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**Original Article**

# Dexamethasone-cyclophosphamide pulse therapy in pemphigus: A 5-year retrospective study

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**Abstract**

***Objective*** The present work was conducted to assess the outcome of dexamethasone-cyclophosphamide pulse (DCP) therapy in pemphigus.

***Methods*** The present work was designed as a retrospective tertiary urban hospital based, observational study during the period from Jan 2012 to Dec 2016. Data regarding clinical details about the disease, previous treatments, phases of therapy, remission, relapse, cure, default and reasons for default, death and causes of death and adverse effects of therapy were evaluated.

***Results*** Out of 102 patients of pemphigus on DCP therapy, majority (n=42) of them belonged to age group of 40 to 49years. Mean age of patients was 42.08 years with a range of 24 to 65 years. Male to female ratio was 1:1.48. Of the 102 patients, 30 patients were in phase I, 23 were in phase II, 12 were in phase III and 37 were in phase IV. Mean number of pulses required for remission, that is, for completion of phase I were 5.2 months (range, 2-15 months). Majority (n=47, 65.3%) of them needed 4-7 pulses to achieve remission. Among 72 patients who achieved remission, a total 15 patient relapsed. Infusion-related reactions were the most common immediate adverse effect and generalized weakness/malaise were the most common delayed adverse effect recorded. Nine (7.7%) patients died while on DCP therapy and the most common (n=5) cause of death was septicaemia.

***Conclusion*** The DCP therapy was found to be effective in inducing and maintaining remission in pemphigus, provided the patients receive regular and complete treatment. The cost-effectiveness is definitely superior to other treatment modalities (biologics), which is of utmost importance in our setup as majority of patients belonged to poor socioeconomic strata, although the relapse rate and mortality rate were higher compared to other studies.

***Key Words***
Dexamethasone cyclophosphamide pulse (DCP), pemphigus, relapse.

## Introduction

Pemphigus is a group of serious and potentially life-threatening autoimmune blistering disorder characterized by intraepidermal split leading to blisters and erosions on the skin or mucosal membranes or both. The term Pemphigus has been derived from Greek word 'Pemphix' meaning blister or bubble.[1]

Pemphigus is broadly classified into pemphigus vulgaris (PV) with its variant pemphigus vegetans (PVeg) and pemphigus foliaceus (PF) with its variant pemphigus erythematosus (PE). Rare described variants are pemphigus herpetiformis, IgA pemphigus, drug-induced pemphigus and paraneoplastic pemphigus.

The introduction of dexamethasone-cyclophosphamide pulse (DCP) therapy for the

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pemphigus group of disorders by Pasricha *et al*.[2] in 1982 has revolutionized the therapy of pemphigus in India. DCP therapy has the potential to affect lifelong recovery from pemphigus if properly used.[3] The standard treatment of pemphigus comprises of systemic steroids and other immunosuppressive agents, however, no internationally accepted treatment guidelines exist.[4] This study aimed to evaluate the therapeutic results and outcome of dexamethasone-cyclophosphamide pulse therapies (DCP) in pemphigus patients.

## Methods

Pemphigus patients irrespective of age and sex who were on dexamethasone-cyclophosphamide pulse (DCP) therapy, were selected for the study. The present work was designed as a retrospective tertiary urban hospital-based, observational study during the period from Jan 2012 to Dec 2016.

The diagnosis of pemphigus was based on clinical features, Tzanck smear, histopathology of the skin/mucus membrane lesions and direct immunofluorescence test. Exclusion criteria for dexamethasone-cyclophosphamide pulse therapy were pregnant and lactating woman, patient with uncontrolled diabetes mellitus, hypertension or systemic diseases where steroids or immunosuppresants were contraindicated and in patients who had not completed their family.

