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Research article

COMPARATIVE STUDY OF PULSE THERAPY WITH DAILY IMMUNOSUPPRESSIVE THERAPY IN STEROID RESPONSIVE DERMATOSIS

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ABSTRACT

Background: Pemphigus, scleroderma and SLE are diseases of unknown etiology for which no specific treatment is effective. The introduction of corticosteroids and immunosuppressive drugs reduced the mortality rate. **Objectives:** To correlate signs and symptoms and incidence of adverse effects in patients with steroid responsive dermatosis before and during DCP therapy and daily immunosuppressive therapy. **Material and Methods:** 100 patients were enrolled in this study. They are divided into 2 groups. The treatment schedule in group 1 consists of giving 100mg dexamethasone on 3 consecutive days and 500 mg cyclophosphamide on day two and repeating these pulses (DCPS) every 4 weeks. In between the DCPS, the patient received only 50mg cyclophosphamide orally daily and generally no corticosteroids. Group 2 patients received daily immunosuppressive therapy in the form of tab prednisolone 1-2mg/kg body weight and tab cyclophosphamide 50 mg after food daily for 6months. **Results:** At the end of 6 months of study period, based on clinical improvement, good response was seen in 82% in group 1 and in 64% in group 2P<0.05 which is significant. Moderate response was seen in 10% in group 1 and in 22% in groups 2.8% in group 1 and 14% in groups 2 recorded poor responses. Better response was seen with DCP therapy. The incidence of adverse effects was less with DCP therapy when compared to daily immunosuppressive therapy. P<0.0001 which is highly significant. **Conclusion:** DCP therapy is safe and effective in the treatment of steroid responsive dermatosis. Incidence of adverse effects was less with DCP Therapy.

Keywords: Dexamethasone, Cyclophosphamide, Pulse therapy, Daily immunosuppressive therapy, Pemphigus, systemic lupus erythematosus (SLE)

INTRODUCTION

Pulse therapy, the big shot [1] refers to administration of large doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects [2]

The auto-immune dermatologic disorders such as pemphigus, systemic sclerosis [3], systemic lupus erythematosus, dermatomyositis, pyoderma gangrenosum, toxic epidermal necrolysis[4],Stevens Johnson's syndrome[5], lichen planus, alopecia aerate, sarcoidosis and systemic vasculitis[6] are considered to be serious diseases with high morbidity and mortality. The outcome of these diseases before the advent of Corticosteroids was death.

The introduction of corticosteroids in therapy reduced the mortality rate. However the requirement of high dose and long term steroid regimens resulted in therapy related morbidity and mortality. Most of the deaths occurred during the first few years of the disease and if the patient survived for five years, the prognosis was considered as excellent. The introduction of immunosuppressive drugs as adjuvants[7]further reduced the mortality rate but no significant improvement was observed in the

frequency of remissions. Dexamethasone cyclophosphamide pulse (DCP) therapy was then suggested as an effective alternate therapy for the treatment of these autoimmune dermatologic conditions.

Pulse therapy consists of giving a very high dose of a drug to bring about a quick result and then withdrawing the drug completely till it is needed again. Pulse therapy took its origin when intravenously administered high dose steroids (suprapharmacological doses of methyl prednisolone) could successfully reverse the rejection of renal transplantation without any undesirable effects [8].Then it became the important mode of management in all renal transplantation cases.

Later, the pulse therapy was extended to the management of other disorders like lupus nephritis, Polyarteritisnodosa (PAN), Rheumatoid arthritis (RA), pyoderma gangrenosum [9]with the obvious benefit of a quick recovery and without undesirable sequelae. Quick recovery was attributed to the anti-inflammatory and immunosuppressive effects of high doses of corticosteroids.

The rapid elimination of intravenously administered drug might be responsible for minimization of side effects, prompt recovery of hypothalamo pituitary adrenal (HPA) axis[10] function and minimal stigmata of Hypercorticism. Life threatening complications such as severe adverse cardiovascular effects reported in some of the studies appeared to be restricted mostly to the patients suffering from non-dermatological disorders particularly with cardiac[11] and renal disorders.

