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TO ASSESS THE SAFETY OF DIFFERENT CLASSES OF SYSTEMIC CORTICOSTEROIDS IN A SHORT NON-TAPERED THERAPY FOR ACUTE DERMATOLOGICAL CONDITIONS: A PROSPECTIVE COHORT STUDY

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ABSTRACT **BACKGROUND:** A short non-tapered course of corticosteroids (CS) is desirable, especially for acute steroid responsive dermatological disorders. Oral corticosteroids in short course may seem to be free from significant side effects; however, may be associated with increased risk of hyperglycemia, elevated blood pressure, mood and sleep disturbance and severe conditions like sepsis and venous thromboembolism etc . Thus this study was done to assess the safety of short course corticosteroids in terms of HPA axis suppression/ recovery as well as other systemic side effects. **METHODS:** This was a single-center, open-label, prospective cohort study in which consecutive subjects suffering from acute dermatitis , belonging to the age group of 18 years to 40 years were recruited. The three equal study Groups-A, -B and -C received Hydrocortisone, Prednisolone and Betamethasone, respectively in single morning doses of 0.5 mg/kg body weight equivalent of Prednisolone over 5 days. Routine investigation and Morning basal serum cortisol concentration (to assess HPA axis activity) were measured before, during and two weeks after the study to assess the safety of CSs. **RESULTS:** In our study, all the three CSs were found to have excellent clinical effect and safety. In all the study groups, morning cortisol levels falls below the base line values on first visit, then start to rise on second follow up, however never achieve the baseline values again during the study period. **CONCLUSION:**A five day single-morning-non-tapered dose 0.5 mg/kg body weight of prednisolone equivalent of hydrocortisone, prednisolone and betamethasone are safe.

SUMMARY:

- Short course intensive corticosteroid therapy however safe, but has been known to affect HPA axis reversibly.
- No study is available to address comparative effect of different classes of corticosteroid on HPA axis, particularly in short course of therapy.
- This study has analyzed the effect of effect hydrocortisone, prednisolone and betamethasone, one each from short-, intermediate- and long-acting corticosteroid class, respectively. A short course of corticosteroids is desired in contrast to conventional tapering doses, especially for acute, brief steroid responsive dermatological disorders.

KEYWORDS : Corticosteroids; Hypothalamus-Pituitary-Adrenal (HPA) Axis; Cortisol.

INTRODUCTION

Oral corticosteroids (CS) are probably the most often prescribed systemic dermatological therapy.[1-3] High-dose (>30-40 mg/day); long term (>2-3 weeks) use may cause Hypothalamus-Pituitary-Adrenal (HPA) axis suppression which being most dangerous side effect of the therapy.[4] However, conventionally it is recommended to taper corticosteroid in order to recover the adrenal glands. [5-7] Tapering of steroids increases the total cumulative dose, as well as total duration of steroid consumption. Most of acute dermatological disorders would respond to a very short course of steroids. Thus a short course is desired, especially for acute, short lived dermatological disorders. Available literature suggests safety of short course corticosteroids in reference of HPA axis suppression/recovery. However, in these studies either a single variety of corticosteroids were assessed or the subjects recruited were with systemic disorders / surgeries.[8-11] The HPA axis is known to behave differently in conditions of systemic stress.[6] Also, in dermatological practice, the choice of CS largely depends on the prescriber because till now, for short term therapy, no one class (Short-, Intermediate- or Long-acting) of CS has shown advantage over the other.[7] Furthermore, in recent studies it has been pointed out that prescribing oral corticosteroids in short course may seem to be free from significant side effects; however, may be associated with increased risk of hyperglycemia, elevated blood pressure, mood and sleep disturbance and severe conditions like sepsis and venous thromboembolism etc.[12-13] Thus it is required to assess the safety of short course regimen of commonly prescribed corticosteroids.

A variety of tests have been reported in the literature to evaluate HPA axis insufficiency, screening test like estimation of the morning serum cortisol concentration or the 24 hour urine free cortisol and dynamic tests like the insulin tolerance test or the ACTH stimulation test or the glucagon stimulation test or the Corticotropin-releasing factor or the Acylated ghrelin provocative test. The insulin tolerance test is a cumbersome test during which medical supervision is required. Furthermore, it is contraindicated in patients with epilepsy, cerebro-vascular or cardiovascular disorders, and it needs to be cautiously used in elderly patients.[14] The short ACTH test has a potential risk, albeit small, of allergic reactions.[15] Other tests also have shortcomings in the form of having variable responses or being expensive. Furthermore, several studies have confirmed the utility of morning basal cortisol estimation as an effective screening test for HPA insufficiency.[15-17] Compared to other tests for evaluation of HPA axis, the morning basal cortisol estimation is a cheaper, safer and practical option. Therefore, we utilized morning basal serum cortisol level as a surrogate marker for HPA axis activity.

