Iatrogenic Cushing's Syndrome in Admitted Patients to a Rural Based Medical College Hospital

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ABSTRACT

Introduction: Drug induced hypercorticolism is the most common cause of Cushing's syndrome. Study aimed to find out various presentations of iatrogenic Cushing's Syndrome, occurrence and to make the clinicians and public aware of this probably avoidable disease.

Material and methods: This is an observational study conducted in the department of Medicine SVS Medical College and Hospital at Mahabubnagar of Telangana State from 1-1-2010 to 31-12-2014. The diagnosis of drug-induced Cushing's syndrome was made by measuring the fasting serum cortisol levels, well documented clinical features, as well as history of taking oral steroids in any form of medicine. The early morning cortisol levels are low with no increase in levels after administering ACTH.

Results: 70 patients were women and 24 men. Average age of the cases was 44.04 years. Most common features were moon shaped face (95.7%), truncal obesity (74.7%), hyperglycemia (74.7%), hypertension (70%), cataracts (55.32%). The patients were started on steroids for various indications. The most common indication for steroid therapy was joint pain followed by respiratory diseases. All the cases of connective tissue disorders, nephritic syndrome ulcerative colitis, bronchial asthma was having a regular follow with prescription. All patients with joint pains did not have authentic prescription by a qualified doctor above MBBS degree. The dermatological patients were diagnosed as Psoriasis, eczema or some other chronic skin ailments; the qualified dermatologist prescribed only topical steroids but the patients were taking oral and topical steroids by some quacks.

Conclusion: The present study was compared with earlier studies. Most features are similar and some differences existed. The main concern was about irrational use of these extremely useful drugs. Enforcement strictly of laws existing and public education may help to minimize the side effects of the corticosteroids.

Keywords: Steroids, iatrogenic Cushing's syndrome, clinical features, public medical education.

INTRODUCTION

It was way back in 1948 steroids were used for the first time in clinical medicine[1] for severe rheumatoid arthritis. This practice went on till lots of side effects occurred. Exogenous drug induced hypercorticolism is most common cause of Cushing's syndrome.[2] But the literature is scanty in this regards. Iatrogenic hypercorticolism was reported in the literature when the steroids were administered in various forms viz., topical[3-7], inhalational[8-13], nasal drops[14-15] oral, parenteral and local administration.[16] All forms were shown to cause iatrogenic Cushing's syndrome.About 1% of the general population are longterm users of systemic glucocorticoids[15-18] and about twothirds exhibit iatrogenic manifestations related to excessive exposure to glucocorticoids.[19-22] The situation is further compounded by the irrational uses of these drugs.[23] Study aimed to find out various presentations of iatrogenic Cushing's Syndrome, occurrence and to make the clinicians and public aware of this probably avoidable disease.

MATERIAL AND METHODS

This was an observational study conducted in the department of Medicine SVS Medical College and Hospital at Mahabubnagar of Telangana State from 1-1-2010 to 31-12-2014. The patients were attending the Hospital for various complaints mainly non-specific symptomatology. The cases suspected to be steroid abuse were screened and confirmed cases were included. The authors had taken written and informed consent from all patients. A total of 94 cases were included in this study.

A detailed history and clinical examination regarding use of corticosteroids, occupation, family details, blood pressure recording, and fasting blood glucose values were carried out in each study subject according to a pre-structured protocol. The demographic and anthropometric profiles of all the patients were also recorded. A thorough and detailed history was obtained regarding the corticosteroid intake, stating the duration and indication. Blood was drawn in red top container for estimation of steroid at 8 AM and in EDTA tube for ACTH measurement.

The diagnosis of drug-induced Cushing's syndrome was made by measuring the fasting serum cortisol levels, well documented clinical features, as well as history of taking oral steroids in any form of medicine, i.e., Allopathic, Ayurvedic, Unani, or any other form of alternative medicine. The early morning cortisol levels are low with no increase in levels after administering ACTH.[23]

STATISTICAL ANALYSIS

Results were plotted on a master chart and the values reported as medians, non-parametric statistical methods were used to express.

