DEXAMETHASONE-CYCLOPHOSPHAMIDE PULSE THERAPY IN PEMPHIGUS- A CLINICAL STUDY

Yerrajwala Arunakumari[1], Panthalla Vijayalakshmi[2], Indukuri Chandrasekhar Reddy[3]

[1]Associate Professor, Department of DVL, Kurnool Medical College, Kurnool, Andhra Pradesh.
[2]Associate Professor, Department of DVL, Kurnool Medical College, Kurnool, Andhra Pradesh.
[3]Professor and HOD, Department of DVL, Kurnool Medical College, Kurnool, Andhra Pradesh.

ABSTRACT

BACKGROUND

Pemphigus is an autoimmune bullous disorder which was life threatening before the advent of steroids and immunosuppressants. Dexamethasone Cyclophosphamide Pulse Therapy introduced by Pasricha and Gupta in 1981 has lifelong recovery from the dreadful disease. We wanted to study the efficacy of DCP with certain modifications in pemphigus group of disorders.

METHODS

Irrespective of age, sex and severity of disease, 37 patients of pemphigus admitted between 2011 to 2014 who are being treated with DCP and followed for 2-5 years in department of DVL, GGH attached to medical college were included in the study. All patients completed the formalities and were investigated before and after the pulse. DCP regimen was repeated every 28 days with the cycle comprising of 100 mg of Dexamethasone in 500 ml of 5% glucose given intravenously for 3 consecutive days. 500 mg of cyclophosphamide given on Day 1. In between the pulses, 50 mg of oral cyclophosphamide given. Few modifications for better outcome were, additional dose of betamethasone to control disease activity in few severe cases, secondly, use of systemic antibiotics in all cases, anti candidal in cases with oral lesions, thirdly wound care, hygiene, nutritional supplements for fast healing.

RESULTS

All the patients were in remission. Number of pulses for remission in phase II varied from 11-22. 7 patients required additional 2 mg of oral betamethasone in Phase I. Additional use of mycophenolate mofetil was given in 2 cases with severe recalcitrant mucosal lesions instead of cyclophosphamide. Disease free follow up period was >5 years in 16 pts (45.71%), 3-5 years in 13 pts (37.14%), 2-3 years in 6 pts (17.14%). No deaths occurred in our study. 1 patient was withdrawn from study because of avascular necrosis of femur. Another patient relapsed after 2 years who has taken some native medicine and was found HBsAg positive, was given plain dexamethasone pulse in place of DCP.

CONCLUSION

Our study clearly established the efficacy of DCP with regard to bringing complete remission and improvement of quality of life. Additional use of betamethasone and MMF in selected cases will further help in complete clearance of lesions.

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BACKGROUND

Pemphigus disorders are a group of serious and potentially life threatening autoimmune bullous dermatoses. Before the advent of immunosuppressive therapy, systemic corticosteroids were the main stay for pemphigus therapy which ultimately lead to patient's death due to complications of steroids.[1] An attempt was made to diminish the adverse effects of conventional daily dose regimens, with pulse doses of steroids and immunosuppressants. With introduction of DCP therapy designed by Pasricha et al. and Gupta patients can hope for a cure of this dreadful disease.[2] Pulse therapy is not absolutely free from side effects, but they are not very serious and not a contraindication for continuing therapy. Risk benefit ratio weighs more towards the benefits. Subsequently DCP therapy has been reviewed and modified.[3,4]

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Corresponding Author:
Dr. Yerrajwala Arunakumari,
Flat 203, A Block,
S. V. Pride Apartment,
Birla Guest House Compound,
Kurnool, Andhra Pradesh.
E-mail: arunayerrajwala.kmc@gmail.com
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Aim of the Study

To study the efficacy of DCP therapy in the treatment of pemphigus disorders.

