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Outcome of Dexamethasone cyclophosphamide pulse therapy in immunobullous disorders: a prospective study from a tertiary Centre in north Kerala, India

[1]Dr. RAHIMA S,MD,DNB,FRCP, Associate Professor, Dept of Dermatology ,Venereology & Leprosy, Govt Medical College ,Kozhikode, Kerala, India

[2]Dr. NAJEEBA R, MD DNB, MRCP

Former Professor, Dept of Dermatology, Govt. Medical College, Kozhikode, Kerala, India.

[3]Dr. ABDUL LATHEEF E.N, MD, FRCP

Additional Professor, Dept of Dermatology, Govt. Medical College, Kozhikode, Kerala, India.

[4]Dr. BINDU V, MD DNB

Associate Professor, Dept of Dermatology, Govt. Medical College, Kozhikode, Kerala, India.

[5]Dr. Sarita S, MD, DNB

Associate Professor, Dept of Dermatology, Govt. Medical College, Kozhikode, Kerala, India.

Department and institution: Dept of Dermatology, Govt. Medical College, Kozhikode, Kerala, India.

Correspondence Author: Dr. RAHIMA S,MD,DNB,FRCP, Associate Professor, Dept of Dermatology ,Venereology & Leprosy, Govt Medical College ,Kozhikode, Kerala, India

Conflicts of Interest: Nil

Abstract

Background: Dexamethasone – Cyclophosphamide Pulse (DCP) therapy has created miracles in the treatment of pemphigus group of diseases. It has given the patient a chance to cure rather than control of the disease.

Aims: The objective of the study was to assess the efficacy and side effects of DCP therapy.

Methods: Patients who had been treated with DCP therapy from 2004 to 2012 were prospectively assessed and analyzed.

Results: A total of 64 patients were treated with DCP ranging from 20-71 years. Male to female ratio being 1:1.37. Most of the patients were pemphigus vulgaris (58), 3 had pemphigus foliaceous, pemphigus erythematosus in two patients and one patient had bullous pemphigoid. Twenty five patients have completed more than two years after phase IV and have been considered as cured. Three patients are in phase I, 7 in phase II, 1 in phase III and 6 in phase IV. There were eight relapses and five patients died. Side effects were mostly minor and treatable without discontinuing DCP.

Conclusion: DCP therapy is a real boon in the treatment of pemphigus group of patients. It was found to be very effective with minimal serious side effects.

Key words:

Pulse therapy, Dexamethasone, Cyclophosphamide, Pemphigus, Side effects

Introduction

Dexamethasone cyclophosphamide pulse therapy has revolutionized the treatment of pemphigus group of disease from an incurable, debilitating disease to a probable cure. The use of suprapharmacological dose of steroids was first tried by Kountz and Cohn in 1969 to prevent renal graft rejection.[1] Since then there was no looking back. Feduska et al in 1972, were the first to use the term pulse.[2] Burton and Schuster used 2gm

prednisolone as a single dose IV for treating 22 cases of severe alopecia areata. Johnson and Lazarus were probably the first to use pulse therapy in a patient with pemphigus foliaceus and obtained a rapid remission.[4] It was Pasricha and his team in 1981 who introduced pulse therapy in India by treating a patient with Reiter's disease as a life saving measure.[5] Here, we report the outcome of DCP therapy in 64 patients with immunobullous disorders.

Methods

All the patients treated with DCP therapy from August 2004 to March 2012 in our department were prospectively analysed for the effectiveness and side effects of DCP therapy. Once the patient is diagnosed using clinical, histopathology and DIF , patient is thoroughly evaluated for any contraindication for the high pulse steroid and cyclophosphamide. Then the patient is put on 100mg of Inj dexamethasone dissolved in 500ml of 5% dextrose as slow IV infusion on day 1,2 and 3 of the pulse. On 2nd day, a bolus dose of 500mg of cyclophosphamide was added to the same drip and an extra pint of 500ml of 5% dextrose was also administered. Cyclophosphamide 50mg tablets were given from 4th to 28th day. Strictly on 29th day, next pulse is repeated. Phase I continues till there are no cutaneous or mucosal lesions. Same pulse is continued for 9 months in Phase II and only oral cyclophosphamide 50mg given for 9 months in phase III. Patient is monitored without any treatment for 2 years in Phase IV.

