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Original Research Article

Determination of HPA axis suppression in patients on systemic steroids in dermatology

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ABSTRACT

Background: Steroids are mainstay of treatment in most of the non-infectious dermatological conditions. The study was conducted to determine how various doses and duration of systemic steroid therapy affects HPA axis.

Aim: To determine HPA axis status in patients on systemic steroids in dermatology. To study how various doses and duration of steroid treatment affects HPA axis.

Materials and Methods: This longitudinal study was conducted on 77 patients who were on systemic steroids for dermatological conditions. Patients were categorized into 6 groups depending on the dosage and duration of steroid treatment. Serum 8 a.m. Cortisol and ACTH levels were tested.

Results: About 54 patients were on long term steroids and 23 were on short term steroids. 44 patients (81.5%) on long term steroids had suppressed levels of cortisol and 39 patients (72.2%) had suppressed levels of ACTH. Suppression was maximum in patients on high dose and taken for long duration ($p<0.001$). There was significant lowering in mean 8AM cortisol and ACTH levels after short term steroid therapy; however, no suppression was seen. Duration of steroid therapy and suppression of 8AM cortisol and ACTH values were associated significantly.

Conclusion: Patients on short term steroids showed no suppression of both serum 8 a.m. cortisol and ACTH levels but there was statistically significant lowering of levels. The study found that longer the duration and higher the dose of steroid therapy, the greater is the suppression of both serum 8 a.m. cortisol and ACTH levels.

1. Introduction

Steroids are a mainstay of therapy for most of the noninfectious dermatological conditions and have been in use for more than 50 years.[1] Steroids are used by various routes like oral, intravenous, topical, intralesional and by inhalational routes. Steroids are used in dermatological conditions like bullous dermatoses, autoimmune connective tissue diseases, vasculitis, neutrophilic dermatoses, papulosquamous dermatoses and so on.[2]

The hypothalamic–pituitary–adrenal axis (HPA axis) is an interactive neuroendocrine unit. Hypothalamus is the centre for coordination of endocrine system. The hypothalamic-pituitary axis influences thyroid, adrenal, and gonad functioning, as well as growth, milk production, and water balance.[3–6]

Administration of steroids can lead to adverse effects like, HPA axis suppression, adrenal crisis, hyperglycemia, hypertension, congestive cardiac failure, hyperlipidemia, cushingoid changes, growth impairment, osteoporosis, osteonecrosis, peptic ulcer disease, cataracts, myopathy and many other systemic adverse effects.[2]

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The effect on HPA axis is the most important one. Suppression of normal HPA axis due to exogenous steroids leads to disturbance of many endocrinal functions. The suppression of HPA axis depends on the dosage and duration of steroid taken, the serum half-life of corticosteroids administered, as well as glucocorticoid sensitivity and metabolism rates, which differ from person to person. The hypothalamus is the most vulnerable and adrenal glands are more resistant to for drug-induced suppression. HPA axis suppression might even last up to a year after corticosteroid therapy is stopped.[7] Cortisol levels range from 10 to 30 g/dL. Cortisol levels below 10 g/dl show reduced basal HPA axis activity with long-term therapy.[2]

2. Materials and Methods

This longitudinal study was conducted in Department of Dermatology, Venereology and Leprology at MGM hospital, Aurangabad from December 2020 to November 2021 after taking the clearance from the institutional ethical committee. Enrollment for the study included patients from the Department of Dermatology who were currently on systemic steroids. A total of 77 patients participated, with exclusion criteria applied to those who were unwilling to participate in the study. Every patient provided written informed consent before participating in the study. Demographic information, medical history, and treatment history data were collected from each participant.

The main goal of the study is to determine the status of the hypothalamic-pituitary-adrenal axis in patients on systemic steroids with dermatological conditions and it is focused on the need for steroid supplementation for patients who were on long term maintenance therapy with steroids. To know the effect of various doses and duration of steroids on HPA axis, we have divided the patients in to 6 groups.

Serum 8 a.m. Cortisol and ACTH levels (Adrenocorticotropic Hormone) were tested to determine the level of HPA axis suppression. Patients who were on long term steroids were directed included in the study whereas those patients on short term systemic steroids underwent prior testing (Visit 1) before starting steroids. They were tested again after the short course of steroids (Visit 2) i.e., after stopping steroids.