METHODS

Patients diagnosed as pemphigus irrespective of the severity and duration of the disease admitted from 2011 to 2014 at GGH attached to medical college were included in the study. All patients treated with DCP regimen and who were in clinical remission were followed for minimum of 2 years and maximum 5 years. Clinical remission was defined as having

no lesions on the skin and mucous membrane. Data regarding age, gender, age of onset, clinical details, previous treatment, adverse effects were recorded. Diagnosis of cases was based on clinical features, histopathology of skin, Tzanck smear and direct immunofluorescence in affordable patients. Exclusion criteria were DM, HTN, PT, malignancy cardiac disease, glaucoma, unmarried and serious infections. All patients were subjected to baseline investigations like CBP, RFT, LFT, RBS, Sr. electrolyte, urine analysis, CXR and special investigation like USG abdomen, ECG, 2D ECHO and tonometry. Investigations were done before each pulse and alterations were noted.

DCP regimen comprised of dexamethasone 100 mg dissolved in 500 ml of 5% Dextrose administered by slow intravenous infusion for 3 consecutive days. 500 mg of cyclophosphamide was given on the 1st day. DCP was repeated every 28 days. In between DCP, 50 mg of oral cyclophosphamide was given.

Those patients who had active skin lesions were given systemic antibiotics and anticandidal drugs for those who had oral lesions. Patients are encouraged to bath every day and maintain oral hygiene to promote quick healing. Systemic antibiotics were withdrawn after healing.

Phase 1 was the period lasting until all the lesions healed and there were no lesions. All other drugs were withdrawn. In phase 2 patients are normal, DCP was repeated for every 28 days along with 50mg daily cyclophosphamide for 9 months. After this DCP stopped and oral dose of 50 mg cyclophosphamide was continued for next nine months this was phase 3. Subsequently all treatment was withdrawn, and patient was followed for 5 years

RESULTS

A total of 35 patients were enrolled in this study. Out of 35, 20 newly diagnosed were started DCP regimen directly and remaining 15 were on conventional corticosteroid therapy and were switched to DCP therapy. 23 were women and 12 were men with age ranges from 27-56 years. Mean age was 41.5 years. All patients completed their family. The duration of the disease before treatment was minimum of 3 months to maximum of 1½ years. Mean was 5.87 - 7.8. 7 males and 8 females had severe skin and mucosal lesion (>40 + >10). 3 males and 7 females had moderate to severe disease. Only skin involvement was present in 2 males and 8 females.

Severity	Males	Females
Severe	7	8
Moderate	3	7
Mild	2	8
Total	12	23

Table 1. Disease Severity

The number of pulses for the clearance of lesions in Phase-I varied from 2-13 pulses, followed by Phase-II during which 9 pulses were given. The number of pulses required for clinical remission at the end of Phase – II were shown in Table II. 7 patients required daily oral corticosteroids 2 mg betamethasone in phase 1.

No. of Cases	No. of Pulses	Total Pulses
6	11(2+9)	**66**
8	13(4+9)	**104**
2	14(5+9)	**28**
4	15(6+9)	**60**
9	17(8+9)	**153**
6	22(13+9)	**132**
35	**92**	**543**

Table 2. No. of Pulses Required to Induce Clinical Remission at The End of Phase II

Disease free follow up period has already been more than 5 years in 16 patients (45.71%), 3-5 years in 13 patients (37.14%) & 2-3 years in 6 patients (17.14%). No death occurred in our study. All patients were well except one who developed relapse after 2 years as she has taken some native medicine and she was diagnosed HBsAg positive.

Disease Free Period	No. of Patients	Percentage
>5 Years	16	45.71%
3-5 Years	13	37.14%
2-3 Years	6	17.14%

Table 3. Follow Up- Patients in Remission

Regarding adverse effects generalized weakness, myalgia, gastric irritation, hypertension and diabetes were majority, next was oral candidiasis and 2 patients developed pyogenic infections. 1 female patient suffered amenorrhea. Regarding delayed adverse effects, one patient developed avascular necrosis at 7th pulse and discontinued from treatment.

