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Original Research Paper

METABOLIC, EYE AND BONE RELATED ADVERSE DRUG REACTIONS OF LONG TERM GLUCOCORTICOID THERAPY (A study of 80 cases)

Dermatology

KEYWORDS: : corticosteroids, adverse drug reactions, cushingoid features.

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ABSTRACT

Background: In dermatology, Corticosteroids (CSs) are widely prescribed in either topical or systemic formulations in various potencies to tailor therapy according to severity of the underlying condition, area of involvement. Corticosteroids, however, are associated with a number of serious adverse events, particularly with long-term use. Aims: To study adverse drug reactions (ADRs) of long term glucocorticoids (GC) in relation to the musculoskeletal system, Metabolic and Blood sugar levels and Eye. Methods: This was a hospital based prospective study done on 80 patients on daily glucocorticoid therapy for more than 6 months duration from September 2015 to September 2016 over a period of 1 year. Results: Among 80 patients included in our study, 50(62.5%) patients developed adverse effects while 30(37.5%) had none. Metabolic side effects were observed as Diabetes Mellitus (SDM) in 25(31.25%), Hypertension in 18(22.5%), Cushingoid features in 17(21.25%) and Lipid abnormalities (in the form of raised cholesterol and triglyceride levels) in 4(5%). Eye changes and bone changes were seen in the form of Cataract (2.5%) and osteoporosis (2.5%) respectively. Conclusion: In dermatology, while using daily glucocorticoid therapy, continuous monitoring should be done and prevention measures should be considered for preventing various side effects resulting from daily oral glucorticoids use.

INTRODUCTION

Corticosteroids play a major role in the dermatologist's armamentarium. Corticosteroids in dermatology, have been amongst the most widely used and effective treatment to control inflammatory and autoimmune diseases. However, their clinical efficacy is compromised by the metabolic effects of long-term treatment, which include osteoporosis, hypertension, dyslipidemia and insulin resistance/type 2 diabetes mellitus.[1]

Safe and effective use of this class of agents, therefore, requires knowledge of their mechanism of action and potential complicating factors. Glucocorticosteroids however have proven to be the "archetypal double edged sword of medicine."[2]

Glucocorticoids exert their clinical effects predominantly by up regulating the transcription of anti-inflammatory genes (transactivation) or by downregulating the transcription of inflammatory genes (transrepression) to affect the downstream production of a number of pro-inflammatory cytokine and chemokine proteins, cell adhesion molecules and other key enzymes involved in the initiation and/or maintenance of the host inflammatory response.[3]

Despite their beneficial effects, long-term systemic (oral or parenteral) use of these agents is associated with well-known adverse events (AEs) including: osteoporosis and fractures; adrenal suppression (AS); hyperglycemia and diabetes; cardiovascular disease (CVD) and dyslipidemia, gastrointestinal events; psychiatric disturbances; and immunosuppression. [3] In general, the risk of adverse effects of corticosteroids increases with the duration of therapy and frequency of administration. [3]

METHODS

This was a hospital based prospective study done on 80 patients who attended the Dermatology OPD at P.D.U. Govt. Medical College and Hospital and were on systemic oral glucocorticoid (GC) therapy given on daily basis for more than 6 months duration from September 2015 to September 2016.

All patients on systemic oral glucocorticoid therapy (tab prednisolone 1-2mg/kg/day) given on daily basis for more than 6 months duration with minimum 6 months of follow up were recruited in the study. Patients on oral mini pulse therapy and pulse therapy like Dexamethasone-azathioprine pulse, dexamethasone-cyclophosphamide pulse, dexamethasone pulse etc. were not included in our study. Patients with past history of diabetes, hypertension, and hyperlipidemia were excluded.

In our study, the dose of prednisolone was tapered according to clinical response. Patients were counselled regarding the side effects of corticosteroids and various measures taken to minimize the side effects of steroids such as taking medication after a meal, low sodium, low fat, low cholesterol diet, calcium and vitamin supplements, tab alendronate(35mg) once a week.

