Original Article

Oral Betamethasone-azathioprine pulse : a patient compliant modification of Dexamethasone — cyclophosphamide pulse therapy for pemphigus

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Pemphigus vulgaris (PV) is an autoimmune vesicobullous disorder in India with a very high mortality rate (>90%) if untreated. Immunosuprresives are the mainstay of treatment. Dexamethasone-cyclophosphamide pulse (DCP) therapy has also gained popularity in early remission in these patients. But it has also got some disadvantages. So we have modified the therapy with oral betamethasone and azathioprine. (1)To reduces loss of working hours of patients by giving a therapy requiring minimum hospital stay. (2) Reducing side effects and cost of DCP therapy. (3) Keeping the effectiveness of treatment at par with DCP therapy. A prospective, randomized study was carried out in a tertiary care setting in Kolkata among sixty - seven consecutive patients of pemphigus vulgaris & foliaceous attending the Dermatology OPD from February 2008 to December 2010. Like the original DCP therapy in our study also we have four phases. The first phase of remission in this study is for 12 months, the main changes being — (1) Use of oral betamethasone instead of injectable dexamethasone, (2) Use of azathioprine as steroid sparing drug instead of cyclophosphamide, (3) Home therapy for the last 6 pulses of phase.

Sixty two patients completed the study; out of them 27 were males and 35 females. Forty eight patients achieved remission in 3 pulses, 7 patients needed up to 6 pulses and 7 patients needed more than 6 pulses (up to 17 pulses) to achieve remission. Recovery was noticed as early as one week in cutaneous lesions and 2 weeks in mucous lesions. Regular patients achieved remission early. Betamethasone Azathioprine Pulse Therapy is more acceptable to the pemphigus patients due to its flexibility regarding hospital attendance. It is cheaper, and at the same time it is at par in affectivity to other modalities of pulse therapy like DCP with lesser or same side effects.

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Key words **: Oral betamethasone, azathioprine, pulse therapy, pemphigus vulgaris, compliance.**

Pemphigus vulgaris (PV) is a relatively common autoimmune vesicobullous disorder in India with a very high mortality rate[1]. Although the worldwide incidence of pemphigus has been reported to be in the elderly (more than 50 years), Sehgal[2] observed 50% of pemphigus in north India occurred between 21 and 40 years of age. Studies from North India have reported a higher incidence of pemphigus in patients from poor socioeconomic strata[3-5].

The prognosis of PV has dramatically improved with the use of systemic corticosteroids and various anti-inflammatory and immunosuppressive agents. However, prolonged daily therapy that is required to achieve a good control of PV is associated with several distressing side-effects. Pulse therapy (administration of a supra-pharmacological dose of a drug over a short period at a fixed interval) initiated with the aim of completely suppressing the cyclical proliferation of immunocompetent cells, gave a new vision to the treatment of pemphigus[2]. Since the advent of the fixed dose, fixed duration regimen of dexamethasone-cyclophosphamide pulse (DCP) with daily oral cyclophosphamide for PV in India in 1983 and its subsequent modification (addition of daily oral steroid in the initial stage in very active cases), long-term remissions have been reported in large case series of patients[6,11]. The efficacy of DCP regimen in management of pemphigus has been reported time and again. This concept of pulse therapy has virtually revolutionized the treatment of pemphigus by providing faster control, longer remission and providing the concept of "cure" in pemphigus, which was unknown previously[4,7,8,9].

Although side effects are common, DCP is one of the mainstays of treatment of pemphigus in India[4]. However this therapy has some drawbacks like:

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(1) Three days of hospital stay each month is a prolonged period where day-care facilities are lacking.

(2) Cyclophosphamide is contraindicated in the child bearing period.

(3) Last of all, cost of therapy is relatively high for a developing country.

Keeping these issues in mind, we propose oral betamethasone azathioprine (BAP) pulse in the treatment of PV, as an alternative to DCP regimen. The main changes being— (1) Use of oral betamethasone instead of injectable dexamethasone. (2) Use of azathioprine as steroid sparing drug instead of cyclophosphamide. (3) Home therapy for the last 6 pulses of phase II.

Aims and objectives: (1)To reduce loss of working hours of patients by giving a therapy requiring minimum hospital stay. (2) To reduce side effects and cost of DCP therapy. (3) To keep the effectiveness of treatment at par with DCP therapy.

Materials and Methods

This was a prospective, randomized study carried out in a tertiary care setting in Kolkata. Sixty - seven consecutive patients of pemphigus vulgaris & foliaceous attending the Dermatology OPD from February 2008 to December 2010 were enrolled.