3. Results

Age distribution among total 77 patients showed 49 cases in 18-40 years age group, 25 cases in 41-60 years age group and 3 cases were more than 60 years. Mean age of patients was 38.18 ± 12.05 years. Sex distribution among 77 patients showed 42 cases were females and 35 patients were males

Majority (42.9%) of the patients belonged to group C i.e. medium dose and long duration, followed by group F (16.9%) and groups A (14.3%). Group C and D consist of 10 (13%) patients each.Table 2

22 (28.57%) were on low dose steroids, 44 (57.14%) were on medium dose and rest 11 (14.3%) were on high dose steroid.Table 3

54 (70.1%) patients were on long term steroids, of which 44 patients (81.5%) had suppressed levels of cortisol.

39 patients (72.2%) had suppressed levels of ACTH, followed by normal levels in 14 (25.9%) patients. One patient had raised levels of ACTH (51.9 pg/dl) despite long term steroid therapy (Prednisolone 10mg). 44 (81.5%) patients had suppressed 8 a.m. cortisol levels and 10 (18.5%) patients had normal levels.Table 4

The mean 8 am cortisol in these patients were 4.03 ± 3.68 μg/dl (Range 1-17.4). Mean value was lowest (1.77 ± 0.69 μg/dl) in patients with high dose and long duration i.e., group A patients. This difference was statistically significant ($p<0.001$).

The mean serum ACTH levels in these patients were 8.24 ± 10.49 (Range <1.5-51.9) pg/dl. Mean value was lowest (2.11 ± 0.91 μg/dl) in patients with high dose and long duration i.e., group A patients. This difference was statistically significant ($p<0.001$).Table 5

Patients on short term systemic steroids underwent prior testing (Visit 1) before starting steroids. They were tested again after the short course of steroids (Visit 2) i.e., after stopping steroids. 23 patients (29.9 %) patients were on short term steroids. None of them had suppression of 8 am cortisol level and serum ACTH levels.Table 6

There was a significant lowering in mean 8 am cortisol and mean ACTH level after short term steroid therapy, however no suppression was seen.Table 7

There is a highly significant association ($p<0.001$) between duration of steroid therapy and suppression of 8am cortisol. Patients who have been taking steroids for a long time have more suppression.Table 8

There is a highly significant association ($p<0.001$) between duration of steroid therapy and suppression of ACTH levels. Greater suppression is seen in patients with long term steroids.

4. Discussion

The hypothalamus-pituitary-adrenal (HPA) axis stands as a pivotal neuroendocrine system that governs responses to stress and oversees various bodily functions such as digestion, immune response, mood, emotions, sexual activity, and energy storage and expenditure. This intricate system serves as a common mechanism orchestrating interactions among glands, hormones, and components of the midbrain, contributing to the mediation of the general adaptation syndrome (GAS).[8,9]

Playing a central role, the HPA axis is instrumental in regulating multiple homeostatic systems within the body, encompassing the metabolic system, cardiovascular system, immune system, reproductive system, and central nervous system.[10]

Table 1: Patient grouping according to dosage and duration of steroid therapy

S.No.	Group	Dosage	Duration
1.	A	>30mg but ≤ 100mg prednisolone or equivalent per day (Higher dosage)	More than four weeks (longer)
2.	B	>30mg but ≤ 100mg prednisolone or equivalent per day (Higher dosage)	Less than 4 weeks duration (shorter)
3.	C	> 7.5mg but ≤ 30mg prednisolone or equivalent per day (Medium dosage)	More than four weeks (longer)
4.	D	≤7.5 mg prednisolone or equivalent per day (Medium dosage)	Less than 4 weeks duration (shorter)
5.	E	≤7.5 mg prednisolone or equivalent per day (Shorter duration)	More than four weeks (longer)
6.	F	≤7.5 mg prednisolone or equivalent per day (Shorter duration)	Less than 4 weeks duration (shorter)

Table 2: Group wise distribution of patients based on dose and duration of steroids (n=77)

Group	Number of patients	%
A: High dose and long duration	11	14.3
C: Medium dose and long duration	33	42.9
D: Medium dose and short duration	10	13.0
E: Low dose and long duration	10	13.0
F: Low dose and short duration	13	16.9
Total	77	100.0

Table 3: Dosage and type of steroids (n=77)

Dosage		Number of patients	%
Low dose	Methylprednisolone 4mg	1	1.3
	Prednisolone 5mg	21	27.3
Medium Dose	Hydrocortisone 100mg	1	1.3
	Prednisolone 10mg	14	18.2
	Prednisolone 15mg	11	14.3
	Prednisolone 20mg	10	13.0
	Prednisolone 25mg	4	5.2
	Prednisolone 30mg	4	5.2
High dose	Dexamethasone 8mg	1	1.3
	Prednisolone 35mg	5	6.5
	Prednisolone 40mg	4	5.2
	Prednisolone 50mg	1	1.3
Total		77	100.0

Table 4: 8 am cortisol and Serum ACTH values in patients on long term steroids (n=54).

