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**Original Research Article**

# Modifications of pulse therapy in pemphigus: a retrospective study of 72 patients

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## ABSTRACT

**Background:** Pulse therapy defines as the administration of supra-pharmacologic doses of drugs in an intermittent manner to enhance the therapeutic effects and reduce the side effects. Dexamethasone-Cyclophosphamide pulse (DCP) therapy is known since 1986 but there are certain limitations due to side effects of cyclophosphamide.
**Methods:** A retrospective study was carried out where 72 patients of pemphigus were treated with modified pulse therapy like DCP, DAP, DMP from 2006-2016. Modifications were made in DCP therapy protocol and substitution of cyclophosphamide with either azathioprine or methotrexate in few patients.
**Results:** Male to female ratio observed was 1:0.7. Majority of them belonged to age group of 31-40 years (41.66%) followed by 41-50 years (33.3%). Maximum number of patients had pemphigus vulgaris (86.1%) followed by pemphigus foliaceous (12.5%) and IgA pemphigus (1.38%). Good response was observed in patients who took pulse therapy regularly.
**Conclusions:** Modifications to the original DCP therapy protocol were found to be very effective, useful and it shortened the duration of phase I. Side effects were minimal and manageable.

**Keywords:** Pulse therapy, Dexamethasone-cyclophosphamide therapy, Dexamethasone-azathioprine therapy, Dexamethasone-methotrexate therapy

## INTRODUCTION

Pulse therapy is defined as the administration of supra-pharmacologic doses of drugs in an intermittent manner to enhance the therapeutic effects and reduce the side effects.[1] Pulse therapy initiated with the aim of completely suppressing the cyclical proliferation of immunocompetent cells, gave a new hope to the treatment modalities of pemphigus.[2]

Pulse therapy was first used in India by Pasricha et al for a patient with Reiter's disease and thereafter it was introduced in management of pemphigus vulgaris in 1982.[3-5]

Long term corticosteroids can lead to more mortality and morbidity as compared to pulse therapy.

Aims and objectives of the study are to evaluate role of various types of pulse therapy and modified regimens in pemphigus patients.

## METHODS

A retrospective study of total 72 pemphigus patients treated with modified pulse therapy with follow up over a period of 11 years from 2006 to 2016 in the Department of Dermatology, venereology and leprosy, PDU Govt Medical College and Hospital, Rajkot was done. Study

Data was excruited from registers and calculated via Microsoft excel 08. Pregnant and lactating women and patients below 18 years of age were excluded from the study. Patients with uncontrolled diabetes mellitus, hypertension and severe systemic disease were excluded.

Different types of pulse therapies were used.[6]

1. Dexamethasone-cyclophosphamide pulse (DCP)
2. Dexamethasone–azathioprine pulse (DAP)
3. Dexamethasone-methotrexate pulse (DMP)

*DCP pulse*: In phase I, 100 mg dexamethasone dissolved in 500 ml of 5% dextrose was given intravenously over 3 hours, repeated on three consecutive days. On the second day 500 mg of cyclophosphamide was added to the infusion. DCP was repeated after every 28 days. Cyclophosphamide 50 mg/day was given orally. In phase II, DCP was continued for 9 months with oral cyclophosphamide. In phase III only oral cyclophosphamide 50 mg was given for 9months. In phase IV patients were followed up for as long as possible.

*DAP pulse*: Cyclophosphamide was replaced by 50 mg of azathioprine daily during the first 3 phases.

*DMP pulse*: Cyclophosphamide was replaced by 7.5 mg/week of methotrexate (three doses of 2.5 mg at 12 hourly interval)

It was given in four phases:

*Phase I*: Pulse therapy cycles were continued till all the previous lesions had completely healed and no new lesions developed and patient was off daily corticosteroids.

*Phase II*: In this phase pulse was continued for another 9 months with daily oral immunosuppressive drugs.

*Phase III*: Monthly pulse cycles were stopped and daily Immunosuppressive dose was continued for another 9 months.

*Phase IV*: It was "Disease free, drug free" period of observation where patient was off medications and just kept under follow-up to note for any recurrences and complications either related to treatment or disease condition.