Detailed history was taken which included demographic data, medical history and history regarding duration of treatment. They were repeated at fifteen days initially and then monthly. Thorough clinical examination was done including weight, Blood Pressure and Abdominal Girth. Ophthalmological examination and X-rays were carried out at baseline and 6 monthly thereafter. Baseline Complete Blood Count, Urine examination, Fasting Blood Sugar, 2 hours Post prandial Blood Sugar, S. Creatinine, Liver Function Test, S. Cholesterol, Chest X-ray, X-ray Dorso Lumbar spine and pelvis with both hip joint were carried out and repeated as and when required.

RESULTS

Out of 80 patients included in the study on daily glucocorticoid therapy, 39(48.75%) were males and 41(51.25%) were females with a male to female ratio of 1:1.05. The maximum number of patients were

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in the age group of 40-49 yrs(20%) with a mean age of 46.18± 17.28 year.[Table 1] The mean duration of treatment with prednisolone (1-2mg/kg/day) was 13.95 ± 5.9 months.[Table2]

Most common indication for daily glucocorticoid therapy was autoimmune vesiculobullous disorders (40.1%) followed by lepra reactions (16%) and connective tissue disorders (13.75%).[Table3]

Out of 80 patients on daily long term glucocorticoid therapy, 50(62.5%) patients developed various metabolic, eye and musculoskeletal adverse effects as illustrated in table 4.

Glucocorticoids can cause hyperglycemia via insulin resistance, which augments hepatic gluconeogenesis and lowers glucose uptake by peripheral tissues such as muscle cells and adipocytes. For these reasons, it is not uncommon to observe abnormal glucose tolerance among patients receiving steroid therapy.[4] In our study, 25(31.25%) of the patients experienced steroid induced diabetes mellitus and hypertension was observed in 18(22.5%).

17(21.25%) patients developed cushingoid features such as weight gain (based on weights taken on initiation and after 6 months of therapy), moon face, truncal obesity, buffalo hump. Among these, weight gain (18.75%) was the commonest followed by moon face (7.5%).[Table4]

AGE GROUP	NO OF PATIENTS	NO. OF PATIENTS DEVELOPING SIDE EFFECTS	MALES	MALES DEVELOPING SIDE EFFECT	FEMALES	FEMALES DEVELOPING SIDE EFFECTS
10-19 YR	3(37.5%)	0	0	0	3(7.31%)	0
20-29 YR	14(17.5%)	6(7.5%)	3(7.69%)	1(2.56%)	11(26.82%)	5(12.19%)
30-39 YR	12(15%)	6(7.5%)	4(10.2%)	3(10.25%)	8(19.51%)	3(7.3%)
40-49 YR	16(20%)	11(13.75%)	7(17.9%)	6(15.38%)	9(21.95%)	5(12.19%)
50-59 YR	14(17.5%)	12(15%)	9(23.7%)	7(17.94%)	5(12.9%)	5(12.19%)
60-69 YR	10(12.5%)	9(11.25%)	8(20.5%)	7(17.94%)	2(4.87%)	2(4.87%)
>70YR	11(13.75%)	6(7.5%)	8(20.5%)	5(12.82%)	3(7.3%)	1(2.43%)
TOTAL	80	50	39	29	41	21

TABLE 1: AGE AND SEX WISE DISTRIBUTION OF PATIENTS INCLUDED IN OUR STUDY.

Bone changes as osteoporosis were seen in 2(2.5%) out of 50 cases which developed adverse effects in our study as compared to other studies[10],[11]. The low incidence of musculoskeletal side effects may be due to less number of patients included, preventive measures taken such as daily calcium supplements and tab alendronate (35mg) once per week.

In our study, eye changes were seen in the form of cataract (2.5%) and herpes simplex keratitis (2.5%).