The aim of this study was to assess the safety of short course corticosteroids in terms of HPA axis suppression/ recovery as well as other systemic side effects.

MATERIALS AND METHOD

The single-center, open-label, cohort study was performed over 24 months in the Department of Dermatology, Venereology and Leprosy of Mahatma Gandhi Memorial Medical College, in association with Maharaja YashwantRao Holkar Hospital, Indore, India. Permission from our institutional ethics committee was granted, prior to initiation of the study. Written informed consent was obtained from all subjects for participation in the study.

A total of 30 eligible candidates between 18-40 years of age were randomly (based on random table) allocated into 3 equal groups: A, B and C. Patient, in the group A, B and C were administered intravenous hydrocortisone, oral prednisolone, oral betamethasone respectively in the dose of 0.5 mg/kg equivalent of prednisolone for 5 days as once a day morning dose. Therapy was not extended beyond 5 days. No topical corticosteroids were given concomitantly, however, topical antibiotics were used when required.

Subject with acute primary cutaneous conditions requiring short

courses of steroid, such as allergic contact dermatitis, irritant contact dermatitis, urticaria / angioedema, photoallergic dermatoses , Polymorphous light eruption (PMLE), paederus dermatitis, were screened for recruitment. However, patients already taking steroid treatment, either topical or systemic or who have received systemic corticosteroids within last 6 months were excluded from study. Similarly, patients requiring long term (>5 days) systemic CS or pulse therapy of intravenous steroids were also excluded. Known cases of diabetes mellitus, hypertensive, thyroid disorder and any other systemic disorders, immunocompromised patients, as well as smokers, chronic alcoholics and drug abusers, and patients carrying out any form of intense physical activity or having psychological stress were also not recruited in the study. During the study period all the subjects very aggressively monitored for systemic side effects

Recruited subjects were investigated for serum basal morning cortisol as well as baseline routine investigations (complete blood count, liver and renal function test, blood sugar, serum electrolyte, thyroid function test) and clinical examination (blood pressure, pulse, weight, edema). Study participants were analysed before, during and two week after the therapy. Blood samples for cortisol determination were collected in the morning between 8 AM to 9 AM. The collections were performed by a peripheral venous access. The volume of blood drawn for sample was 4 ml. The blood sample was sent to the laboratory where cortisol level were determined by performing Chemiluminescence Immunoasssay. The lower and the upper cut-off values for serum cortisol were 4.30 µg/dl and 22.40 µg/dl. The assay was highly specific for cortisol, with low cross-reactivity to other glucocorticoids.

Based on previous studies[10] three morning cortisol samples were collected from all the study participants ; baseline , after 2 days of treatment and after ten days of initial dose. Subjects with all the three cortisol readings were only recruited. Subjects with dearranged baseline investigation were excluded. Subjects excluded in such a manner were replaced to complete the study population according to the protocol.

Statistical analysis

All randomized patients who received study medication and completed the study were included for analysis. The data collected was entered in MS excel sheet and thereby analyzed using the software SPSS version 20.0. For the continuous variables, mean and standard deviation were calculated. The categorical variables were expressed as frequencies and percentages. Inter- and intra-group comparison was done using One-way ANOVA along with Post hoc Bonferroni test for the Pair-vise comparison of the test groups. Repeated measures test was employed to study the change in the Serum cortisol level over time for the group of the steroid given. A p-value <0.05 was considered statistically significant with confidence interval of 95%.

OBSERVATIONS AND RESULTS

Over the study period, a total of 5299 patients were screened for possible recruitment. From these, a total of 38 consenting participants were recruited. Lost to follow up subjects account for the recruitment of extra 8 subjects.

Baseline characteristics of the study participants have been presented in Table-1.The groups appears to be balanced with respect to their baseline characteristics. The values of individual morning cortisol concentrations of all the study participants is given in Table-2.