Levels	8 am cortisol		Serum ACTH	
	n	%	n	%
Normal	10	18.5	14	25.9
Suppressed	44	81.5	39	72.2
Raised	0	0	1	1.9

Table 5: Group wise mean 8 am cortisol of patients who are on long term steroids (n=54)

Group	Mean	S. D	Range	p-value
8 am cortisol				
A	1.77	0.69	1.10-3.10	
C	3.49	2.51	1.0-13.90	<0.001
E	8.28	5.43	1.70-17.40	
serum ACTH levels Table				
A	2.11	0.91	<1.5- 3.89	
C	6.77	9.03	1.6-51.90	<0.001
E	19.86	12.41	6.9-45.78	

*test applied – ANOVA

Table 6: 8 am cortisol and serum ACTH values in patients on short term steroids (n=23)

Levels	8 am cortisol				Serum ACTH levels			
	Initialvisit -1		Visit 2- after stopping steroids		Initial visit -1		Visit 2- after stopping steroids	
	n	%	n	%	n	%	n	%
Normal	23	100	23	100	23	100	23	100
Suppressed	0	0	0	0	0	0	0	0

Table 7: Difference in mean 8 am cortisol and mean ACTH in visit 1 and 2 of patients who are on short term steroids (n=23)

Test	Mean	S. D	p-value
8 am cortisol			
Visit 1	10.00	1.84	
Visit 2	9.64	1.82	0.007
Mean difference	0.36	0.58	
ACTH levels			
Visit 1	11.00	2.07	
Visit 2	10.57	1.86	0.016
Mean difference	0.43	0.79	

*test applied -paired t test

Table 8: Association between suppression of 8 am cortisol and ACTH levels and duration of steroid intake

Group	Long term steroids		Short term steroids		p-value
	n	%	n	%	
8 am cortisol					
Normal	10	18.5	23	100.0	P <0.001
Suppressed	44	81.5	0	0	
ACTH levels					
Normal	14	25.9	23	100.0	P <0.001
Suppressed	39	72.2	0	0	

*test applied-Chi-square test

4.1. The fundamental components of the HPA axis include:[11]

1. The paraventricular nucleus of the hypothalamus: This region houses neuroendocrine neurons responsible for synthesizing and releasing vasopressin and corticotrophin-releasing hormone (CRH).
2. The anterior lobe of the pituitary gland: CRH and vasopressin stimulate the anterior lobe of the pituitary gland, prompting the secretion of adrenocorticotropin hormone (ACTH).
3. The adrenal cortex: Responding to ACTH stimulation, the adrenal cortex produces glucocorticoid hormones, with cortisol being the primary one in humans. In a negative feedback cycle, glucocorticoids act on the hypothalamus and pituitary, suppressing the production of CRH and ACTH.

The baseline levels of glucocorticoids demonstrate a consistent variation over the course of the day in a reliable pattern. In humans, the basal circadian profile of adrenocorticotropic hormone (ACTH) and cortisol reveals a peak in activity during the early morning hours.[12]

Suppression of HPA will lead to ineffective coping psychological, behavioural and cognitive function.

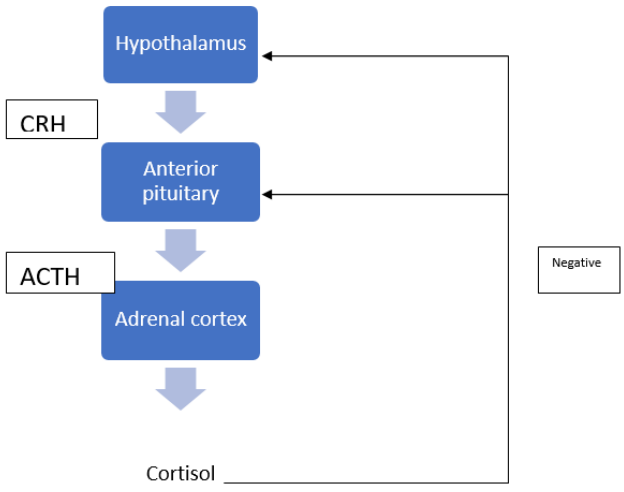

Figure 1:

The secretion of corticotrophin-releasing hormone (CRH) from the hypothalamus is impacted by various factors, including stress, physical activity, illness, cortisol levels in the body, and the sleep-wake cycle (circadian rhythm).[11]

Stress is defined as the state manifested by a specific syndrome which consists of all the non-specifically induced changes within a biologic system.[13] It can acute or chronic. Both acute and chronic stressors may lead to a range of physiological and psychological impairments.[14,15] When it is extensive and of long durations, it can affect physical and mental health negatively.