DISCUSSION

Out of 80 patients included in the study on daily glucocorticoid therapy, 39(48.75%) were males and 41(51.25%) were females with a male to female ratio of 1:1.05. The maximum number of patients were in the age group of 40-49 yrs (20%) with a mean age of 46.18± 17.28 year. Side effects were most commonly seen in age group of 50-59 years followed by 40-49 yr.[Table1]

DURATION OF TREATMENT (MONTHS)	TOTAL NO. OF PATIENTS	ADVERSE EFFECTS						
		DM	HTN	CUSHING	HYPER-LIPIDEMIA	OSTEO-POROSIS	CATARACT	HERPES SIMPLE
7-12 MONTHS	25(31.25%)	10	5	8	0	0	0	1
13-18 MONTHS	38(47.5 %)	9	8	3	1	0	0	0
19-24 MONTHS	17(21.25%)	6	5	6	3	2	2	1

TABLE 2: RELATION BETWEEN DURATION OF TREATMENT AND SIDE EFFECTS OBSERVED

The mean duration of treatment with prednisolone (1-2mg/kg/day) was 13.95 ± 5.9 months. The maximum patients (47.5%) included in our study, were on long term glucocorticoid therapy for 13-18 months. Eye and bone changes were observed in those patients, who received treatment for 19-24 months.[Table2]

Most common indication for daily glucocorticoid therapy was autoimmune vesiculobullous disorders (40.1%) followed by lepra reactions (16%) and connective tissue disease (13.75%). 37(77.08%) out of 48 vesiculobullous disorders, 10(76.9%) out of 13 lepra reactions, and 1(9.09%) out of 11 connective tissue disease patients developed adverse effects while on long term corticosteroid therapy.[Table3]

Diabetes mellitus was seen in 25(31.25%) patients out of 80 patients on daily glucocorticoid therapy in present study which is comparable to 36(25%) out of 145 in Arner et al[5] study.

Proposed risk factors for Steroid induced diabetes mellitus included old age, high BMI, impaired glucose tolerance before therapy, cumulative dose, and long duration of steroid therapy. However, these results were not always consistent across studies.[4] In our series of 80 patients treated with steroid, old age was an independent risk factor for diabetes mellitus. All diabetic cases in present study belong to mean age of 54.32 years.

TYPE OF DISEASE	NUMBER OF PATIENTS(n-80)	No of patients developing side effects
VESICULOBULLOUS DISOREDRS		
Pemphigus Vulgaris	33	26
Pemphigus Foliaceus	6	4
Oral Pemphigus	1	1
Bullous pemphigoid	8	6
LEPRA REACTIONS		
TYPE I	4	4
TYPE II	9	6
KERATINISING DISORDERS		
Erythroderma	4	0
Photodermatitis	4	2

CONNECTIVE TISSUE DISEASE		
SLE	8	1
Scleroderma	3	0

TABLE 3: DISEASE WISE DISTRIBUTION OF PATIENTS ON LONG TERM GLUCOCORTICOIDS INCLUDED IN OUR STUDY

ADVERSE EFFECTS	NUMBER OF PATIENTS DEVELOPING ADVERSE EFFECTS
METABOLIC	
Diabetes mellitus	25(31.25%)
Hypertension	18(22.5%)
Hyperlipidemia	4(5%)
Cushingoid features	
Weight gain	15(18.75%)
Moon face	6(7.5%)
Truncal obesity	4(5%)
MUSCULOSKELETAL	
Osteoporosis	2(2.25%)
EYE RELATED	
Cataract	2(2.25%)
Herpes simplex keratitis	2(2.25%)

TABLE 4: METABOLIC, MUSCULOSKELETAL AND EYE RELATED SIDE EFFECTS ASSOCIATED WITH LONG TERM GLUCOCORTICOIDS.

Glucose tolerance declines progressively with age, resulting in a high incidence of type 2 diabetes and impaired glucose tolerance in the old population. With aging, beta-cell function declines, and basal insulin secretion level decreases. In addition, the interaction of many factors associated with aging likely contributes to the altered glucose tolerance. These factors include obesity, decreased physical activity, medications, and coexisting illness (4). Considering the vulnerability of the aged population to glucose intolerance, the association of steroid induced diabetes mellitus and age in our study can be understood.