Table 1 : Baseline Characteristics of Study Population

Characteristics	Group A	Group B	Group C
Total number of patients	10	10	10
Male	6	6	6
Female	4	4	4
Mean Age (Year)	23.7	24.5	27.2
Mean Weight (Kg)	54.2	56	62.5
Mean Height (cm)	158.8	159.3	166.1
CLINICAL DIAGNOSIS			
Allergic contact dermatitis	4	3	4
Irritant contact dermatitis	2	3	2
Polymorphous light eruption	4	4	4

Table 2: Serum morning cortisol concentration of all the study participants (Values in µg/dl)

	Group A Hydrocortisone			Group B Prednisolone			Group C Betamethasone		
Serial No.	Baseline	First follow up	Second follow up	Baseline	First follow up	Second follow up	Baseline	First follow up	Second follow up
1	18.25	14.63	13.51	20.38	9.11	10.88	17.17	14.24	10.05
2	15.82	13.13	10.89	19.12	5.21	14.15	17.37	1.6*	12.31
3	16.43	12.08	10.55	11.99	5.97	10.41	19.2	4.93	11.68
4	13.18	11.54	12.89	11.01	11.18	12.67	14.91	0.45*	15.18
5	19.36	11.31	13.43	17.88	17.43	17.05	18.54	8.21	11.78
6	11.48	12.74	12.99	17.77	18.71	17.62	20.69	10.33	15.97
7	19.63	15.79	16.36	10.86	4.48	0.91*	17.22	9.56	15.17
8	18.11	17.58	17.73	10.98	8.26	6.89	20.18	11.65	8.44
9	15.67	14.39	15.12	13.86	11.72	10.19	11.95	10.74	10.23
10	17.98	16.34	17.45	19.12	18.54	17.22	16.7	10.26	5.32

Lower cut-off value for morning basal cortisol levels was 4.30 µg/dl. Values below cut-off are marked with asterisk sign.

An overall trend from the analysis of cortisol levels reveals that in all the groups morning cortisol levels falls below the base line values on first visit. Furthermore, the cortisol concentrations, although start to rise on second follow up but didn't achieve the baseline values [Figure-1].

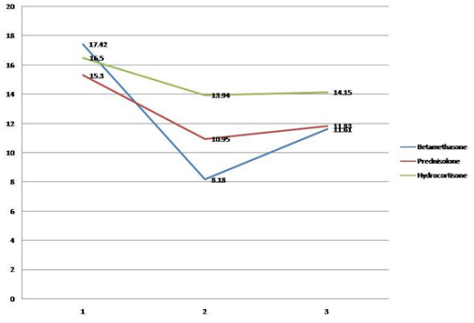

Figure-1: Changes in mean morning cortisol concentrations occurring from baseline to 2 days- and 5 days-after completion of therapy.

All the three types of CSs used were well tolerated in terms of reduction of cortisol concentrations (never dropping below cut-off value) from baseline values, however in Betamethasone groups two of the participants showed Cortisol concentrations below cut-off value [Table-2]. Also, Prednisolone group showed more variable individual responses and Hydrocortisone group appears to be safest in terms of fluctuations in cortisol concentration [Figure-2]. Percent reduction on first follow-up in the three groups were 53% reduction in Group C (Betamethasone) 28.4% Group B (Prednisolone) and 15.5%. in Group A (Hydrocortisone); suggesting highest HPA-axis affecting potential of Betamethasone among the three CSs.

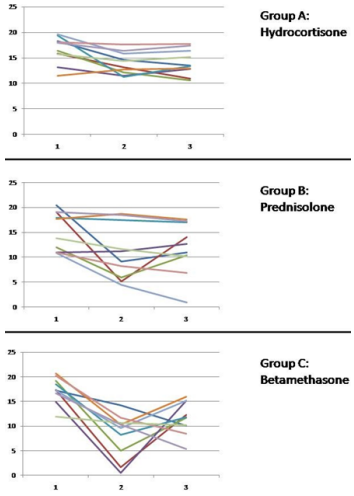

Figure-2: Effect of corticosteroids on morning cortisol concentrations of study participants

Intergroup analysis of cortisol concentration among the groups showed no statistical significant difference on one-way ANOVA (p value = 0.324); meaning all the three CSs are safe to use in a 5-day therapy.

In our study, all the three CSs were found to have excellent clinical effect and safety (data not shown). None of our study subjects developed any serious systemic side effects.

DISCUSSION

We have studied most commonly used member each from the three classes of systemic corticosteroids; namely hydrocortisone from short acting, prednisolone from intermediate acting and betamethasone from long acting corticosteroids class.