For the first time in India, Pasricha et al successfully carried out pulse therapy with dexamethasone In a patient with Reiter's disease[12]. The promising results encouraged them to try the same in potentially fatal diseases like Pemphigus, systemic sclerosis,SLE, etc.

To achieve a prolonged remission, they arbitrarily designed a regimen with dexamethasone and cyclophosphamide termed the DCP therapy. The treatment followed four phases (first three are treatment phases, last phase being the post treatment follow up). The choice for dexamethasone was based on availability and economy. Dexamethasone being the long acting steroid, treatment for three days was found adequate reducing the hospital stay and ensuring prompt recovery of HPA axis. The negligible mineralocorticoid activity further reduced the incidence of life threatening complications. Of the 300 patients enrolled in their study for DCP therapy, 190 patients were reported to have completed the treatment till date. The maximum duration of remission with post treatment follow up was 9 years. The major advantage was that almost every patient could be induced into remission.Furthermore, the side effects associated with conventional daily use of corticosteroids such as diabetes, hypertension osteoporosis, electrolyte imbalance, cushingoid changes, cataract, weight gain, striae and acne were either not seen or minimal. Dietary changeslike salt or calorie intake restriction or supplements of calcium or potassium were not required.

Encouraging results of these challenging trials made the subject an interesting one from the view point of therapeutic study. Hence the present study was undertaken to compare the DCP therapy with daily immunosuppressive therapy in steroid responsive dermatosis.

MATERIALS AND METHODS

Study design: Open label and parallel group, prospective comparative clinical study between daily immunosuppressive therapy and dexamethasone cyclophosphamide pulse [DCP] therapy in patients with steroid responsive dermatosis.

The study was conducted at department of dermatology in OGH Hyderabad andthe duration of study is for 6 months

Sample size: 100 patients with dermatosis (like pemphigus vulgaris, SLE, scleroderma, etc.)

Ethical approval: Approval from the Ethics Scientific Committee of Osmania Medical College, Hyderabad was obtained (annexure). After selection of the patients based on the above criteria, patient was explained about the study in their own understandable language & written informed consent was obtained.

Inclusion criteria: 1. Age group- Patients in the age group 16-60yrs receiving oral immunosuppressive therapy for steroid responsive dermatosis were included in the study.2. Sex- Both male & female patients were included in the study.

Exclusion criteria: Cardiac patients suffering with hypertension, angina, myocardial infarction, cardiac arrhythmias and stroke.Patients with uncontrolled diabetes mellitus, psychiatric problems, renal and liver diseases, on immunosuppressive drugs for other conditions, any disorder where high dose

corticosteroids are contraindicated, evidence of major systemic disease, and 8.Pregnant &lactating women.

The cases for this study were taken from Dermatology department Osmania General Hospital, Hyderabad. Patients showing signs and symptoms suggestive of steroid responsive dermatosis like [pemphigus, Systemic lupus erythematosis (SLE), systematic sclerosis, etc.] were selected for this study.

Grouping:A total of 100 patients, divided into 2 groups [group1 and group2] of 50 patients each were studied

Group 1: Received pulse therapy regimen called as dexamethasone cyclophosphamide pulse [DCP] therapy. It consists of giving 100mg dexamethasone dissolved in 500ml of 5% dextrose as a slow intravenous [IV] drip over 2 hrs repeated on 3 consecutive days every month and on 2nd day the patient is given cyclophosphamide 500mg in the infusion followed by ± prednisolone 1mg/kg daily and cyclophosphamide 50mg daily orally for 6 months.

Group2:Received daily immunosuppressive therapy. Tab prednisolone 1-2mg/kg body wt after food along with an antacid before breakfast. Tab cyclophosphamide 50mg after food daily orally for 6 months.

Methodology: For pulse therapy all the patients were hospitalized (minimum 4 days for every pulse)daily immunosuppressive therapy patients were treated in the OPD.Recording of present complaints with duration, personal and family history of autoimmune dermatological conditions. General examination of the patient.4. Dermatological examination of the patient.Investigations:Before treatment following investigations were done- haemogram, complete urine analysis, blood sugar (fasting & post lunch) blood urea, serum creatinine, serum electrolytes, liver function tests, Electrocardiogram &stool examination for occult blood was done X-ray chest and bones (lumbar spine, proximal end of femur etc.) and ophthalmic examination forcataract, glaucoma etc. were done before starting the treatment and whenever required and at the conclusion of study. Vital data and weight were recorded at every visit. Serum cortisol level estimation could not be done which helps to know the HPA axis functional state, but endocrinologist's opinion was taken in this regard.