DISCUSSION

Pulse therapy is administration of supra pharmacological doses of drugs in an intermittent manner. In Pemphigus, high doses of dexamethasone infusions on three consecutive days for every four weeks gives quick & better efficacy with least adverse effects.[1,5]

In the present study, 28 (80%) patients had pemphigus vulgaris, 7 patients (20%) had pemphigus foliaceus. There was female predominance observed which is similar to other studies. With respect to age of onset of the disease, majority were between 30-40 years similar to study of Rao et al. and Varala S et al. in contrast to higher age group observed in study of Kandan et al. Duration of disease in our study was 3 months to 1.5 years, concerning with study of Kandan et al and varied with other studies.[6]

The number of pulses for clearance of lesion in phase I were 2-13 months in our study. It was highly variable and did not depend on clinical characteristics like age or sex as already observed in other studies. Roy R. Kalla et al [7] achieved phase I in 4-12 months, it was 4-24 months in Varala S et al. study,[8] 4 months in Manzoor S. Bhat et al.

study.[9] Minor modifications like addition of oral betamethasone in severe cases in phase I and use of systemic antibiotics in all cases and MMF in 2 recalcitrant cases instead of cyclophosphamide will facilitate early clearance of lesions that reduce the period of phase I which correlates with observation of Pasricha et al.[3] In the present study 16 patients (45.7%) were followed for more than 5 years and were considered completely cured, 13 patients (37.14%) were followed for 3-5 years and 6 patients (17.14%) for 2-3 years. Another advantage of DCP regimen was the absence of adverse effects which is usually seen with conventional steroid therapy. The absence of cushingoid obesity, striae, hirsutism, osteoporosis, cataract, diabetes makes the regimen more acceptable and affordable for the patients.

Disease	Present Study	Varala S et al.	Roy R. Kalla et al	Manzoor S. Bhat et al
Type	PV:PF - 28:7	PV:PF-112:9	PV:PF-28:9	PV-20
Age	27-56 years	19-58 Yrs.	10-58 Yrs.	32-60 Yrs.
Sex	35-23 (F) 12(M)	122-80 (F) 42 (M)	37-22 (F) 15 (M)	20-11 (F) 9 (M)
Duration	3 months-1.5 Yr	7 Days-3 yrs.	5-10 Yrs.	1 Month – Max Years
No. of Pulses Phase I	2-13 pulses	4-24	N. A.	13
Relapse	1 patient	7 Patients	4	Nil
Death	Nil	4 Patients	4	Nil

Table 4. Comparison with Other Studies

The important result of DCP therapy is achievement of complete remission. At the time of writing this article 45.7% were in remission for 62-70 months. 37.1% of the patients were in remission for 36-58 months without any maintenance therapy

Relapse is defined as appearance of 3 or more lesions that do not heal spontaneously within 1 week or by extension of established lesion. Patients in the present study have completed monthly regimens strictly in phase I and II schedules with good outcome and least relapse rate of 2.85% and no drop outs or deaths. Pasricha reported low relapse rate of 7.7%. Certain modifications were proposed and practiced in the regimen of pulse therapy in pemphigus. It has been observed that 12 patients of Pemphigus Vulgaris with severe mucosal lesions treated with additional daily 2 mg betamethasone demonstrated earlier wound healing.

Mycophenolate mofetil 500 mg TID PO was given daily for 2 patients replacing Cyclophosphamide. One patient continued to develop new lesions in phase 2 at 9th pulse and another female patient whose skin lesions healed completely but oral lesions were recalcitrant. Both patients responded well to MMF.[10] Acneiform eruptions developed in one patient with MMF.

The adverse effects according to severity are immediate and late. Immediate were include anaphylactic reactions, arrhythmias, hypotension, hypertension, electrolyte imbalance, sudden death etc., Late were HPA suppression, avascular necrosis, osteoporotic fractures, coronary artery disease, stroke, diabetes, cataract, haemorrhagic cystitis, gonadal failure etc.,

One female patient aged 36 years developed avascular necrosis of femur after 7 pulses and DCP was discontinued, similar complication reported in Varala S et al. study.[8]

Two (male) patients developed new oral lesions in phase 2 and both showed improvement with methotrexate 7.5 mg weekly.