A normal physiological response to any stressor, acute or chronic leads to activation of HPA axis and there is increased levels of catecholamine's as a fight and flight response but the patients who are on long term systemic steroids this response might be blunted.

Prolonged exposure to stress has been demonstrated to diminish the cortisol awakening response, contributing to symptoms such as morning fatigue, pain, and inflammation.[16,17] Additional, compelling evidence indicates a pronounced dysregulation of the HPA axis, correlating with an elevated risk of various psychiatric disorders, including depression, schizophrenia, and anxiety disorders.[18,19]

Also another important aspects in patients with long term steroids is look for signs of adrenal insufficiency especially during times of acute stress like sepsis or patients undergoing surgeries or in ICU admissions as they might require additional steroid supplementation A random level of less than 10 mcg/dl cortisol in a case of hemodynamic instability is diagnostic of critical illness related corticosteroid insufficiency and glucocorticoid therapy should be initiated.[20,21]

In our study out of 77 patients enrolled, 54 (70.1%) patients were on long term steroids of which 44 (81.5%) patients had low levels of 8 a.m. cortisol and 39 (72.2%) patients had low levels of serum ACTH. Normal levels of 8 a.m. cortisol was seen in 10 (18.5%) patients and normal levels of serum ACTH was seen in 14 (25.9%) patients. The mean value of both 8 am cortisol and serum ACTH levels was lowest in patients with high doses and long duration i.e., group A patients. In our study, 1 (1.9%) patient on long term steroids showed raised (51.9 pg/dl) levels of serum ACTH. A study by K. Pelewicz et al[7] reported that if elevated ACTH levels (>100 pg/mL) are present it may be due to primary adrenal insufficiency rather than corticosteroid- induced adrenal insufficiency. In our study out of 77 patients, 23 patients were on short term steroids. The difference in mean 8 a.m. cortisol and mean ACTH levels in visit 1 and visit 2 patients had a significant lowering, but there was no suppression. Patients who were on medium dose steroids and for shorter duration (Group D) showed more lowering of both levels when compared to group F which was not statistically significant. There was a significant association ($p < 0.001$) between the duration of steroid therapy and suppression of 8 a.m. cortisol and serum ACTH levels.

As expected HPA axis suppression is seen in patients on long term steroids. In our study It is revealed that the patients who were on long term corticosteroid therapy have Hypothalamic-pituitary- adrenal axis suppression, thus would require supplementation of steroid therapy in stressful situation.

Important finding showed that patient on low dose and short term steroid also showed lowering of cortisol level indicating alteration in HPA normal rhythm even with low dose and short term steroid, making it necessary to closely monitor patients on short term steroids for stress induced corticosteroid insufficiency.

5. Conclusion

In patients who were on short term steroids there was no suppression of both serum 8 a.m. cortisol and ACTH levels but there was statistically significant lowering of levels. This necessitates the proper follow up and adequate monitoring of patients even in patients on short term steroids as there is a risk of "Critical Illness Related Cortisol Insufficiency" (CIRCI). CIRCI is a clinical entity that has inappropriately reduced internal production of corticosteroid combined with peripheral receptor resistance.[22] In our study it was found that longer the duration of steroid therapy and higher the dose, the greater is the suppression of both serum 8 a.m. cortisol and ACTH levels. So, these patients require supplementation of steroid therapy till the recovery of HPA axis.

Also raising awareness regarding the psychological, cognitive, and behavioral dimensions of HPA axis dysfunction is crucial, as this goes beyond merely supplementing steroids and involves implementing strategies for managing associated symptoms.

Our study was limited by the fact that smaller sample size and limited number of systemic steroids were included, larger and multicentric studies would provide more insights in relation between Systemic steroids and HPA axis.

6. Source of Funding

None.

7. Conflict of Interest

None.

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