RESULTS

The demographic values of the cases were tabulated in Table 1. The patients were started on steroids for various indications. The most common indication for steroid therapy was joint pain followed by respiratory diseases. The details regarding the indication of starting steroids are shown in Table 2 and 3.

The most common clinical presentation of iatrogenic Cushing's syndrome was moon facies followed by truncal obesity. Table 4

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shows the clinical presentation of the patients presenting with iatrogenic Cushing's syndrome.

The cortisol values of the patients are shown in Table 5 in which the patients were divided in three groups as per the cortisol values. Morning (8 AM) normal adrenocorticotropic hormone (ACTH): 5.6 pg/mL (N: 5-27 pg/mL) and morning (8 AM) serum cortisol: <0.2 µg/dL (N: 4.3-22.4 µg/dL). According to these findings, the patient was diagnosed with iatrogenic Cushing's syndrome.

Fourteen cases had been included in this study did not have any valid prescription from any authorized medical practitioner. These cases were on some so called local doctors of alternate medicine; they used to take either prednisolone or betamethasone or dexamethasone without their knowledge. Four patients were taking some powdered drug given; this drug when analysed proved to be steroid [the sample was analysed by Pharmacy department of BITS, Pilani (Hyderabad)] by Liquid chromatography/mass spectrometry (LC–Mass).

The patients were started on steroids for various indications. The most common indication for steroid therapy was joint pain followed by respiratory diseases. The details regarding the indication of starting steroids are shown in Table 2 and 3. The most common clinical presentation of iatrogenic Cushing's syndrome was moon facies followed by truncal obesity. Table 4 shows the clinical presentation of the patients presenting with iatrogenic Cushing's syndrome. The cortisol values of the patients are shown in Table 5 in which the patients were divided in three groups as per the cortisol values. The results also depicted that the value of cortisol is not dependent upon the dose or nature of steroid; however, it was found that the values are dependent upon whether the patient is presently on steroids; or if the patient is not on steroids, then the steroid-free interval prior to consultation. Morning (8 AM) adrenocorticotropic hormone (ACTH): 5.6 pg/mL (N: 0-46); morning (8 AM) serum cortisol: <0.2 µg/dL (5.5 nmol/L) (N: 4.3-22.4). As per these

Serial number	Demographic values	Values
1	Age	44.04+9.21
2	Gender	M: F = 24:70 (1: 3.43)
3	Height in centimetres	152.22 ± 7.99
4	Weight in kilograms	64.22 ± 10.46
5	BMI	27.45 ± 4.22
6	Systolic blood pressure in mmHg	136.24 ± 12.6
7	Diastolic blood pressure in mmHg	81.90 ± 5.44
8	Haemoglobin in Gm/dL	11.57 ± 2.64
9	Leucocyte count /cc.mm.	7644 ± 1268
10	E.S.R. mm/1st hour	56.67 ± 20.54
11	Serum creatinine mg/dL	0.87 ± 1.82

Table-1: Demographic details of the iatrogenic Cushing's syndrome cases

Serial number	Condition/ Diagnosis	Number of cases	Percentage
1	Joint pains	24	25.53
2	Bronchial asthma	20	21.27
3	Dermatalogical conditions	14	14.89
4	Connective tissue disorders	14	14.89
5	Ulcerative colitis	4	4.25
6	Nephrotic syndrome	4	4.25
7	Miscellaneous	14	14.89

Table-2: Indications for Glucosteroids

Serial number	Condition	Number of cases
1	Paralysis	4
2	Nervousness	3
3	General debility	2
4	For weight gain	2
5	Drug allergy	2
6	Fibromyalgia	1

Table-3: Miscellaneous indications

Serial number	Clinical/ biochemical anomaly	Number of cases	Percentage
1	Moon shaped facies	90	95.74
2	Truncal obesity	74	78.72
3	Fasting hyperglycemia	70	74.47
4	Hypertension	66	70.21
5	Cataract	52	55.32
6	Dyslipidemias	44	46.81
7	Hypokalemia	32	34.04
8	Myopathy	20	21.27
9	Ecchymosis	16	17.02
10	Striae	08	08.51
11	Fungal infections	06	6.67

