. It is also important to consider that in our study only adults were included. Nevertheless, the risk of adrenocortical insufficiency in children can be possible and dependable on steroid potency, frequency of application, affected body surface area, and barrier function of the skin. This has been demonstrated by Kwinter et al.,\cite{24} in a retrospective study, where abnormal cortisol levels were found in 29% of pediatric patients with vitiligo (intact skin barrier) and topical steroids (moderate to high potency, 1-4 applications per day, daily and on-and-off regimens for 3-8 weeks). Head and neck were involved in 67% of patients. The children with head and neck involvement were 8.26 times more likely to have an abnormal cortisol level compared with children with other affected areas.\cite{2} In our study we also included patients with head and neck involvement, and again no adrenocortical alterations were found.

Despite its proven strength, it should be emphasized that the 1 µg ACTH stimulation remains a screening test. However, it can replace the standard high dose ACTH stimulation in screening for adrenal insufficiency.\cite{19} By knowing the accuracy and precision of the 1 µg ACTH test and that no significant statistical differences were found in both inter- and intragroup cortisol values, we consider this test as nonessential in adults, but only if intact cutaneous barrier is present and the maximum steroid dose is not exceeded. Regarding local adverse effects, cutaneous atrophy has been considered the most common side effect,\cite{10} but in our study we found that the most common was pruritus followed by acne and xerosis. This can be evidenced by decreased formation of lipid lamellar bodies and delayed barrier recovery with increased transepidermal water loss.\cite{24,28} Although it was not frequent (only three cases), but with statistical significance, the risk of developing telangiectasias has to be considered as steroids stimulate human dermal microvascular endothelial cells, being characterized by an abnormal dilatation of capillary vessels and arterioles.\cite{26} Non-mycotic cutaneous infections were the most common infections (foliculitis and herpes), with lower rates as compared to other studies (6.8 vs 16-43%).\cite{27} Vitiligo response to steroid treatment is variable. In children, Kwinter et al.,\cite{2} reported repigmentation rates of 64%, but many combination regimens and more than single day application treatments were included.

The studies of Clayton et al.,\cite{28} and Kandil et al.,\cite{29} showed that the use of a highly potent (clobetasol) or potent (betamethasone) topical steroid can repigment vitiligo, but only in a small proportion of cases. Clayton found 15-25% repigmentation in 10 of 23 subjects (ages not stated) and >75% in two of 23 (the other 11 showed no response),\cite{28} while Kandil et al.\cite{29} found 90-100% repigmentation in six of 23 subjects (ages not given for all but one was aged 12 years) and 25-90% in three (with six showing ‘beginning’repigmentation).\cite{28} Westerhof et al.,\cite{30} in probably the best controlled study to date of a topical treatment, compared topical fluticasone alone or combined with Ultraviolet A (UVA) phototherapay in 135 adults. They found that the potent topical steroid fluticasone used alone for 9 months induced mean repigmentation of only 9% (compared with UVA alone of 8%) whereas the combination of fluticasone and UVA induced mean repigmentation of 31%.\cite{30} Although in our study, response to treatment was present in 8 of 44 patients (18%), we believe that this finding was due to the short period of treatment (6 or 12 weeks) and also because a single day application regimen was used. If patients with any percent of repigmentation (17 of 44) are included, the percentage of response increases to 38.63% (vs 64%,\cite{2} 52%,\cite{28} 39%,\cite{29} and 9%\cite{30}). With this taken into consideration, we also believe that topical steroids could be an acceptable treatment option with the regimen employed in this study, but for longer periods of time or in combination with other treatment modalities, even the actual guidelines describe the evidence that very potent or potent topical corticosteroids can repigment vitiligo in adults. It also has to be considered that the studies supporting this statement have been poorly conducted and side-effects are common if treatment lasts for more than a few weeks. As the guideline suggests, treatment with a potent or very potent topical steroid should be considered for a trial period of no more than 2 months in children and adults with recent onset of vitiligo.\cite{9}
to be safe in adults, lacking the capacity to induce significant adrenocortical alterations if we take as a reference cortisol levels before, during, and after treatment and also against placebo. If the maximum dose (50 g per week) of high potency topical steroids in adults is not exceeded, it is not necessary to perform the ACTH test. Even class I topical steroid treatment has shown to be an acceptable option for vitiligo, it seems to be incomplete as a single therapy as presented in our study, making combined therapy a better option. Treatment for 12 weeks has a better response than treatment for 6 weeks, although local adverse effects are possible.

