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Long Term Glucocorticoids effects on Underlying Dermatological Conditions: A Tertiary Care Center Study

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ABSTRACT

Background: In Dermatology, corticosteroids (CSs) are widely prescribed in various formulations to tailor the therapy according to severity of the condition, area of involvement, and patient's age. CSs, are associated with a number of serious adverse effects, particularly with long-term use.

Aims: To study the relationship of adverse drug reactions (ADR) of long term glucocorticoids (GC) with age, sex, smoking, alcoholism, underlying dermatologic conditions and co-existing medical disorders.

To study them in relation to the musculoskeletal system,metabolic *** levels and eye.

Material and Methods: This was a prospective study done on 130 patients on glucocorticoid therapy for more than 1 month duration during a period of 2 years in the department of dermatology over a tertiary care centre. Thorough clinical examination, and relevant investigations were done.

Results: Cushingoid features and weight gain were observed in both groups. Bone changes, DM and HT (Hypertension) were seen in patients on DGC therapy. Bone changes (in form of osteopenia, osteoporosis and AVN-avascular necrosis) were seen in 17 (18.88%), Steroid induced Diabetes Mellitus (SDM) in 27 (30%), HT in 12 (13.3%), Lipid abnormalities (in the form of raised cholesterol and triglyceride levels) in 7 (7.77%), Cataract in 12(13.33%) and glaucoma was seen in 1(1.11%) out of 90 patients on Daily glucocorticoid therapy. 1 patient out of 40 in the OMP group developed cataract and HT.

Maximum patients were in the age group of 31-40 years. Cushingoid features were observed in both groups.In the DGC group, Weight gain (82.22%), Bone changes 17(18.88%),Steroid induced Diabetes Mellitus 27 (30%),hypertension 12(13.3%),altered lipid profile 7(7.77%),Cataract in12 (13.33%) and glaucoma 1 (1.11%) were the side effects. Weight gain 10(25%) 1(2.5.% Hypertension and 1 (2.5.%) developed cataract.

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Conclusion: In conditions like vitiligo, alopecia areata and lichen planus particularly in children, it is preferable to give OMP. In pemphigus group of disorders while using daily GC therapy continuous monitoring and ADR prevention measures should be considered for patient's benefit. Females and elderly patients are at the risk of bone related side effects particularly due to long term usage of daily glucocorticosteroids. OMP , Pulse Therapy and other steroid sparing agents can be considered to prevent the side effects of long term GC therapy.

Keywords: Glucocorticoids, Oral Mini-Pulse, Dermatological etc

INTRODUCTION

CSs play a major role in the dermatologist's armamentarium. CSs have long been a mainstay of pharmacotherapy in a variety of disorders and conditions for the suppression of inflammation and of the immune system.

CSs are widely prescribed in dermatology, however they are associated with a number of serious adverse events, particularly with long-term use. Safe and effective use of this class of agents, therefore, requires knowledge of their mechanism of action and potential complicating factors. GCs, however have proven to be the "archetypal double edged sword of medicine."

In general, the risk of adverse effects of corticosteroids increases with the duration of therapy and frequency of administration. Side effects such as gastrointestinal intolerance, mood changes, nervousness, and insomnia can occur with short courses of corticosteroids. It can cause various metabolic adverse effects like hyperglycemia, hypertension, cushingoid changes, etc.

A high index of suspicion is needed to catch adverse effects such as osteopenia, avascular necrosis and cataract as they are not visible clinically and may be missed.

MATERIAL & METHODS

This was a hospital based prospective study done on 130 patients who attended the Dermatology OPD of Amaltas Institute of Medical Science Dewas and were on systemic oral glucocorticoid (GC) therapy given on daily basis or in Oral Mini-Pulse (OMP) therapy (for more than 1 month duration) from April 2019 to May 2022.