Inclusion criteria : All consecutive patients with pemphigus vulgaris and foliaceous who expressed consent after information.

Exclusion criteria : (1) Patients above >65years and <12 years. (2) Patients with preexisting hypertension, renal failure, pregnancy & lactation, psychiatric disorders, uncontrolled diabetes, active tuberculosis, ischemic heart disease with or without chest pain, dyselectrolytemia.

Evaluation of the patients : All patients were examined thoroughly. Investigations included complete blood count, blood urea, sugar-fasting and post prandial (PP), glycosylated Hb (HbA_{1C}), serum Na^+ & K^+, SGOT, SGPT, bilirubin, electrocardiogram (ECG), sputum for AFB, chest X-Ray and urine for routine and microscopic examination. Specific investigations like Tzanck smear, skin biopsy for routine staining and for direct immunoflourescence test (DIF) were also done.

Schedule of home administered pulse:

Tablet pantoprazole (40 mg) along with domperidone was administered early in the morning.

One Hundred tablets of betamethasone (1mg) were dissolved in a glass of water. This was taken orally sip by sip for 3-4 hours daily along with 3-4 bananas. This schedule was followed for 3 consecutive days. Patients with history of dyspepsia were advised to take two teaspoon of antacid gel in addition.

Later on, keeping compliance and comfort issues in mind, we modified the schedule as: 30, 30 and 40 tablets of betamethasone 1 mg dissolved in each glass of water and consumed consecutively with one banana for each glass in three hours (one glass in one hour) along with liquid antacid. We called this as steroid cocktail. Patients were given 12 such pulses after they went into remission. Azathioprine was administered 50 mg daily (arbitrarily chosen) for eighteen months and then stopped. Patients were followed up for eighteen months thereafter.

Blood pressure, ECG, serum Na^+, K^+, fasting blood sugar and urine for routine and microscopic examination were monitored every month.

Pulses were administered under direct supervision till six pulses after remission. For last six month patients took pulse at home at predetermined dates and reported to us day-before and day-after, provided there were no serious side-effects. Twelve consecutive pulses were given after patient went into remission. Additional daily doses of prednisolone (0.3-0.5 mg/kg) were continued till remission and tapered off. Diabetic patients were given oral hypoglycemic and/ or insulin as per endocrinologist's advice.

To look for hypothalamic-adreno-cortical axis suppression, we estimated early morning serum cortisol in patients selected in a randomized manner.

Results

Duration of disease at presentation varied from 2 months to 2 years with only cutaneous lesions in 9 pts, only mucosal in 2 pts and muco-cutaneous in 54 patients, respectively (Table 1.).

Sixty two patients completed the study; out of them 27 were males and 35 females. Forty eight patients achieved remission in 3 pulses, 7 patients needed up to 6 pulses and 7 patients needed more than 6 pulses (up to 17 pulses) to achieve remission. Recovery was noticed as early as one week in cutaneous lesions and 2 weeks in mucous lesions. It was also noticed that regular patients achieved remission early (Fig 1).

Patients who had delay in subsidence of the initial lesion or who had extensive lesions in the beginning, additional daily oral betamethasone 2 -3 mg /day given. Patients, who had relapse in phase III and IV again put in BAP therapy(Table 2).

Side-effects were seen in 18 (29%) patients (Table 3,4,5). Major side-effects were gastrointestinal and sleep related which were managed with increasing antacid and h2 blocker and sedatives as required. Infections, fungal, bacterial and viral were treated accordingly. Although some of them were extensive but we didn't face any problem to control them.

Discussion

At this moment, when dexamethasone and cyclophosphamide in different permutation and combination showed very good results for the management of pemphigus vul-

Table 1 — *Showing Duration of Disease*

Age group of patients treated	Number of patients	Male	Female	Attended regularly	Attended irregularly	Reason for irregularity
Upto 30 yrs	8/11.94%	3	5	8/100%		
30 –45 yrs	42/62.68%	17	24	39/92.85%	3	Occupational
45 -65 yrs	17/25.37%	8	9	15/88.23%	2	Not known
Total	67	29	38	62	5 (3/2)	

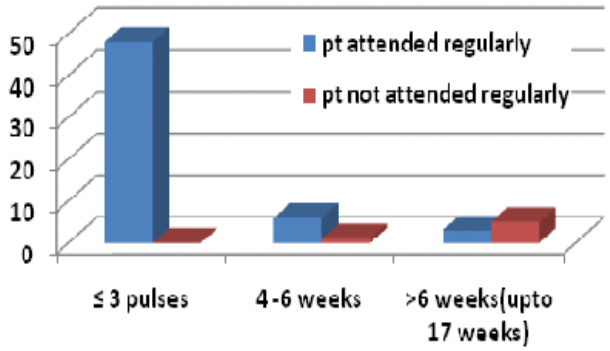


Fig 1 — Response to treatment, duration of phase one

Table 2 — *Status of patients at the end of the study*

Remission	Non- compliant, Left out from study	Death phase III	Relapse in phase IV	Relapse in
62	4(3 + 1)	1	9	4

garis[10-13,6] (Table 1), we thought some other type of corticosteroid and non-corticosteroid immunosuppressant to manage some specific problems.