Results

Of the total 64 cases, there were 27 males and 37 females with a sex ratio of 1 : 1.37. Youngest patient was 20 years and the oldest 71 years. Maximum affected was in the 40-60 years age group. Most of the cases were pemphigus vulgaris 58 (90.48%); Pemphigus foliaceus in 3 (4.68%), pemphigus erythematosus in 2 (3.12%) and bullous pemphigoid was found in 1 (1.56%) patients.

Most of the cases 50 (78%) had both cutaneous and mucosal involvement [Fig1a] but purely mucous membrane lesion was noted in 5 (7.80%) patients[Fig2]. In 9 (14.04%) patients, lesions were limited to the skin. We also had 3 patients with esophageal involvement. There were 3 (4.68%) patients with vitiligo and 1 (1.56%) patient with keloid and psoriasis each.

Outcome of DCP is given in Table (1). Twenty five (39%) patients are declared cured. Number of pulse required in phase I varied from patient to patient. Details are tabulated in Table (2).

Interval steroid had to be given to almost all patients (95.16%) except three (4.68%). Interval pulse of dexamethasone had to be given in 3 (4.68%) patients with extensive lesions. Of the 8 relapsed cases, 3 were in phase II, 1 in phase III and 4 in phase IV. 4 of them were given re DCP, 1 was given DMP, 3 of them were given DAP. All these patients were cured except two cases who were further treated with mycophenolate mofetil, pulse IVIg for 4 days per month, azathioprine 100mg and intralesional steroids for their persistent oral lesions.

One of the common side effect noted was cutaneous infection followed by melanonychia[Fig 3].The details of side effects in various phases of treatment are tabulated in Table 3.

Raised ESR was observed in 14 (21.89%) patients, anaemia in 7 (10.92%), raised liver function in 9 (13.94%), ECG changes in 10 (15.6%), hypokalemia in 6 (9.36%), monocytosis and fatty liver in 5 (7.8%) each, leucopenia and leucocytosis in 4 (6.24%) each, urinary infection with pus cells seen in 7 (10.92%) patients. ANA positivity was found in two (3.12%) patients with pemphigus erythematosus.Diagnosis was confirmed by histopathology and DIF in all the patients [Fig 1b]

Culture from cutaneous lesions revealed staphylococcus aureus in 9 (13.94%) patients, pseudomonas in 2 (3.12%), klebsiella and E.coli in one patient each (1.56%) .

Five (7.8%) of our patients died. All of them were in phase I. Two (3.12%) of them had discontinued treatment and resorted to indigenous medicine and died due to septicemia in a local hospital. Two (3.12%) female patients with severe cutaneous lesions died in our ward due to aspiration pneumonia soon after the first pulse. Another patient had died due to respiratory failure in a local hospital. Of the patients who died had extensive palmar and mucocutaneous lesions and three (4.68%) patients had discontinued treatment.

Discussion

Immunobullous disorders are a group of severe bullous disorders that affect the skin and mucous membranes. Since the introduction of Dexamethasone - cyclophosphamide pulse therapy by Pasricha et al in 1981, the treatment of these immunobullous diseases have taken a new dimension from a controllable disease to a probable cure.[5] DCP is also now tried in systemic sclerosis, SLE, pyoderma gangrenosum, lichen amyloidosis, lichen planus, alopecia totalis, prurigo nodularis, sarcoidosis, Darier's disease, scleroderma and porokeratosis of Mibelli. The aim of pulse therapy is administering suprapharmacologic doses so as to achieve a faster response and stronger efficacy and to decrease the long term adverse effects associated with systemic daily corticosteroids. At such doses, the auto antibody producing B lymphocytes are knocked down and before these cells could regenerate, next dose is repeated at regular intervals until all such cells are inactivated.