All patients on systemic oral GC therapy given either on daily basis or OMP therapy for more than 1 month duration with minimum 6 months of follow up were recruited in the study. Daily glucocorticoid (DGC) therapy comprises daily administration of Prednisolone (l-2mg/kg/day) or Methylprednisolone whereas OMP therapy consists of administering Betamethasone (0.1mg/kg) on two consecutive days per week. In both cases the dose was tapered according to clinical response.

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.

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Ophthalmological examination and X-rays was 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.

Other immunosuppressive therapy like cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil as steroid sparing agents were given to the patients who developed steroid ADR or who did not respond to treatment. Pulse therapy was considered wherever possible.

OBSERVATION & RESULTS

Out of 130 patients included in the study, 90 (69.23%) cases were on DGC and 40 (30.77%) were on OMP therapy. Out of 40 cases in OMP group, 20 were males and 20 were females. Out of 90 cases in DGC group, 40 were males and 50 were females.

15 (37.5%) out of 40 cases in OMP group and 29 (32.2%) out of 90 in DGC group were in the age group 31- 40 years. 34 (85%) out of 40 patients in OMP group and 60 (66.67%) out of 90 cases in DGC group were on treatment for 1-6 months at the time of inclusion. Mean duration of therapy was 5.2 months in OMP group whereas it was 7.88 months in the DGC group.

Most common indication for DGC was autoimmune vesiculobullous disorders like pemphigus vulgaris and its variants (40%) followed by lepra reactions (18.88%). On the other hand lichen planus constituted the most common indication (40%) followed by alopecia areata (25%) and vitiligo (17.5%) for OMP therapy. The various indications for which GC therapy of more than 1 month duration was given are shown in Table 1.

Table 1: Conditions for which GC therapy of more than 1 month duration was given: OMP vs. DGC (n= 130)

Indication	OMP (n= 40) Number	Percent %	Daily GC (n=90) Number	Percent %
Lichen planus	16	40	4	4.4
Alopecia areata	10	25	1	1.1
Bullous pemphigoid	-	-	2	2.2
Vitiligo	7	17.5	-	-
Lepra Reactions	-	-	17	18.88
Airborne contact Dermatitis	-	-	2	2.2
Pemphigus group	5	12.5	36	40
Morphea	1	2.5	-	-
Photolichenoid eczema	1	2.5	-	-

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Atopic Dermatitis	-	-	3	3.3
Photodermatitis	-	-	4	4.4
Vasculitis	-	-	3	3.3
MCTD/UCTD/SLE/SS/RA	-	-	14	15.55
Granuloma annulare	-	-	1	1.1
Disseminated eczema	-	-	3	3.3
Total	40	100	90	100

Bone and metabolic ADR seen in both groups are shown in Table 2. Side effects like bone changes and DM were seen only in patients on DGC therapy. Maximum number of patients 29 (32.2%) on DGC were of age group 31-40 years, and pemphigus group of disorders was the major indication.

Cushingoid features and weight gain (based on weights taken on initiation and after 6 months of therapy) was observed in both groups, while 1 patient in OMP group suffered from hypertension.

Table 2: Bone and Metabolic ADR due to GC therapy: OMP vs. DGC Therapy (n=130)

Sr. no.	ADR	OMP(n= 40)	Daily GC(n=90)
1	Bone changes	(0%)	17(18.88%)
2	Steroid induced DM (SDM)	(0%)	27(30%)
3	Arterial HT	01(2.5%)	12(13.33%)
4	Cushingoid Features	07(17.5%)	36(40%)
5	Weight gain	10(25%)	74(82.22%)

MAS[1] et al reported weight gain-79.6%, SDM-52.4% and HT-71.8% in kidney and pancreas transplant recepients receiving long term steroid therapy compared to present study(Weight gain-82.22%, SDM-30% and HT-13.33%).