Dexamethasone-cyclophosphamide pulse (DCP) therapy was used in four phases:

*Phase I* Dexamethasone 100 mg in 500 ml of 5% dextrose was given as a slow intravenous infusion over two hours for three consecutive days, along with 500 mg of cyclophosphamide was added in the same drip on the second day as in the regimen by Pasricha *et al*.[5] Diabetic patients were given ten units of soluble insulin for each bottle of 500 mL 5% glucose used for the infusion, in addition to their antidiabetic treatment. This constituted one DCP and was repeated at exactly 28 days interval counted from the first day of the previous DCP. In between DCPs, 50 mg of cyclophosphamide orally per day was given. Some patients who continued to develop >3 new lesions in between DCPs additional prednisolone 0.5-1.5 mg per kg per day orally was given to achieve quick remission (absence of new or established lesions).[6] Prednisolone was tapered stepwise by 25% reduction in biweekly period followed by more slowly reduction at <20 mg prednisolone during the subsequent DCPs. The first phase was continued until the patient attained remission, defined as the absence of fresh lesions and disappearance of existing lesions. After the skin and mucosal lesions subsided completely and the additional prednisolone was withdrawn, the patient was shifted to phase II.

*Phase II* consisted of the DCP therapy along with 50 mg cyclophosphamide orally per day given for a fixed duration of 9 months.

*Phase III* only oral cyclophosphamide 50 mg/day was given for 9 month.

*Phase IV* all the drugs were withdrawn and the patient was followed up for as long as possible for any tendency to relapse (appearance of >3 new lesions per month that do not heal spontaneously within 1 week). If relapse does not develop for two years in phase IV, patient is declared to be cured of disease.

All patients were considered for DCP therapy in patients with moderate to severe disease or patients with mild disease who were refractory to steroid therapy. Severity was evaluated by a 'severity index for pemphigus' namely, mild, moderate and severe.[7] We reviewed the data recorded regarding the age, sex, age of onset of disease, clinical details about the disease, previous treatment details, phases of therapy, remission, relapse, cure, default and reasons for default, death and causes of death and adverse effects of therapy.

## Results

### *Patient characteristics*

Out of 127 patients of pemphigus on DCP therapy we could collect details of 102 patients registered in our department, from January 2012 to December 2016. Mean age of patients was 42.08 years with a range of 24 to 65 years. Of the 102 pemphigus patients enrolled for DCP therapy, 61 (59.8%) were females and 41 (40.2%) were males. Male to female ratio was 1:1.48. Majority (n=42) of them belonged to age group of 40 to 49years (**Table 1**).

**Table 1** Demographic and clinical characteristics of study population (n=102).

| *Feature* | |
|---|---|
| *Age (years)* | |
| Mean | 42.08 |
| Range | 24-65 |
| *Sex* | |
| Male | 41 (40.2%) |
| Female | 61 (59.8%) |
| *Disease profile* | |
| Pemphigus vulgaris | 88 (86.3%) |
| Pemphigus foliaceus | 12 (11.8%) |
| Pemphigus vegetans | 2 (2.0%) |
| *Sites of involvement* | |
| Mucocutaneous | 72 (70.6%) |
| Cutaneous | 26 (25.5%) |
| Mucosal | 4 (3.9%) |

### *Disease profile*

Amongst the 102 pemphigus patients, 88 (86.3%) had pemphigus vulgaris, 12 (11.8%) had pemphigus foliaceus and 2 (2.0%) had pemphigus vegetans. Most of them (n=72, 70.6%) had mucocutaneous involvement followed by cutaneous (n=26, 25.5%) and mucosal (n=4, 3.9%) involvement (**Table 1**).

Severity was evaluated by a 'severity index for pemphigus' namely, mild, moderate and severe.[5] Accordingly, 8 patients (7.8%) had mild, 59 patients (57.9%) had moderate, and 35 patients (34.3%) had severe forms of the disease.

Of 102 patients, 14 patients were diabetic, 8 were hypertensive and 2 patients had hypothyroid disorder as comorbidities prior to initiation of DCP therapy.

### *Phases of DCP*

Of the 102 patients, 30 patients were in phase I, 23 were in phase II, 12 were in phase III and 37 were in phase IV (**Table 2**).

*Phase I* Among the 30 patients, 11 patients were receiving DCPs, 8 patients discontinued therapy, 4 patients were shifted to other forms of treatment for various reasons and 7 patients expired.