Why betamethasone? The target of this study was to modify the management of pemphigus patients with pulse therapy as such that patient can self- administer the therapy in such a convenient place and technique , so that it will help him to lose less working days and earning, without compromising the quality of the therapy . Betamethasone can be taken orally. The comparison with other systemic glucocorticoids is as follows.

For several decades, dermatologists have utilized azathioprine to treat numerous debilitating skin diseases. This synthetic purine analog is derived from 6-mercaptopurine. It is thought to act by disrupting nucleic acid synthesis and has recently been found to interfere with T-cell activation. The most recognized uses of azathioprine in dermatology are for immunobullous diseases, generalized eczematous disorders, and photodermatoses[14] . The most common side effects of azathioprine includes nausea and vomiting, sometimes accompanied by abdominal pain or diarrhea. Less often, azathioprine may cause hepatitis , pancreatitis or an allergic reaction that may include a flu-like illness or a rash and leucopenia.

Pasricha and Poonam[6] treated 123 patients over a 5-year study period with modified pulse regimen. The modifications over standard DCP pulse incorporated use of oral betamethasone on tapering doses according to disease severity in phase 1 with the result of significant shortening of the phase 1. As the plasma half life of Betamethasone is significantly more than dexamethasone (300 minutes in comparison to 200 minutes of dexamethasone), we thought the possibility of less interpulse relapse in this study, and it also helped to design our study. Our studies showed that less number of patients needed daily corticosteroid in the form of daily oral betamethasone in the first phase, and also for shorter duration. This benefit may be due to the same reason of longer half life of betamethasone.

The left out rate in pulse therapy is very high. Reason behind the lack of patient compliance are various, but after perusal of many studies (Table 7), it was obvious to us that, regular hospital admission is one of the most important reason, loss of work hours and cost of therapy (Table 8) inclusive of hospital admission charges was a factor.

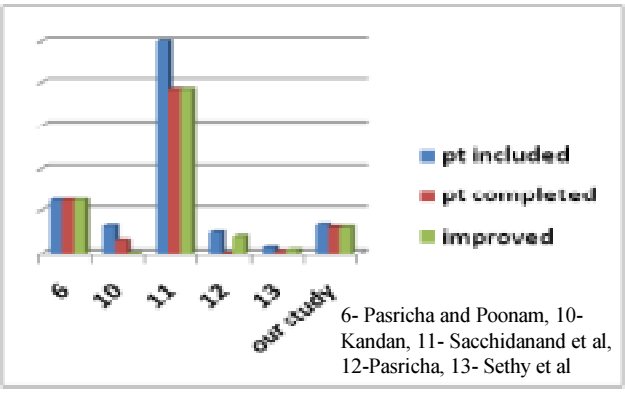
Table 3 — *Immediate side effects during phase I*

Adverse effects	No of patients (n=62)
Anorexia	13
Nausea /Dyspepsia	11/7
Insomnia /mood changes/anxiety	9/2/3
Myalgia/weakness after pulse	9/2
Hypertension/ palpitation/chest pain/epigastric pain	4/2/1/4
Headache/blurred vision/ urticaria/ pedal edema	2/1/2/2
Cough/ dyspnoea	5/2

Table 4 — *Delayed side effects in phase II/III*

Adverse effects	No of patients (n=62)
Oral candidial infection / dermatophytosis/ furunculosis	11/5/3
Obesity/cushingoid features	16/18
Hypertension/hyperglycemia	3/9
Oligomenorrhoea/ amenorrhoea	11(29 females of premenopausal age)
Osteopenia/cataract/DVT/ diffuse scalp hair loss	3/2/1/3
Eczema Herpeticum / Acne/pneumonia	1/4/2

It has been observed that those patients who were regular in their pulses required less number of pulses to go into clinical remission[15]. In our study majority of patients went into remission in as early as 3 months, all of them were regular in taking pulse therapy. Cutaneous lesions disap-



6- Pasricha and Poonam, 10- Kandan, 11- Sacchidanand et al, 12-Pasricha, 13- Sethy et al

Fig – 2 Types of pulses with result

peared faster than mucous lesions.