In our subjects, we found that the morning basal cortisol levels declined from the baseline value and started to recover within five days following the stoppage of systemic corticosteroid. Some of the available literature[8-11] have found a similar effects on short courses of CS therapy. Also, the short term regimen have been regarded as relatively free of serious suppressive effects on HPA axis, despite a lack of consistent evidence.[8] However, because of heterogeneity of patients evaluated in previous studies, it has been very difficult to interpret their effect and the specific effect of steroid dose and duration. In the study by Speigel et al[8], effect of prednisolone on HPA axis were assessed. However, other chemotherapeutic agents were also concomitantly given for variable duration. The study subjects were patients of hematological malignancy. In an another study, Hedner et al[9] used perioperative betamethasone 16 mg in divided doses for 4-5 days in patients undergoing stereotactic thalamotomy and withdrawn without tapering. Streck et al[10] also studied recovery of the hypothalamic- pituitary-adrenal axis in ten healthy volunteer following the administration of suppressive doses of prednisone (25 mg twice daily for five days). One more study addressing the same subject has been performed by Henzen et al.[11] They used different corticosteroids in the doses above 25 mg prednisone equivalent. These study subjects were patients of several systemic disorders.

In our study we found that about 37% (3 subjects in Group A; 4 each in Group B and Group C) of study subjects showed a persistent decline in morning basal cortisol level from baseline through until second follow up. Individual susceptibility of HPA-axis differ among people, which may be the cause of this trend. However, because we took only two follow up measurements, it is difficult to predict the final fate of cortisol levels in such subjects. A delayed suppression of HPA axis has been found with prednisolone[10] and betamethasone[9].

Percentage reduction of mean morning basal cortisol level was highest in betamethasone group and lowest in hydrocortisone group. Hydrocortisone appears to be the safest among the three CSs studied. However, hydrocortisone being an intravenous therapy, prednisolone comes out as the most practical CS for short term therapy. Intensive short term non-tapered corticosteroid therapy has been advocated in dermatoses where the underlying conditions are not exacerbated as a result of abrupt withdrawal.[18]

Previous studies[8,10,19] have found that after five days of corticosteroid therapy, most patient would require two to four days for adrenal function recovery. Salasa et al[19] have found that cortisone given for less than five days does not induce any structural changes in adrenal glands; whereas a longer dosing causes histological changes characteristics of adrenal atrophy.

Some authors believe that adrenal response in patients treated with glucocorticoids shows little correlation with the dose and duration of glucocorticoid treatment, and a random plasma cortisol concentration does not reliably assess the adequacy of the adrenal response to stress.[11] Therefore, dynamic or stimulation tests like the insulin-induced hypoglycaemia test or the corticotropin-releasing hormone test are considered accurate.[11] However, some of these tests are expensive, physician-intensive, and best done in an endocrine unit, whereas others are contraindicated in some patients.[11] On the other hand,[15] it has also been proposed that a basal morning cortisol determination may be the only test needed to assess adreno-corticol insufficiency[16,15] provided that the patient is not in a stressed condition, not pregnant, does not use estrogen and does not have thyrotoxicosis. Therefore use of basal cortisol level as surrogate marker of HPA-axis in our study is valid.

It would have been better, if we could perform dynamic testing in our subjects for corroboration of our results obtained with morning cortisol concentrations. However, several recent studies supports the concept of estimation of morning basal cortisol level as a sole indicator for assessing HPA axis activity in an unstressed subjects.

To summarize, out study demonstrates that a short non-tapered course is well-tolerated and clinically effective, and is a desirable treatment in many of the dermatological disorders. In our study participants, the HPA axis showed a transient depression with a quick recovery. In most of the instances the suppression is of the level, where no major concern arises.

In conclusion, our study confirms the safety of the three most commonly used corticosteroids. A five day single early morning non-tapered dose 0.5 mg/kg body weight of prednisolone equivalent of hydrocortisone, prednisolone and betamethasone are safe, even on abrupt withdrawal. In this dosing schedule, effect of betamethasone is strongest on HPA axis, whereas effect of hydrocortisone is the weakest. Thus corticosteroids given in a short course foe purely dermatological conditions are safe, at least in young population ranging from 18 years to 40 years of age.