One female patient was HBsAg positive and was given plain dexamethasone pulse therapy and betamethasone 2 mg, Azathioprine 50 mg daily, obtained complete remission after 19 pulses.

CONCLUSION

The present study involves 37 patients; majority of them were followed for 5 years and all the patients are free from the disease for more than 2 years, clearly establishing the efficacy of DCP pulse therapy in bringing out complete remission and in reducing mortality and improving quality of life.

It was observed that patients with severe mucosal lesions benefited when 2 mg betamethasone was added. In another case where severe mucosal involvement was not improving, substitution of MMF instead of cyclophosphamide showed near complete clearance. Another female patient with HBsAg positivity who was treated with plain DP pulse therapy had good outcome and she was on Azathioprine maintenance therapy without lesions, thus establishing the fact that changing of immunosuppressants may be considered in cases unresponsive to conventional DCP.

With regard to adverse effects, they are very minimal in the present study. One case was discontinued from therapy due to avascular necrosis of femur and in another patient due to new onset hypertension which was diagnosed and managed.

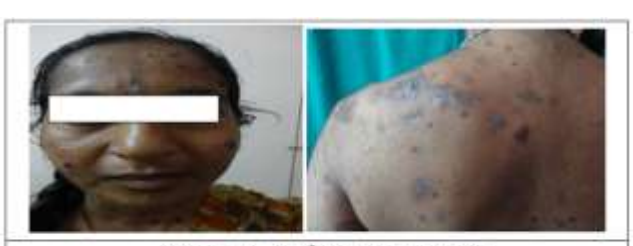

Figure 1. Before Treatment

Figure 2. After 5 Pulses of DCP – Lesions Persisted

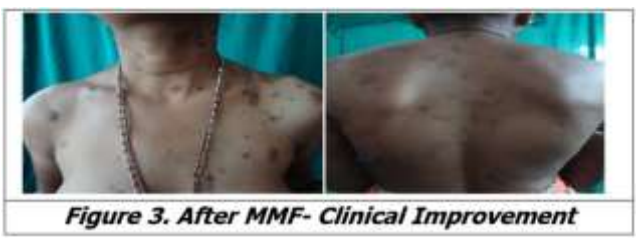

Figure 3. After MMF- Clinical Improvement

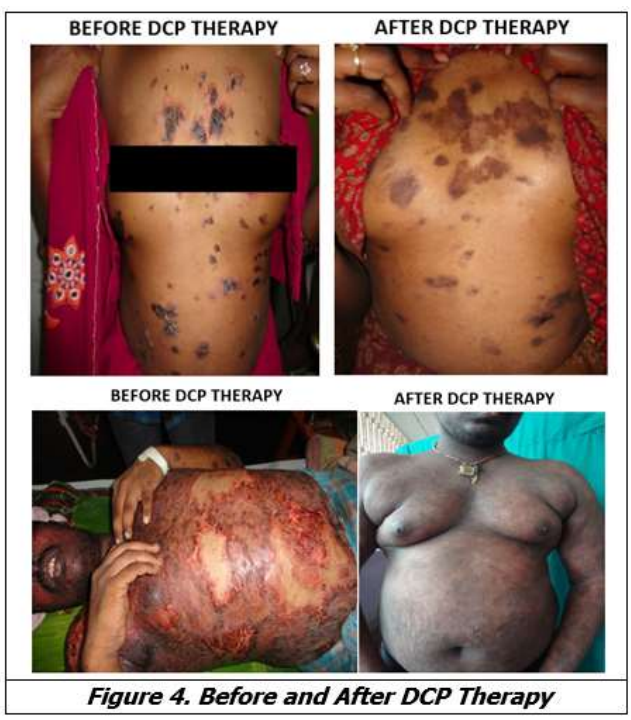

Figure 4. Before and After DCP Therapy

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