Treatment: Group1 patients received dexamethasone cyclophosphamide pulse (DCP) therapy. It consists of giving 100mg dexamethasone dissolved in 500ml of 5% dextrose given by a slow intravenous infusion, over a period of not less than 2 hours and this was repeated on 3 consecutive days. In addition, 500m g of cyclophosphamide was added to dexamethasone in the same drip on the second day. The dexamethasone cyclophosphamide pulses [DCP] were repeated at 4weekely Intervals. In between the DCPs, the patients were given 50mg cyclophosphamide orally every day.

Group 2-Patients received Tab prednisolone 1-2mg /kg body wt after food along with a proton pump inhibitor before breakfast .In addition to this Tab cyclophosphamide 50mg after food daily orally for 6 months.The treatment with DCP regimen has been divided into four phases namely –

Phase 1 – It lasts till complete remission is achieved.During this phase monthly DCP and daily cyclophosphamide 50mg are given. Lesions heal very quickly after pulse but reappear after a variable period. Recurrences become progressively less severe with repeat pulses.

Phase 2- Once complete remission is achieved, the patient is said to be in phase 2. Duration of phase 2 is fixed and lasts for 6 months during which monthly and daily cyclophosphamide are continued.

Phase 3-It lasts for a year during which time daily cyclophosphamide is continued. The patient continues to be disease free in this phase.

Phase 4-In this phase treatment is stopped and the patient is followed up i.e., treatment free and disease free followsup.

The clinical course of the disease, therapeutic benefits and side effects of therapy were recorded in specific proforma. The patients were advised to take regular bath with soap and water even during the phase of clinical activity. Topical medications like steroid and steroid- antibiotic preparations were prescribed as per requirement. Treatment of other concomitant diseases was continued and drug induced complications such as infections, diabetes, hypertension, acid peptic disease etc. were simultaneously treated without interrupting the specific treatment. Salt restriction and potassium supplementation were not advised during pulse therapy. However high protein diet and calcium supplementation were advised to some patients who received high dose steroids. The response rate based on clinical improvement was graded as follows: [13]

1+ Poor response

2+ Moderate response
3+ good response

The response rate was assessed on the basis of clinical improvement. Clinical improvement in pemphigus was assessed by healing of old lesions, decrease in new lesions and disappearance of oral lesions. Clinical improvement in SLE was assessed by improvement in rash, photosensitivty, arthralgia, myalgia and decrease in proteinuria.

Response in scleroderma was assessed by softening of skin, improvement in shortness of breath, improvement in joint mobility, myalgias and arthalgias. Follow up: This included recording of any improvement in symptoms and signs, any adverse effects of the treatment.End point: Primary end point : Complete clinical improvement (assessed by healing of old lesions, decreasing new lesions, decrease in arthralgia and myalgia) Secondary end point: To assess the incidence of any adverse effects.

Statistical analysis : All the values are expressed as mean ± SD. Improvement in clinical response and incidence of adverse effects between the two groups was done by using chi-square test and unpaired t test, p value < 0.05 was considered as significant.

RESULTS

Table1: Age distribution of patients among two groups

Age Group(years)	Group I		Group II	
	N	%	N	%
16-25	6	12	9	16
26-35	13	26	11	22
36-45	23	46	13	26
46-60	8	16	18	36

Group I: DCP Therapy, Group II: Daily immunosuppressive therapy

Table 2: Sex distribution of patients among two groups

Group	Males		Females	
	n	%	n	%
Group I	12	24	38	76
Group II	17	34	33	66

Table3: Categories of patients

Group	Group I		Group II	
	Male	Female	Male	Female
Pemphigus	12	36	17	28
SLE	-	1	-	3
Scleroderma	-	1	-	2