After taking written consent all patients were considered for DCP therapy. Patients who were unmarried or had not completed family were given DAP therapy. DMP therapy was instituted in patients who did not complete phase I even after 12 pulses of DCP or DAP.

Data regarding the age, sex, age of onset, disease progression and remission were noted in detail. Details of all the phases of therapy, patient's response, default and adverse effects were recorded thoroughly. Clinical examination and investigations were carried out for diagnosis, complications and treatment purpose. Baseline investigations like complete blood count, Routine blood biochemistry, urine examination, electro-cardiogram, serum electrolytes and chest x-ray were done. Complete blood count, Urine routine and microscopy, Serum electrolytes and Electro-cardiogram were repeated at each follow up of 28 days.

Patients with altered laboratory investigations or lost in follow up due to personal reason or irregularity were excluded.

*Modifications of pulse therapy.*[7]

1. The first pulse was initiated when the secondary infection was fully controlled. Systemic antibiotic coverage was given along with pulse therapy. Antifungal medication was given to control oral candidiasis. Conventional steroid therapy was given to control the activity of pemphigus.
2. In DCP therapy, when cyclophosphamide was given during second day of infusion it was followed by additional 500 ml in 5% dextrose to prevent urinary complications.
3. As a part of protocol preventive measures like oral calcium 500 mg daily, weekly bisphosphonates and monthly calcitriol sachet were given.

All the side effects were noted during study that were mild and manageable.[8]

## RESULTS

Mean duration of the disorders, prior to initiation of pulse therapy was 2.34±2.5 years. Male to female ratio observed was 1:0.7. Majority of them belonged to age group of 31-40 years (41.66%) followed by 41-50 years (33.3%) (Table 1). Diagnosis was confirmed by clinical examination, bed side skin test (Tzancksmear) and histopathological examination. Maximum number of patients had pemphigus vulgaris (86.1%) followed by pemphigus foliaceous (12.5%) and IgA pemphigus (1.38%) (Table 2). All pemphigus patients had skin involvement and 73.56% had oral involvement.

**Table 1: Age wise distribution of patients.**

| Age group (years) | Number of patients (%) |
|---|---|
| **11–20** | 2 (2.7) |
| **21–30** | 14 (19.5) |
| **31–40** | 35 (48.6) |
| **41–50** | 25 (34.7) |
| **51–60** | 6 (8.3) |
| **61-70** | 5 (6.9) |

Out of 46 patients on DCP pulse therapy, 30 patients entered into phase II, 19 patients followed into phase III

and 16 patients followed into phase IV. Among which 29 patients had good response and 10 patients were dropped out from study. 40 (86.95%) patients completed phase I within 6-12 pulses. 6 patients who required more than 12 pulses were shifted to DAP pulse therapy (Table 3 and 4).

**Table 2: Type of disease and type of pulse therapy.**

| Diagnosis | Numbers of patients (%) | Type of pulse therapy | | |
|---|---|---|---|---|
| | | DCP | DAP | DMP |
| **Pemphigus vulgaris** | 62 (86.11) | 40 | 24 | 5 |
| **Pemphigus foliaceous** | 9 (12.5) | 6 | 2 | - |
| **IGA pemphigus** | 1 (1.38) | - | - | 1 |
| **Total** | 72 (100) | 46 | 26 | 6 |

**Table 3: Type of pulse therapy and no of patients in different phase.**

| Type of pulse | Phase I | Phase II | Phase III | Phase IV |
|---|---|---|---|---|
| **DCP** | 46 | 30 | 19 | 16 |
| **DAP** | 26 | 15 | 8 | 4 |
| **DMP** | 6 | 4 | 2 | 2 |
| **Total** | 72 | 49 | 29 | 22 |

Out of 26 patients on DAP pulse therapy, 15 patients entered into phase II, 8 patients followed into phase III and 4 patients followed into phase IV. Among which 12 patients had good response and 9 patients were dropped out from study 17 (65.38%) completed phase I within 6-12 pulses (Table 3 and 4).