Pulse therapy is extremely safe regarding side effects. The AIIMS experience[11] showed that there is no risk of increase bodyweight, or development of diabetes or hypertension, peptic ulceration, osteoporosis, striae, acne, hirsutism or other side effects commonly associated with corticosteroids unless the patient was receiving or had received conventional daily doses of corticosteroids, side effects associated with cyclophosphamide were also generally very infrequent. Leukopenia, thrombocytopenia and anemia were rarely seen also hemorrhagic cystitis and generalized hyperpigmentation, major side effects of cyclophosphamide were diffuse hair loss, amenorrhoea, azoospermia. Side effects were more in the first phase of the regimen when daily corticosteroids in addition to pulse were given. Other studies[4,6,13,15] on DCP were also had significantly less side effects. In comparison to other studies our studies also has remarkably less and minor side effects.

Table 7 — *Reason behind left out from study*

Study Reference number	Number of patients Included	Number of patients completed	Left out in different stage	Reason
11 Pasricha JS	500	384	97	(+19 died)
6 Pasricha JS, Poonam	143	123	17	not known
13 Sethy PK *et al*	28	25	3	Went abroad, stopped
4 Pasricha JS, Khaitan BK, Raman RS	300	227	61 (12 died)	Various reasons
10 Kandan S, Thappa DM.	65	33(phase 1)	14	Male-work related /financial; Female- family reason, financial.
15 Mahajan VK, Sharma NL, Sharma RC, Garg G.	54	58%		Frequent hospitalisation High cost
17 Rao PN, Laksmi TS.	41	34	7	not known
This study	67	62	4	Shifted far-away, stopped own, not known.

During the initial stages of this therapy, we were in dilemma how patients would tolerate it, particularly gastritis and its response to control the dreaded disease. As our target was to allow the patients to take few pulses in there home, we evaluated every patients before starting, during taking and after completing the pulse to look for side effects. The side effects in BAT pulse were insignificant, infrequent and random, and also in comparison to other type of pulse it was not much. Major side-effects were gastro-intestinal, gastritis being the commonest. Initially, patients were complaining of that, so we divided in 30, 30 and 40 tablets of betamethasone in each glass of water and mixed with liquid antacid and was taken with fruit juice or banana. These combinations were tolerated by the patients better. We named it Steroid Cocktail. The risk of increased pyogenic infections on the skin, and candidiasis of the mouth persisted only as long as the patient had ulcers on the skin and oral cavity, and therefore adequate treatment with standard systemic antibiotics and antifungal agents during this period was enough and very helpful. No side effects of azathioprine were noted. Amongst almost half of the patients pituitary-adrenal function was found to be suppressed 1 month after the last pulse of phase II but, all these patients were asymptomatic and remained well during subsequent follow up[18].

Table 8 — *Expenditure per pulse*

DCP	BAP
Rs 650/ per pulse excluding mid cycle pulse, and daily cyclophosphamide, oral prednisolone	Rs 150/ pulse excluding daily azathioprin,, and daily oral prednisolone.

Table 5 — *Side-effects detected (*n = 62) *in investigations*

	No of patients
Chest X-ray(pneumonitic changes)	2
Anaemia leucocytosis/leucopenia	13/24/5
Pyuria/albuminuria	13/6
Raised urea/creatinine /liver enzymes/blood sugar	
Serum cortisol(less)	4/1/9

Table 6 — *Comparison between Hydrocortisone and other glucocorticosteroid*

	Potency relative to Hydrocortisone			Half-Life	
	Equivalent Glucocorticoid Dose (mg)	Ante inflammatory	Mineral corticoid	Plasma (minutes)	duration of action (hours)
Intermediate Acting :					
Prednisolone	5	4	0.8	200	12-36
Methylprednisolone	4	5	0.5	180	12-36
Long Acting :					
Dexamethasone	0.75	30	0	200	36-54
Betamethasone	0.6	30	0	300	36-54

Reference : Adrenal Cortical Steroids. In Drug Facts and Comparisons. 5th ed. St. Louis, Facts and Comparisons, Inc.:122-128, 1997

Conclusion

We concluded that, Betamethasone Azathioprine Pulse Therapy is more acceptable to the pemphigus patients due to its flexibility regarding hospital attendance. It is cheaper, and at the same time it is at par in affectivity to other modalities of pulse therapy like DCP with lesser or similar side effects. Work hours are not lost and patient compliance was better. It also provides as a new armamentarium in the fight against pemphigus. However, initial counseling is required to convince patients of taking 100 tablets a day. We also suggest STEROID COCKTAIL a new way to circumvent gastritis associated with pulse therapy.

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