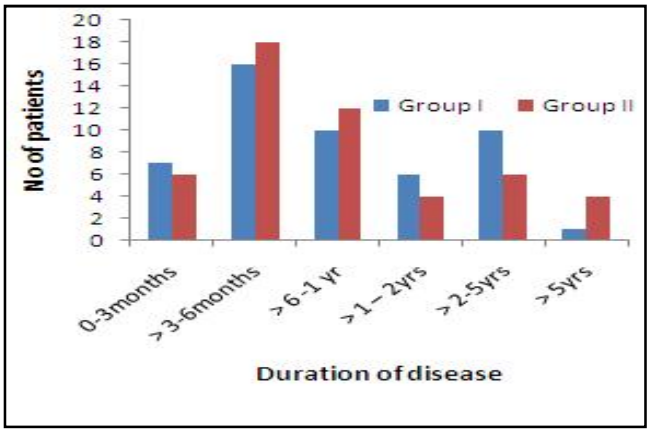

Fig 1:Duration of disease before treatment

Table 4:Side effects

Side effects	Group I	Group II	P value
Cushingoid features	4	88	<0.0001
Pyoderma	16	74	<0.0001
Dermatophytosis	18	66	<0.0001
Striae	18	66	<0.0001
Diffuse hair loss	14	62	<0.0001
Acne	24	58	<0.0001
Candidiasis	24	56	<0.0001
Hyper acidity	18	54	<0.0001
Weight gain	11	46	<0.0001
Hyper pigmentation	14	42	<0.0001
Ecchymosis	4	38	<0.0001
Flushing	44	36	0.05
Hypertension	16	36	0.0001
Loss of appetite	16	36	0.0001
Diabetes mellitus	6	34	<0.0001
Cataract	12	34	0.0001
Hirsutism	6	12	> 0.05
Psychosis	4	10	> 0.05
Hiccup	16	8	> 0.05
Hemorrhagic Cystitis	2	6	> 0.05
HPA axis separation	0	6	< 0.01
Tuberculosis	2	6	>0.05
Aseptic necrosis of bone	2	4	>0.05
Glaucoma	0	0	0

P value:< 0.0001, highly significant

DISCUSSION

Pemphigus, SLE and scleroderma are autoimmune diseases associated with high morbidity and mortality. Though several factors have been

identified to have important role in determining the prognosis' the course of the disease is variable and unpredictable for a given patient. Hence early diagnosis and effective therapy may greatly modify the course of the disease. According to Lever and Schaumberg Lever early intensive treatment can lead to complete remission in pemphigus.[14]The use of high dose steroids and immunosuppressive drugs for prolonged periods could effectively control the disease, but it was associated with significant morbidity and mortality. Hence DCP therapy regimen has been tried to achieve prolonged remission which may amount to cure in pemphigus, SLE and scleroderma.

The combined immunosuppressive [suppression of the monoclonal antibody responses] and anti-inflammatory effects of both, immunosuppressive drugs and suprapharmacological doses of corticosteroids have been utilized in pulse therapy to induce immune tolerance. Adding to the benefits, the rapid elimination of the intravenously administrated drugs allows little time for the development of any undesirable side effects.

The primary objective of our study was to compare the safety and efficacy and the incidence of adverse effects between the two treatment groups (DCP therapy and daily immunosuppressive therapy) for 6 months. The first reported use of pulse steroid therapy (PST) was by Kountz and Cohn in 1969 and Bellet al in 1971 to prevent and treat rejection of kidney transplantation. [15] The first use of DCP therapy in dermatology was reported two decades ago. At that time, it represented a radical change in the approach to skin diseases as pulse therapy had previously been used. Mainly to prevent transplant rejection and in the treatment of lupus nephritis. [16]

In 1982, Pasricha et al introduced DCP therapy in order to reduce the side effects of conventional steroid therapy. The therapy has since been used to treat a very large number of patients at several centers[17-24] in India and elsewhere.[25-30] The reason behind the effectiveness of pulse therapy is that the treatment has evolved in response to observations of the results of treatment in patients who were receiving DCP therapy. Cyclophosphamide was added to dexamethasone because relapses were frequent with dexamethasone alone. Clinical studies by Pasricha et al have also shown that DCP therapy has produced quick control of the disease and reduced hospital stay. Later it was noted to lead to long lasting remissions (extending up to 9 yrs.) even after stopping therapy, virtually amounting to cure[31]. The efficacy of pulse steroid therapy reflects the complex interplay of multiple physiologic and biochemical events. Large doses of intravenous (IV) steroids affect the numerous facets of the immunologic and inflammatory process which involve immunoglobulins, lymphocytes, monocytes, macrophages, polymorphonuclear leucocytes.