**Table 4: Type of pulse therapy and effects on patients.**

| Type of pulse therapy | Present study (n=72) No. of patients | Present study (n=72) No. of drop out | No. of patients on therapy | Present study (n=72) good response | No. of patients in phase IV | Serious side effects related to pulse therapy |
|---|---|---|---|---|---|---|
| **DCP** | 46 | 10 | 36 | 29 | 16 | Cardio-respiratory arrest-1 |
| **DAP** | 26 | 9 | 17 | 12 | 4 | Amenorrhoea (Pre menopausal women): 1 |
| **DMP** | 6 | 2 | 4 | 4 | 2 | - |
| **Total** | 72 | 21 | 57 | 45 | 22 | - |

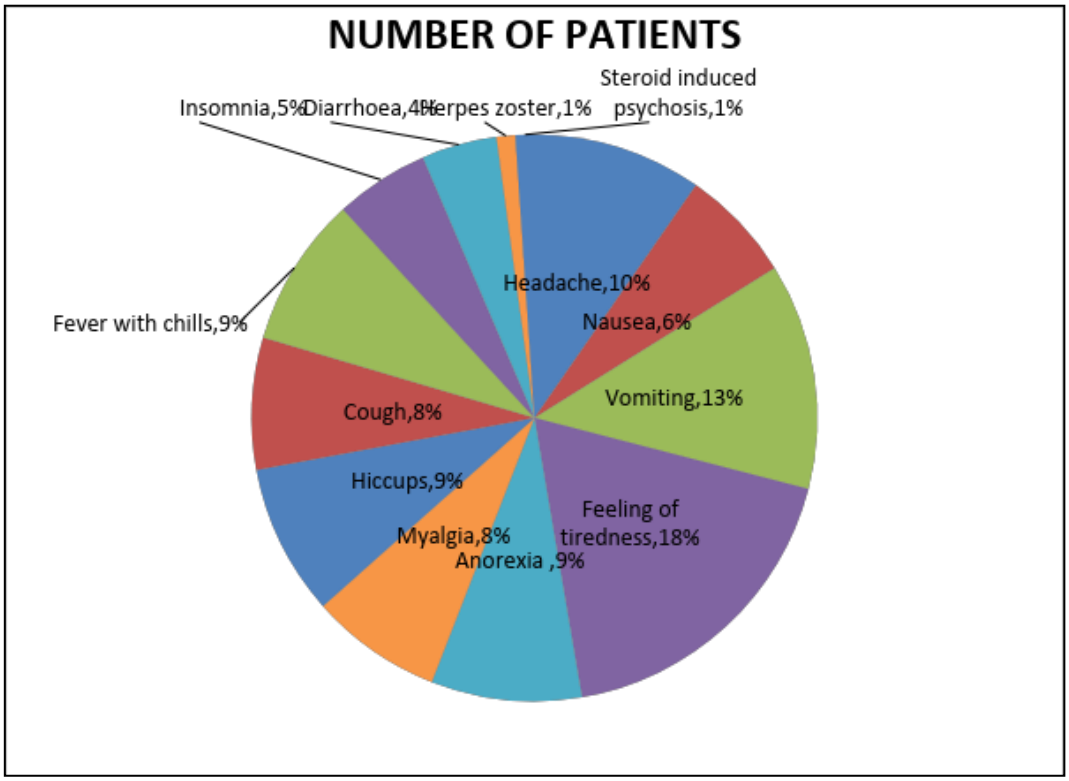


**Figure 1: Mild and manageable side effects of pulse therapy.**

Out of 6 patients on DMP pulse therapy, 4 patients entered into phase II, 2 patients followed into phase III and 2 patients followed into phase IV Among which 4 patients had good response and 2 patients were dropped out from study. 5 (83.33%) patients on DMP pulse completed phase I within 8-12 pulses (Table 3 and 4).

Drop outs were either due to irregularity or loss of follow up. We had stopped pulse therapy in 2 patients due to HbsAg positivity.

25 (34.72%) patients required oral steroid supplements ranging from 10-40 mg/day during phase I of pulse therapy. Scalp and oral lesions were the last ones to respond and heal in most of the patients.