*Phase II* 23 patients reached phase II, of which 14 patients were continuing therapy, 4 patients discontinued therapy, 3 patients were shifted to other forms of treatment and 2 patients expired.

*Phase III* 12 patients reached phase III of which 9 patients were in remission and 3 discontinued.

*Phase IV* 37 patients reached phase IV, of which 16 patients completed two years in phase IV and were declared cured of disease.

### *Remission*

Mean number of pulses required for remission, that is, for completion of phase I were 5.2 (range, 2-15). Majority (n=47, 65.3%) of them needed 4-7 pulses to achieve remission (**Table 3a**).

Among 72 patients who achieved remission, most (n=52, 72.2%) of patients also received daily oral prednisolone in between DCPs in phase I. Thirteen (18.1%) patients did not receive oral steroids in between DCPs. Seven patients also received additional dexamethasone pulses (ADP) in between DCPs in phase I at two weeks interval along with daily oral prednisolone.

**Table 2** Frequency of patients in different phases of DCP (n=102).

| | *Phase I* | *Phase II* | *Phase III* | *Phase IV* |
|---|---|---|---|---|
| On treatment | 11 | 14 | 9 | 0 |
| Discontinued | 8 | 4 | 3 | 0 |
| Shifted | 4 | 3 | 0 | 0 |
| Death | 7 | 2 | 0 | 0 |
| Total | 30 | 23 | 12 | 37 |

**Table 3a** No of pulse required to attain remission (n=72)

| *Number of pulses* | *Patients* | *Male* | *Female* |
|---|---|---|---|
| 1-3 | 11 | 8 | 3 |
| 4-7 | 47 | 27 | 20 |
| 8-9 | 10 | 7 | 3 |
| 10-12 | 3 | 1 | 2 |
| 13-15 | 1 | 1 | 0 |
| Total | 72 | 44 | 28 |

**Table 3b** Cumulative dose of steroid (prednisolone equivalent) required to attain remission (n=59).

| *Cumulative dose of steroid* | *Male* | *Female* |
|---|---|---|
| ≤1000 mg | 4 | 1 |
| 1001-2000 mg | 14 | 9 |
| 2001-3000 mg | 12 | 8 |
| >3000 mg | 9 | 2 |

Six patients received only one ADP and one patient received two ADPs. Among 59 patients who required steroid in between DCPs in phase I, most (n=23, 39.0%) required 1001 to 2000mg of prednisolone equivalent to achieve remission (**Table 3b**).

***Relapse***

Among 72 patients who achieved remission, a total 15 patient relapsed. Relapsed were observed in 5 patients while in phase II, 2 patients in Phase III and 8 patients in phase IV. The relapses of the disease, were mostly observed (n=11) in those patients who had taken irregular treatment or had discontinued treatment. Mean number of pulses required in phase I was 7.2 in those patients who relapsed.

***Adverse effects***

The adverse effects that were observed during infusion or within 7 days of starting each pulse were considered as immediate adverse effects. Those side effects that occurred later than 7 days after each pulse, in between various pulses (during phase I and II) or later on during phase III and IV were taken as delayed adverse effects.

Infusion-related reactions (flushing, headache, fever, chills, shortness of breath, skin rash, edema, myalgia, backache, etc.) were the most common immediate adverse effect recorded in 65 patients (**Table 4**).

Generalized weakness/malaise was the most common delayed adverse effect recorded in 45 patients (**Table 4**). Eleven patients developed diabetes who were earlier nondiabetic. Among the known 14 diabetic pemphigus patients, eight required higher doses of insulin and four patients were shifted from oral hypoglycaemic drugs to insulin.

***Deaths***

Nine (7.7%) patients died while on DCP therapy. The causes of death were septicemia in 5 cases and sudden cardiac arrest in 2 patients. Cause of the death in 2 patients could not be ascertained as they died at home.