Studies carried by Pai et al[21]have enrolled 5 women with scleroderma aged between 30-60yrs, all the patients had symptomatic clinical improvement. The vital capacity improved in three and post treatment histopathologic regression was seen in two patients. Whereas in our study there was only one patient of scleroderma on DCP therapy and two patients on daily immunosuppressive therapy. The patient on DCP therapy showed good response whereas the two patients on daily immunosuppressive therapy showed moderate response. Several studies have reported the effectiveness of DCP therapy in scleroderma. Cathcart et al[32] treated SLE patients with DCP therapy and observed that DCP therapy was effective in treating these patients of bullous lupus erythematosis. Our study enrolled one patient of SLE on DCP therapy and 3 patients on daily immunosuppressive therapy. A better response was seen in patients on DCP therapy, the rash was decreased glomerular filtration rate (GFR) improved. Myalgiasand arthralgias improved.

At the end of six months of treatment in our study, the incidence of adverse effects recorded in both the groups showed that the adverse effects with DCP therapy were less than with daily immunosuppressive therapy. DCP therapy minimized the need for long term, high dose oral steroid therapy (elimination of the intravenously administered corticosteroids allows little time for the development of any undesirable side effects. The adverse effects of pulse therapy are those of its constituent drugs, corticosteroids (infections, diabetes mellitus, hypertension, hyperacidity and osteoporosis) and cyclophosphamide (leucopenia, hematuria, gonadal failure, hyperpigmentationand hair loss). The major side effect reported with immunosuppressive regimen in the literature is increased susceptibility to infections like candidiasis, dermatophytosis and pyoderma. Similarly in the present study we observed that the infections were

less frequent with DCP therapy than with daily immunosuppressive therapy.

Pyoderma was found in 16% in group 1 and 74% in group 2, dermatophytosis was found in 18% in group 1 and 66%. Candidiasis was seen in 24% in group 1 and in 56% in group 2 ((P<0.0001 which was highly significant). Cushingoid features were seen in 4% in group 1 and 88% in group 2. (p<0.0001 which was highly significant) HPA axis suppression was seen in 6% of patients in group 2. Whereas none of the patients in DCP therapy had HPA axis suppression (p<0.0001, which was highly significant). Ecchymosis was found in 4% in group 1 and in 38% in group 2 (p<0.0001, which was highly significant), Flushing was noted in 44% in group 1 and 36% in group 2 (p<0.05, which was significant), 16% in group 1 and 8% in group 2 had hiccups(p>0.05, which was not significant)

Similarly, previous studies have reported that the side effects peculiar to pulse therapy include hiccups, facial flushing, diarrhea, weakness, generalized swelling, muscle and joint pains[33]. These side effects are usually observed with each pulse and last for a few days afterwards. Most of the patients are able to tolerate these symptoms and continue treatment.

White et al presented a review of adverse effects associated with DCP therapy in various dermatologic disorders. Of 188 patients reviewed in this category, majority about 69% were treated for pemphigus (especially in India) with a specific regimen called dexamethasone cyclophosphamide pulse (DCP) therapy. Most of the adverse effects reported were mild and / or transient and included hyperglycemia, metallic taste during infusion, facial flushing[34], hiccups, malaise, mild hypertension and focal infections. Serious adverse effects reported in 14 patients (7%) included death due to sepsis (four patients), reactivation of pulmonary tuberculosis (3), heart failure (2), perforated duodenal ulcer (one) and euphoria followed by depression (one). However, all the side effects could not be attributed to DCP therapy alone, as the patients were also treated with oral corticosteroids and cyclophosphamide. Furthermore there was no clear evidence to suggest a correlation between DCP therapy and cardiovascular side effects. Kaur and Kanwar reported the development of transient arrhythmias in two patients with no changes noted in ECG. Barrett reported the precipitation of left ventricular failure with DCP therapy in a patient who was hemodynamically unstable before receiving pulse therapy.