Most of the side effects were tolerable and did not pose any problem in continuing treatment (Figure 1).

Out of 72 patients, 20 (22.98%) patients had abnormalities in urine routine and microscopic examination, 12 (13.79%) patients had ECG abnormalities, 6 (6.89%) patients had leukocytosis and 5 (5.74%) patients had leucopenia. *Staphylococcus aureus* was found in the pus c/s of 7 patients, *Klebsiella* was found in 2 patients and pseudomonas in 1 patient. Pulse therapy was delayed in 4 patients due to leukocytosis, 3 patients due to leucopenia, 3 patients due to upper respiratory tract infection, 3 patients due to pus cells in urine and in 1 patient due to cardiac problem. Pulse therapy was stopped due to HBsAg positivity in 2 patients. 1 patient developed amenorrhea during the pulse therapy. 1 patient developed psychosis on 2$^{nd}$ day of pulse therapy. The only serious complication encountered during pulse therapy was the death of a 36 years old female patient due to cardio –respiratory arrest. She had no past history of any cardiac illness.

## DISCUSSION

Pulse therapy for pemphigus has revolutionized therapy from control of the disease to probable cure. [9] In general, phase I is the most difficult phase of pulse therapy and treatment dropouts tend to occur during this phase as was observed in our study. Among pemphigus disorders, most cases were of pemphigus vulgaris (87.01%) followed by pemphigus foliaceous (11.68%) and IgA pemphigus (1.29%) as comparable to Kandan et al and Sacchidanand et al.[10, 11]

Male to female ratio in our study was 1:1.97 as comparable to Kandan et al.[10] Majority of them belonged to age group of 31-40 years(56.32%) followed by 41-50 years (37.93%) which is comparable to Kandan et al and Sacchidanand et al[10, 11]

In our study modification in form of treatment of infections like bacterial infections and candidiasis were considered. As well as preventive measures were taken to prevent side effects of steroids.

The use of cyclophosphamide is relatively contraindicated in patients who are unmarried and not completed family.

In our study, at the time of initiation of pulse therapy 100% patients had skin involvement among which 73.56% had oral involvement which is comparable to Kandan et al.[10]

Out of 46 patients on DCP pulse therapy 30 patients followed into phase II, 19 patients followed into phase III and 16 patients followed into phase IV. Among which 29 patients had good response and 10 patients were dropped out from study. Out of 26 patients on DAP pulse therapy 15 patients followed into phase II, 8 patients followed into phase III and 4 patients come for regular follow up in phase IV. Among which 12 patients had good response and 9 patients were dropped out from study. Out of 6 patients on DMP pulse therapy among which 4 patients followed into phase II, 2 patients followed into phase III and 2 Patients in phase IV comes for regular follow up. Among which 4 patients had good response and 2 patients were dropped out from study. All of the above data is comparable to the study conducted by Rao et al.[7]

Most of the immediate side effects were mild, temporary and manageable. They are listed in table 4. Slower administration over 3 to 4 hrs has minimized many other serious side effects. The laboratory changes observed in our study were transient or correctable and did not pose any contraindication for continuing therapy.

As a part of protocol to prevent side effects, measures like oral calcium (500 mg) daily at night time, tab. Alendronate (35 mg) once a week and calcitriol sachet (60, 000) IU once a month were added. The side effects were comparatively mild, anticipated and manageable.

## CONCLUSION

Pulse therapies for pemphigus group of disorders are presently being practiced in many dermatology centers all over India. Significantly, the patient compliance to this form of therapy is very good. The results of this study indicate a high degree of positive outcome among Pemphigus patients who responded well to this pulse therapy regimen. Result was very good in young adult patients who took pulse therapy regularly. Although the overall response varies from patient to patient, there appears to be a correlation between the overall response and the stage of the disease at initiation of the therapy. In addition, this therapy is also associated with a significant decrease in disease-related mortality. Another important advantage reported with pulse therapy is a remarkable freedom from the side effects which is commonly associated with long-term steroid therapy and other immunosuppressive agents.

We found the modifications in DCP pulse therapy most effective in inducing and maintaining remission in autoimmune pemphigus disorders.

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