Bone changes were seen in 17 (18.88%) out of 90 cases on Daily GC therapy in the present study. This included 12 patients with osteopenia (8 males and 4 females), 3 with osteoporosis (females) and 2 with AVN (a male and female of 28 years each). Out of 17 , 8 were females who belonged to age group more than 40 years. Mean age of developing osteopenia in females was 45 years. Both patients with AVN were young (age 28 years). Bone changes in the current study vs. comparative study are shown in Table 3.

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Table 3: Bone changes due to DGC Therapy: Present study vs. Comparative study

Bone changes	Present study(n=90)	Sharma P et al(n=60)[2]
Osteopenia	12(13.33%)	04(6.7%)
Osteoporosis	3(3.3%)	02(3.3%)
AVN/ON	2(2.2%)	01(1.7%)
Total	17(18.88%)	07(11.7%)

SDM was seen in 27(30%) patients out of 90 on DGC therapy in present study vs. 36(25%) out of 145 in the comparative study. P Arner et al[3] study was carried out in renal transplant recipients and incidence of steroid diabetes correlated with steroid dose, age, body weight and diabetes heredity. All cases in present study were belonging to mean age of 48.51 years age group.

Arterial hypertension developed in 12 (13.3%) out of 90 cases on DGC Therapy in present study, while it was 7 (20 %) out of 35 cases in a prospective study by PVK et al [4] which was done on patients of nephritic syndrome on long term steroids. All cases in present study with HT were belonging to the mean age of 47.91 years. 7 out of 12 were females and 5 out of 12 males. Out of these 12 patients 1 developed nephropathy, 5 cataract, 4 osteopenia, 1 AVN.

7 (17.5%) out of 40 cases in OMP group and 36 (40%) out of 90 cases in DGC group developed cushingoid features. 21 out of 43 (48.83%) cases were females. Moon facies was the most common finding among moon facies, truncal obesity and buffalo hump.

36 out of 90 patients in DGC group were of Pemphigus. LS et al[5] study on 159 patients of pemphigus on long term steroid therapy showed SDM in 37(23.2%) and HT in 23(14.5%) compared to the present study (Bone changes-06(16.66%), SDM-17(47.22%) and HT-06(16.66%)).

When comparing ADR in OMP group (10 patients in present study) for alopecia areata with Goyal NN study [6] (14 patients) both had 2 patients with cushingoid facies and 6 with weight gain. 1 patient had SDM in the comparative study.

7(7.77%) out of 90 patients on DGC developed lipid abnormalities in the present study, as compared to 15(56%) patients out of 27 in study by Gunjotikar et al[7]. The indication in the later study was that of immunosuppresion for renal transplant patients.

11 out of 90 in the DGC group and 1 out of 40 in the OMP group patients out of 90 developed cataract in present study as compared to 54 out of 155 in the Matsunami study[8]. The major indication in this study was for Pemphigus patients, while it was immunosuppression after renal transplantation in the Matsunami study. 1(1.11%) out of 90 and 2(1.29%) out of 155 patients developed glaucoma in present study and Matsunami study respectively.

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DISCUSSION

There were more females in the study as they suffer more from autoimmune disorders like vesiculobullous diseases.

Both the dose and duration of steroid therapy was higher and longer in DGC group as compared to OMP group.

Osteoporosis is one of the most prevalent side effects that occur in patients on long term systemic gulcocorticoid therapy. Osteoporosis occurs in 30-50% of all patients treated chronically with glucocorticoids without proper preventive measures.[9,10] Bone changes were seen in 17(18.88%) out of 90 cases on Daily GC therapy.

Radiographs can detect bone changes only when 30% of density has been lost. 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. Fractures occur in upto 25 % of patients receiving long term GCs but this rate increases in postmenopausal females.[11,12] Out of 17 cases that had developed DGC induced bone changes 8 were females who belonged to age group more than 40 years. Mean age of developing osteopenia in females was 45 years.