REFERENCES

1. Centennial Paper. November 1951 (Arch Dermatol Syphilol: Cortisone acetate administered orally in dermatologic therapy by Marion B. Sulzberger, Victor H. Witten and Stanley N. Yaffe. Arch Dermatol. 1983;119:858-864. doi:10.1001/archderm.119.10.858.
2. REICHLING GH, KLIGMAN AM. Alternate-day corticosteroid therapy. Arch Dermatol. 1961;83:980-983. doi:10.1001/archderm.1961.01580120092023.
3. Jackson S, Gilchrist H, Nesbitt LT Jr. Update on the dermatologic use of systemic glucocorticosteroids. Dermatol Ther. 2007;20:187-205. doi:10.1111/j.1529-8019.2007.00133.x
4. Wolverton SE . Systemic corticosteroids . In: Comprehensive Dermatological DrugTherapy , 3rd edn. London : Elsevier , 2013 : 143 – 68.
5. Krasner AS. Glucocorticoid-induced adrenal insufficiency. JAMA. 1999;282:671-676. doi:10.1001/jama.282.7.671.
6. Wolverton SE. Glucocorticosteroids. In: Wolverton SE, Wilkin JK, editors. Systemic drugs for skin diseases. Philadelphia: WB Saunders; 1991. p. 86–124.
7. Bolognia, JL., Jorizzo, JJ., Schaffer, JV., Callen, JP., Cerroni, L., Heymann, WR., Hruza, GJ., Mancini, AJ., McGrath, J., Patterson, JW., & Schwarz, T, editors. Dermatology, 3rd edition. London: Elsevier; 2012.
8. Spiegel RJ, Vigersky RA, Oliff AI, Echelberger CK, Bruton J, Poplack DG. Adrenal suppression after short-term corticosteroid therapy. Lancet. 1979;1:630-633. doi:10.1016/s0140-6736(79)91077-8.
9. Hedner P, Kullberg G, Bostedt I. Recovery of the hypothalamus-pituitary-adrenal axis after short term high dose corticosteroid treatment in neurosurgical practice. Acta Neurochir (Wien). 1984;73:157-163. doi:10.1007/BF01400849.
10. Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. Am J Med. 1979;66:910-914. doi:10.1016/0002-9343(79)90444-3.
11. Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet. 2000;355:542-545. doi:10.1016/S0140-6736(99)06290-X.
12. Dvorin EL, Ebell MH. Short-Term Systemic Corticosteroids: Appropriate Use in Primary Care. Am Fam Physician. 2020;101(2):89-94.
13. Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: striking the balance between efficacy and safety. Eur Respir Rev. 2020;29(155):190151. Published 2020 Apr 3. doi:10.1183/16000617.0151-2019
14. Simsek Y, Karaca Z, Tanriverdi F, Unluhizarci K, Selcuklu A, Kelestimur F. A comparison of low-dose ACTH, glucagon stimulation and insulin tolerance test in patients with pituitary disorders. Clin Endocrinol (Oxf). 2015;82:45-52. doi:10.1111/cen.12528.
15. Hägg E, Asplund K, Lithner F. Value of basal plasma cortisol assays in the assessment of pituitary-adrenal insufficiency. Clin Endocrinol (Oxf). 1987;26:221-226. doi:10.1111/j.1365-2265.1987.tb00780.x.
16. Yip CE, Stewart SA, Imran F, et al. The role of morning basal serum cortisol in assessment of hypothalamic pituitary-adrenal axis. Clin Invest Med. 2013;36:E216-E222. Published 2013 Aug 1. doi:10.25011/cim.v36i4.19955.
17. Silva IN, Cunha CF, Finch FL, Colosimo EA. Avaliação da recuperação do eixo hipotalâmico-hipofisário-adrenal após corticoterapia por meio do cortisol basal [Evaluation of hypothalamic-pituitary-adrenal axis recovery after corticotherapy by using basal cortisol secretion]. Arq Bras Endocrinol Metabol. 2006;50:118-124. doi:10.1590/s0004-27302006000100017.
18. Melby JC. Drug spotlight program: systemic corticosteroid therapy: pharmacology and endocrinologic considerations. Ann Intern Med. 1974;81:505-512. doi:10.7326/0003-4819-81-4-505.
19. Salassa RM, Bennett WA, Keating FR Jr, Sprague RG. Postoperative adrenal cortical insufficiency; occurrence in patients previously treated with cortisone. J Am Med Assoc. 1953;152:1509-1515. doi:10.1001/jama.1953.03690160009004