Table-4: Clinical features

Cortisol levels	Number	Percentage
<1mg	8	10.256
1 – 5 mg%	40	51.282
5 – 15 mg%	30	38.462

Table-5: Fasting serum cortisol level

Serial number	Form of steroid	Route of admission	Number of cases	Percentage
1	Steroid medicine in Alternate medication/ quack treatment	Oral	13	16.667
2	Dexamethasone	Oral	09	11.538
3	Methyl Prednisolone	Oral	09	11.538
4	Prednisolone	Oral	08	10.256
5	Methyl Prednisolone	Depot Injection	06	7.692
6	Betamethasone	Oral	03	3.846
7	Deflazacort	Oral	02	2.564
8	Triamcinalone	Depot Injection	02	2.564
10	Budeneside / Fluticasone / Beclomethasone	Inhalation	26	33.333

Table-6: Type of steroid used

findings, the patient was diagnosed with iatrogenic Cushing's syndrome.

Only 32 patients had a valid prescription for the disease. All the connective tissue disorders, nephritic syndrome ulcerative colitis, bronchial asthma were having a regular follow with prescription. All patients with joint pains did not have authentic prescription by a qualified doctor above MBBS degree. The dermatological patients were diagnosed as Psoriasis, eczema or some other chronic skin ailments; the qualified dermatologist prescribed only topical steroids but the patients were taking oral and topical steroids by some quacks. So also the cases of joint pains also did the same by repeating the prescription by private practitioner; they went on getting the medication of an NSAID and steroid over the counter.

Co-administered drugs: these are few important drugs patients were taking for various co-morbid conditions.

DISCUSSION

Steroids are lipophilic and may be absorbed systemically via inhaled, intranasal, and topical routes. Case reports exist with inhaled/intranasal fluticasone, inhaled/oral budesonide, intra-articular triamcinolone, dexamethasone ophthalmic drops, topical and intralesional apart from oral and parenteral route of administration.[15-16] Iatrogenic Cushing's Syndrome was suspected if the patient had: AM Cortisol of ≤4 mcg/dL and ACTH of≤10 pcg/mL. Iatrogenic Cushing's syndrome is the most common cause of hypercortisolism.[2,3] About 1% of the general population are long-term users of systemic glucocorticoids5 for the treatment of various diseases, often in very high doses that sometimes lead to the development of severe hypercortisolism. About two-thirds of these exhibit iatrogenic manifestations related to excessive exposure to glucocorticoids.[6] Iatrogenic Cushing's syndrome is not uncommon.[18,19]

	Drug	Number cases
1.	Atorvastatin	14*
2.	Metaprolol	12*
3.	Clonazepam	10
4.	Amitriptyline	10
5.	Fluconazole	03
*Metaprolol + atorvastatin were administered in 8 patients		

Table-7: Various drugs co-administered

Corticosteroids are useful drugs, if prescribed for an evidence-based indication; but if used irrationally, troublesome adverse effects may be noted.[20-22] The corticosteroids should be used for a specific indication, a proper duration, and with an appropriate dosage schedule. The risk – benefit ratio should be evaluated before starting therapy. The physicians must also explore the alternative modes of treatment of various diseases, where steroids are indicated as primary drugs, and these alternative modalities may be used, if troublesome side effects appear following glucocorticoid treatment and warrants discontinuation of the same.

The following table demonstrate the incidence of various clinical features compared with earlier studies

Cushing's syndrome results from chronic pathological exposure to glucocorticoids. Hypertension is present in almost 70% of patients with Cushing's syndrome. This incidence was observed by this present study and by Singh et al, but Srivastav et al.[21] noted only17 % had hypertension. Hyperglycemia or diabetes was found in 74.4 %, similar figures were reportred by Singh and others.[22] Echymotic patches were noted only 12.4 as against 70% in earlier study by Singh et al.[22]

Allcases of prolonged HPA axis suppression were due to misuse of the drug, i.e. prolonged daily application over several years on larger body surface area.[6] Transient and reversible reduction of HPA axis functioncan be observed in up to 48%[23] of patients treated with super potent topical steroid, but is usually not associated with clinical symptoms even with long-term maintenance therapy.Iatrogenic Cushing's syndrome is accentuated when patients are treated with other drugs like ritonavir for HIV treatment[13,26], posaconazole[27], antidepressants like mitrazepin and paroxetine.[28] Steroids are lipophilic and may be absorbed systemically via inhaled, intranasal, and topical routes. These actions are accentuated by liver enzymes.[13] Table 6 shows a summary of various drug enhancements regarding steroid absorption and thereby the toxicity of the latter.