It is generally agreed that long- term, high dose steroid therapy carries a definite risk for steroid induced osteonecrosis(ON), but it is not clear whether short-term, high-dose; or long-term, low-dose steroid use also carries the same risk.[13] There is some evidence to show that daily administration of steroids is more strongly associated with ON compared to steroids administered as a bolus.[14] Two patients of either sex in the current study developed avascular necrosis of femur head, both being 28 years of age. The indications being Pemphigus vulgaris and MCTD.

Steroid induced HT is a known entity, however is controversial. The less no. of cases of steroid induced HT in present study could have been because of the reason that, in the comparative study the indication for long term steroids was nephritic syndrome. The most relevant study was performed 26 years ago, when Jackson and colleagues[15] studied the effects of corticosteroid therapy on BP in 129 asthmatic and 66 RA patients; they concluded that long – term (>1yr) 'low-dose' (<20 mg daily) GCs do not lead to BP increase, and that significant HT may be better explained by age and intial BP than by the use of GCs.

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). 21 out of 43 (48.83%) cases that developed cushingoid features were females. In a study by Fardet et al it was reported that daily corticosteroid induced lipodystrophy was

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higher in women, in subjects younger than 50 years of age, in subjects with a high initial body mass index and in subjects with high energy intake.

Cushingoid features and weight gain (based on weights taken on initiation and after 6 months of therapy) was observed in both groups, while 1 patient in OMP group suffered from hypertension.Verma KK et al reported that except for weight gain in 2 out of 10 patients on oral mini pulse therapy and mild cushingoid features in 1 patient no other side effects were observed in any of the patients on oral mini pulse therapy.[16] In the present study 10 patients out of 40 had weight gain in OMP group.

Pemphigus group of disorders was the most common indication for DGC therapy. 20 (55.55%) out of 36 patients of Pemphigus group were females. Mean age of developing pemphigus was 43.85 years in females and 44.43 years in males. It is a disease of 40-50 years age group who are more prone to develop HT, DM and bone related ADRs of systemic oral GC therapy.

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.[17]

The lipid abnormalities in the comparative study were significantly higher. The indication in the Gunjotikar R V study[7] was that of immunosuppresion for renal transplant patients. In addition to prednisolone, azathioprine and cyclosporine were given and the dose as well as duration was more in the later study. All patients with lipid abnormalities were females. In them, the social stress as well as the stress of disease itself may have aggravated the chances of hyperlipidemia because of GC therapy.

Long term use of topical and systemic steroids produces secondary open angle glaucoma similar to chronic simple glaucoma as well as cataract. Ocular complications in the Matsunami C study were significantly higher than the present study. Here the major indication was for immunosuppression after renal transplantation.

OMP therapy using betamethasone/dexamethasone 5mg on weekdays was successfully used by Pasricha JS et al for arresting progressive vitiligo. They reported minor side effects like weight gain, mild headache, transitory general weakness for 2 days after the pulse and bad taste in the mouth.[18] Kanwar AJ et al reported OMP using low dose dexamethasone 2.5mg on weekdays for progressive vitiligo and concluded that it was effective with minimal side effects.[19] On the contrary Goyal Nilesh N et al had reported that oral mini pulse steroid therapy in alpoecia areata does not confer any significant advantage over daily steroid therapy in terms of adverse effects.[6] Betamethasone on two consecutive days in a week as oral mini pulse therapy may be a safe, effective and a better therapeutic alternative for the treatment of lichen planus (Verma KK).[16]

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To conclude, in conditions like vitiligo, alopecia areata and lichen planus particularly in children, it is preferable to give oral mini pulse therapy. In pemphigus group of disorders while using daily GC therapy continuous monitoring and ADR prevention measures should be considered for patient's benefit. As and when feasible, steroid sparing agents (cyclophosphamide, azathioprine, methotrexate, cyclosporine, rituximab and Intravenous Immunoglobin therapy) and GC pulse therapy should be used, more so in high risk groups like elderly cases having pre-existing diabetes or hypertension.

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