Severe adverse cardiovascular effects of pulse steroid therapy were highlighted in some of the studies and continuous cardiac monitoring wasrecommended during steroid pulse administration. However the complications were restricted to the elderly patients and those with cardiac and renal diseases. Subsequent cardiac monitoring of healthy volunteers on DCP therapy detected no arrhythmias or other significant changes. In the present study cardiac monitoring was done for some patients during initial courses of pulse therapy. Except transient increase in the heart rate during pulse therapy. Cardiac complications like ischemic heart disease, heart failure or arrhythmias were not encountered. Cardiac monitoring was not performed for all the patients but

Certain precautionary measures were taken to prevent the complications. Elderly patients above 60 years and those with compromised cardiac or renal functions were not taken up for pulse therapy. Careful monitoring of vital data was done during the 3 days of pulse therapy and ECG and serum electrolytes were done before and after completion of pulse therapy. In the present study, 16% in group 1 and 36% in group 2 recorded hypertension and they were treated accordingly by anti-hypertensive drugs (p<0.0001, which was highly significant).

Hemorrhagic cystitis a side effect seen with cyclophosphamide was seen in 2 % in group 1 and 66% in group 2 (P>0.05, which was not significant), Hemorrhagic cystitis was confirmed with complete urine examination (CUE) and urologist opinion, Tuberculosis was diagnosed in 2% in group 1 and 6% in group 2 (p>0.05 which was not significant). Aseptic necrosis of bone was seen in 2% patients in group 1 and in 4% patients in group 2 (P > 0.05 which was not significant). Glaucoma was not seen in either of the two groups. (Table 4)

The side effects observed during DCP therapy in 100 consecutive pemphigus patients reported in a study are as follows.[35] Weight gain > 10% body weight (11 patients), weight loss of >10% of body weight (13), pyoderma (3), candidiasis (8), dermatophytosis (7), Tuberculosis (1) diffuse hair loss (29), generalized hyperpigmentation (3) cataract (5), loss of appetite (3), diabetes mellitus (0), Hypertension (3), hyperacidity (1), hemorrhagic cystitis (1), acne (6), hirsutism (1), Striae (0), ecchymosis (3),

glaucoma (1), hiccup (1), and aseptic necrosis of the bones (0).

The other major complication of DCP regimen is gonadal failureand all the patients treated with DCP regimen had amenorrhea / oligomenorrhoea. However the gonadal dysfunction was not a problem in the present study as the patients who were married and completed the family alone were chosen for this treatment and possible complications were explained to them before starting the treatment.

In our comparative study there was statistically significant difference in safety and efficacy between DCP therapy and daily immunosuppressive therapy. Among the two groups we found that DCP therapy was more effective in quick relief of signs and symptoms and cure rate and decreased incidence of adverse effects.

CONCLUSION

DCP therapy was found to have greater efficacy in controlling the symptoms of steroid responsive dermatosis than daily immunosuppressive therapy. With pulse therapy remissions are long amounting to cure as per the previous studies in the Dermatology Department of Osmania General Hospital. With DCP Therapy, quick healing of the lesions (within three days of pulse) reduced the hospital stay to 4-5 days, enabling the patients to resume their routine activities earlier and to lead a normal life.The second major advantage with pulse therapy is relative freedom from the expected side effects of conventional dose of corticosteroids and immunosuppressive drugs. These side effects include disfiguring cushingoid changes, infection, acid peptic disease, diabetes mellitus, hypertension, myopathy, cataract and psychosis. Thus, the treatment became more acceptable to the patients on DCP therapy.

DCP therapy was avoidance of prolonged high dose daily immunosuppressive therapy and its consequences. Considering all the above factors DCP therapy appears to be a better choice in the treatment of steroid responsive dermatosis as compared with daily immunosuppressive therapy. In conclusion further dietary restrictions on salt or calorie intake were not required.

Another main advantage with therapy with steroids and immunosuppressive drugs is superior to daily immunosuppressive therapy in terms of safety, efficacy and longer remissions.

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Conflict of Interest: no conflict of interest

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