REFERENCES

1. Taïeb A, Picardo M. Clinical practice. Vitiligo. N Engl J Med 2009;360:160-9.
2. Kwinter J, Pelletier J, Khambalia A, Pope E. High-potency steroid use in children with vitiligo: A retrospective study. J Am Acad Dermatol 2007;56:236-41.
3. Howitz J, Brodhagen H, Schwartz M, Thomsen K. Prevalence of vitiligo. Epidemiological survey on the Isle of Bornholm, Denmark. Arch Dermatol 1977;113:47-52.
4. Boisseau-Garsaud AM, Garsaud P, Calés-Quist D, Hélénron R, Quénéhervé C, Claire RC. Epidemiology of vitiligo in the French West Indies (Isle of Martinique). Int J Dermatol 2000;39:18-20.
5. Hann SK, Lee HJ. Segmental vitiligo: Clinical findings in 208 patients. J Am Acad Dermatol 1996;35 (5 Pt 1):671-4.
6. Njoo MD, Westerhof W, Bos JD, Bossuyt PM. The development of guidelines for the treatment of vitiligo. Clinical Epidemiology Unit of the Istituto Dermopatico dell’Immunità-Instituto di Recupero e Cura a Carattere Scientifico (IDI-IRCCS) and the Archives of Dermatology. Arch Dermatol 1999;135:1514-21.
7. Mandel AS, Haberman HF, Pawlowski D, Goldstein E. Non PUV A nonsurgical therapies for vitiligo. Clin Dermatol 1997;15:907-19.
8. Gawkrodger DJ, Ormerod AD, Shaw L, Mauri-Sole I, Whitton ME, Watts MJ, et al. Guidelines for the diagnosis and management of vitiligo. Br J Dermatol 2008;159:1051-76.
9. Gilbertson EO, Spellman MC, Piacquadio DJ, Mulford MJ. Super potent topical corticosteroid associated with adrenal suppression: Clinical considerations. J Am Acad Dermatol 1998;38 (2 Pt 2):318-21.
10. Bouillon R. Acute adrenal insufficiency. Endocrinol Metab Clin North Am 2006;35:767-75.
11. Levin C, Maibach HI. Topical corticosteroid-induced adrenocortical insufficiency: Clinical implications. Am J Clin Dermatol 2002;3:141-7.
12. Olsen EA, Cornell RC. Topical clobetasol-17-propionate: Review of its clinical efficacy and safety. J Am Acad Dermatol 1986;15 (2 Pt 1):246-55.
13. Henge UR, Ruzicka T, Schwart RA, Cork MJ. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 2006;54:1-15.
14. González-González JG, De la Garza-Hernández NE, Mancillas-Adame LG, Montes-Villarreal J, Villarreal-Pérez JZ. A high-sensitivity test in the assessment of adrenocortical insufficiency: 10 microg vs 250 microg cosyntropin dose assessment of adrenocortical insufficiency. J Endocrinol 1998;159:275-80.
15. Tordjman K, Jaffé A, Trostanetsky Y, Greenman Y, Limor R, Stern N. Low-dose (1 microgram) adrenocorticotropic (ACTH) stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis function: Sensitivity, specificity and accuracy in comparison with the high-dose (250 microgram) test. Clin Endocrinol (Oxf) 2000;52:633-40.
16. Kazlauskaitė R, Evans AT, Villabona CV, Abdu TA, Ambrosi B, Atkinson AB, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: A metaanalysis. J Clin Endocrinol Metab 2008;93:4245-53.
17. Fitzpatrick TB, Griswold HC, Hicks JH. Sodium retention and edema from percutaneous absorption of fludrocortisone acetate. J Am Med Assoc 1955;158:1149-52.
18. Cornell RC, Stoughton RB. Use of glucocorticosteroids in psoriasis. Pharmacol Ther 1980;11:497-508.
19. Barnetson RS, White AD. The use of corticosteroids in dermatological practice. Med J Aust 1992;156:428-31.
20. Takeda K, Arase S, Takahashi S. Side effects of topical corticosteroids and their prevention. Drugs 1988;36 Suppl 5:15-23.
21. Piérard GE, Piérard-Franchimont C, Ben Mosbah T, Arrese Estrada J. Adverse effects of topical corticosteroids. Acta Derm Venereol Suppl (Stockh) 1989;151:26-30.
22. Allenby CF, Main RA, Marsden RA, Sparkes CG. Effect on adrenal function of topically applied clobetasol propionate (Dermovate). Br Med J 1975;4:619-21.
23. Wester RC, Bucks DA, Maibach HI. In vivo percutaneous absorption of hydrocortisone in psoriatic patients and normal volunteers. J Am Acad Dermatol 1983;8:645-7.
24. Sheu HM, Lee JY, Chai CY, Kuo KW. Depletion of stratum corneum intercellular lipid lamellae and barrier function abnormalities after long-term topical corticosteroids. Br J Dermatol 1997;136:884-90.
25. Kao JS, Flour JW, Man MQ, Fowler AJ, Hachem JP, Crumrine D, et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: Inhibition of epidermal lipid synthesis accounts for functional abnormalities. J Invest Dermatol 2003;120:456-64.
26. Hettmannsperger U, Tenorio S, Orfano CE, Detmar M. Corticosteroids induce proliferation but do not influence TNF- or IL-1 beta-induced ICAM-1 expression of human dermal microvascular endothelial cells in vitro. Arch Dermatol Res 1993;285:347-51.
27. Aucott JN. Glucocorticoids and infection. Endocrinol Metab Clin North Am 1994;23:655-70.
28. Clayton R. A double-blind trial of 0 - 05% clobetasol propionate in the treatment of vitiligo. Br J Dermatol 1977;96:71-3.
29. Kandil E. Treatment of vitiligo with 0.1 per cent betamethasone 17-valerate in isopropyl alcohol-a double-blind trial. Br J Dermatol 1974;91:457-60.
30. Westerhof W, Nieuweboer-Krobotova L, Muller PG, Glazenburg EJ. Left-right comparison study of the combination of fluticasone propionate and UV-A vs. either fluticasone propionate or UV-A alone for the long-term treatment of vitiligo. Arch Dermatol 1999;135:1061-6.

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