Arterial hypertension developed in 18(22.5%) out of 80 cases on daily glucocorticoid therapy in present study, which was comparable to 7 (20 %) out of 35 cases in a prospective study by Klepikov et al (6) which was done on patients of nephrotic syndrome on long term steroids. 5 out of 18 were females and 13 out of 18 were males.

Ljubojevic et al(7) study on 159 patients of pemphigus on long term steroid therapy showed steroid induced diabetes mellitus in 37(23.2%) and Hypertension in 23(14.5%) compared to the present study steroid induced diabetes mellitus -25(31.25%) and Hypertension -18(22.5%).

Glucocorticoids increase lipid levels because of increased lipid production in liver and due to lipolysis from adipose tissue. It causes redistribution of fat, carbohydrate and protein reserves. This along with increase in appetite leads to cushingoid habitus (moon facies, buffalo hump and central obesity). Cushingoid features and weight gain (based on weights taken on initiation and after 6 months of therapy) was observed in 17(21.25%) and 15(18.75%) patients respectively.

Hyperlipidemia is a common side effect of therapy, especially in patients with prior lipid abnormalities. Elevation of triglycerides is most common, but elevations of high-density lipoproteins or low-density lipoproteins occur in some patients. The mechanism of hypertriglyceridemia is likely related to relative insulin insufficiency. (8) 4(5%) out of 80 patients on daily glucocorticoids developed lipid abnormalities in the present study, as compared to 15(56%) patients out of 27 in study by Gunjotikar et al14.

Mathis et al(9) reported weight gain-79.6%, diabetes mellitus-52.4% and Hypertension-71.8% in kidney and pancreas transplant recipients receiving long term steroid therapy compared to present study(Weight gain-18.75%, diabetes mellitus-31.25% and hypertension-22.5%).

Osteoporosis is one of the most prevalent side effects that occur in patients on long term systemic gulcocorticoid therapy. Osteoporosis occurred in 2.25% of all patients treated chronically with glucocorticoids with proper preventive measures. Radiographs can detect bone changes only when 30% of density has been lost (10). If recent techniques like quantitative CT and DEXA scan were employed, more number of cases could have been detected to have osteopenia and early therapeutic intervention could have been possible. (11), (12).

The lower incidence of musculoskeletal side effects may be due to lesser sample size, limitations of technology to assess osteopenia and proper preventive measures taken such as daily calcium supplements and tab alendronate (35 mg) once a week.

Vesiculobullous disorders were the most common indication for daily glucocorticoid therapy. Mean age of developing pemphigus was 49.46 years in females and 50.08 years in males. Age of the patients affected may act as independent risk factor in developing hypertension, diabetes and bone related adverse effects of systemic oral glucocorticoid therapy.

Long term use of topical and systemic steroids produces secondary open angle glaucoma similar to chronic simple glaucoma as well as cataract. 2(2.25%) patients developed cataract and 2(2.25%) patients developed herpes simplex keratitis in our study as compared to 54(34.83%) out of 155 in the Matsunami study(13) in which the indication for the study was immunosuppression after renal transplantation. Ocular complications in the later study were significantly higher than the present study.

CONCLUSION

Systemic glucocorticoids are widely used to treat autoimmune and inflammatory skin diseases. The prolonged use of glucocorticoids, however, is associated with potentially serious adverse effects. Many of these side effects are potentially minimized by careful monitoring and using appropriate preventive strategies. As dermatologists, we can make patients aware of these data and help them decide which prevention/treatment options are best for them. While using daily glucocorticoid therapy, continuous monitoring and adverse effect prevention measures such as life style modification (cessation of smoking and alcohol, regular weight bearing exercise, low fat, low sodium diet) and various medications such as antacids, calcium supplements and bisphosphonates should be considered for patient's benefit. As and when feasible, steroid sparing agents (cyclophosphamide, azathioprine, methotrexate, cyclosporine, rituximab and Intravenous Immunoglobin therapy) should be considered along with glucocorticoids.

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