**Table 4** Immediate and delayed adverse effect of DCP.

| *Adverse effect* | *N* |
|---|---|
| *Immediate* | |
| Infusion related reactions | 65 |
| Secondary pyogenic infection of skin | 17 |
| Polyuria | 4 |
| Diarrhea | 8 |
| Myalgia | 6 |
| Hiccup | 4 |
| *Delayed* | |
| Generalised weakness | 45 |
| Precipitation of diabetes | 11 |
| Secondary pyogenic infection of skin | 11 |
| Oral candidiasis | 10 |
| Weight gain | 10 |
| Cushingoid habitus | 10 |
| Pigmentary changes | 9 |
| Menstrual disorder (among females) | 8 |
| Precipitation of hypertension | 8 |
| Sleep disturbance | 8 |
| Diffuse scalp hair loss | 6 |
| Arthralgia | 6 |
| Azoospermia (among males) | 6 |
| Alteration in taste | 4 |
| Heamorrhagic cystitis | 4 |
| Avascular necrosis of femur | 2 |
| Cataracts | 2 |
| Reactivation of pulmonary tuberculosis | 1 |
| Leprosy infection | 1 |

### *Follow-up*

Mean duration of follow-up was 17 months (range 1 month – 32 month). Thirty seven patients reached phase IV, of which 16 patients completed two years in phase IV and were declared cured of disease.

## Discussion

Pulse treatment with cyclophosphamide and dexamethasone has been tried in many centers with variable results. DCP therapy has revolutionized the treatment of pemphigus from mere control of disease to probable cure.[8] The results of our study indicate high degree of positive outcome in terms of effectiveness of DCP therapy. We were able to achieve remission in 72 (70.6%) cases. Sacchidanand *et al.*[6] reported remission in 41 (82%) patients where as Kandan *et al*.[9] were able to maintain remission in 87.5% of cases who completed phase I. Pasricha *et al*.[3] achieved remission in all the 103 pemphigus patients treated with DCP therapy.

Majority (n=59, 78.2%) of the patients also required additional intervening oral prednisolone in between DCPs in phase I, similar to the finding of Kanwar *et al*.[10] and Pasricha *et al*.[3] Our study highlights the cumulative dose of steroid (prednisolone equivalent) required to attain remission which were 1001-2000 mg in most (n=23, 39.0%) of patients.

Mean number of pulses required for remission were 5.2. Majority (n=47, 65.3%) of patients needed 4-7 pulses to achieve remission similar to the earlier studies.[6,8] Pasricha *et al*.[6] also made similar observation where nearly 49% of patients achieved remission with 6 or less DCPs.

We observed relapse in 15 (20.8%) out of the 72 patients who completed phase I which were higher than Pasricha *et al*.[3] who reported a relapse rate of 7.7%. The relapses of the disease, was mostly observed (n=11) in those patients who had taken irregular treatment or has discontinued treatment similar with other studies.[6,11] Our study highlights the finding that relapse occurred mostly in severe disease and mean number of pulses required in phase I was higher (7.2) in those patients who relapsed.

Pulse therapy is not absolutely free from adverse effects.[12] The adverse effects of DCP therapy are those of its constituent drugs, i.e. dexamethasone and cyclophosphamide.[13] Infusion-related reactions (flushing, headache, fever, chills, shortness of breath, skin rash, odema, myalgia, backache, sudden death etc) were the most common (n=65) immediate adverse effect and generalized weakness/malaise were the most common (n= 45) delayed adverse effect observed in our study. Jain *et al.*[14] also observed flushing as

the commonest (53.4%) immediate complication and weakness as the commonest (55.4%) long-term complication.

In our study, 9 (8.8%) patients died while on DCP therapy and the most common (n=5) cause of death was septicemia which corroborates with earlier studies.[8,6,14]

## Conclusion

The results of this study indicate a high degree of positive outcome in terms of effectiveness of DCP therapy in pemphigus. With DCP therapy, it is possible to induce and maintain remission. The patient compliance to this form of therapy is good and there is low dropout rate. The side effects commonly associated with long-term steroid therapy and other immunosuppressive agents are relatively low. The cost-effectiveness is definitely superior to other treatment modalities (biologics). This is of utmost importance in our setup as majority of patients belonged to poor socioeconomic strata, although the relapse rate and mortality rate were higher compared to other studies.

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***Conflict of interest*** Nil

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