Though it was noted some co-administered drugs like metaprolol, atorvastatin, fluconazole and sedatives and anti-depressants in this study. As this is an observational study only,

Serial number	Clinical/ biochemical anomaly	Singh, Kotwal and Menon[24] 2011 [Percentage]	Srivastav et al[25] 2015 [Percentage]	Present study [Percentage]
1	Moon shaped facies	89	92.6	95.74
2	Buffalo hump		79.2	
2	Truncal obesity	97		78.72
3	Fasting hyperglycemia	70	12.2	74.47
4	Hypertension	76	17	70.21
5	Cataract	52	9.7	55.32
6	Dyslipidemias	44		46.81
7	Hypokalemia	32		34.04
8	Myopathy	20		21.27
9	Ecchymosis	75	12.1	17.02
10	Striae	08	9.8	08.51
11	Gonadal dysfunction	69		
12	Hirsutism	56		
13	Mood disturbances	55		
14	Osteoporosis	40		
15	Fungal infection	10		6.67

Table-8: Comparison of Clinical features with earlier studies

A.	**Inducers of Cytochrome P450: Decreases GC Level**
	1. Anti-epileptics: Barbiturate, Carbamazepine, Phenytoin
	2. Bile acid sequestrants
	3. Antibiotics: Rifampicin
B.	**Inhibitors of Cytochrome P450: Increases GC Level**
	1. Inhibitors of cytochrome P450 dependent CYP 3A4 inhibitors
	a. Antibiotics: Macrolide, Clarithromycin
	b. Anti-fungal: Fluconazole, Itraconazole, Ketoconazole, Posaconazole, Voriconazole
	c. Anti-arrhythmic: Amiodarone, Lidocaine
	d. Calcium channel blockers: Diltiazem, Verapamil
	e. HIV drugs: Ritonavir, Indinavir
	f. HMG CoA reductase inhibitors: Atorvastatin
	2. Inhibitors of cytochrome P450 dependent CYP 2D6
	a. Antipsychotics/Anti-depressants:Amitryptiline, Haloperidol, Resperidone, Clozapine, Fluoxetine.
	b. Cardiac drugs: Flecainide, Propafenone, Carvedilol, Metoprolol.

Table-9: Medications that Alter the Plasma Glucocorticoid Levels[13]

the relationship between the toxicity and other medication was not studied. The association of co-administration was just noted. Only about 21 or 22 cases had definite indication, while in other cases steroids could have been avoided or at least the dose or duration would have been curtailed. One can rely on patient education and/ or restriction of sale. Most of patients in this observational study did not carry a proper prescription. Some had some prescription for steroid use for few days, they keep on repeating the prescription at will without any proper consultation. Probably these can be avoided by proper enforcement of law and patient education.

Limitations of the study

This was only prospective observational study. The dose duration and type of steroid were not studied.

CONCLUSION

94 cases of iatrogenic Cushing's syndrome were reported. Moon shaped face, truncal obesity, hyperglycaemia, hypertension and cataract were the common features observed in our study. Though it was seen some cases using other medicines the exact association was not studied. Iatrogenic (exogenous) Cushing's syndrome is more common than the endogenous forms of hypercortisolemia. For this reason, patients on long-term glucocorticoid treatment must be evaluated for potential adverse effects and withdrawal symptoms by their treating physician. One should remember the drug interaction in cases of not so uncommon iatrogenic Cushing's syndrome. One should recognize the condition to take measures to minimize the complications of the unavoidable most useful drugs. The unaccountable drug intake can probably be reduced by strict implementation of law.

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