In this 8 year study, females outnumbered males which was also noted by Kandan et al and Masood et al,[8,11] indicating that pemphigus is more common in females. Also, we had patients receiving pulses in a wide age range extending from 20 years to 71 years which was comparable to other studies.[11] We had around 8 (12.48%) patients above 60 years indicating that pulse therapy is effective at any age without extra adverse effects. Majority of our patients were pemphigus vulgaris. There was one case of bullous pemphigoid who responded very well just with 1 pulse are in Phase I. Patients with purely cutaneous lesions (14.04%) responded very well but those with mucosal lesions required a prolonged Phase I. Also patients who relapsed also were patients with persistent oral lesions 7 (10.92%).

There were 3 (4.69%) patients with vitiligo who had responded to DCP concluding that pulse immunosuppressants is a treatment option in vitiligo. But a patient with keloid did not respond at all. Also two patients with a suspected mass lesion in the lung disappeared after 2-3 pulses of DCP.

Outcome of the patients in this study are very encouraging where in 25 (39%) patients are cured, i.e.more than 2 years after clinical remission. Pasricha et al also had a cure rare of 84%.[6] Kandan et al noted cure in 6 out of their 65 patients.[11] Comparison of outcome of studies by different authors are shown in Table (4). Two of those who defaulted were due to prolonged treatment and financial constraints.

Number of pulses in Phase I varied in each patient. Prolonged Phase I was mainly due to persistent oral lesion or a persistent single cutaneous lesion which could be overcome by giving intralesional steroid injection or a interval pulse steroid. In our series, 53 (82.68%) required less than 6 pulses in phase I compared to 50% and 16% in a study by Pasricha et al and Kandan et al respectively. Four (6.24%) of our patients required more than 12 pulses which was also comparable with other studies.[6]

Of those who relapse 8 (12.48%) patients, half of them were in Phase IV. Relapse was seen more in patients with

irregular DCP. Also in patients who had only 6 months of II phase (2 patients). Four of these relapses were cured with re DCP. Two patients responded to DAP.

Relapse rate was in tandem with other studies.[6,10,11] All the patients who died 5 (7.80%) were in phase I. Pasricha et al also found more deaths in Phase I.[7] Only two female patients died in the ward due to aspiration pneumonia and not directly related to DCP. Other two patients had opted indigenous medicine and developed exacerbation. Another patient died due to unrelated cause. Thus DCP therapy does not itself contribute to increase in mortality in our series. All these patients who died had extensive lesions and palmar involvement in two patients each. Mortality rate was comparable with other studies.[6,11]

Side effects were minimal and controllable. Flushing and puffiness of the face was seen in majority of the cases by 2nd day of pulse which could have been caused by sodium and water retention due to steroids, which was also noted by Pasricha et al.[7] Patients also complained of fatigue during the first week of pulse. This could be due to a temporary adrenocortical suppression. Weight gain was not noticed, infact patients lose weight in II phase. This may be because the interval steroids were stopped and cushingoid features would subside.

Hiccup was observed in 4 patients during the pulse which subsided with domperidone tablets which was also noted by others.[6,7] Bacterial infections were the most common side effects noted mainly in Phase I. This may be due to immunosuppressive effect and the cutaneous lesions acting as a source of infection. So, it is mandatory to identify and aggressively treat these cutaneous infections. The causative agent was MRSA in majority of them.

Oral candidiasis was also very common in the Phase I, again suggesting that presence of ulcers contributes to the infection rather than DCP therapy. Another interesting finding was varicella in 5 (7.83%) patients and herpes zoster in 2 (3.12%) which were manageable with oral acyclovir and postponing the pulse for 2 weeks.

Only 3 (4.68%) had newly detected diabetes mellitus after the pulse. It is a very low incidence which is also comparable with a study by Pasricha et al.[7] Two patients had developed ketoacidosis. Eight patients had developed hypertension during DCP therapy. This may be due to the sodium and water retention due to DCP therapy.

Cataract was detected in Phase II in 3 (4.68%) patients but cannot be directly attributed to DCP, since most of these patients were on oral steroids for a long time. Fungal endophthalmitis, glaucoma was noted in 1 patient each. Aseptic necrosis of femur head was diagnosed and treated in two patients and pulse regime was continued.

Amenorrhoea was a significant complication observed in 7 (10.92%) patients compared to 50% of his patients by Pasricha et al, which could be due to pulse cyclophosphamide.[7] It started as early as 2nd pulse and some patients resumed their menstrual cycle during the late phase III.

Another important finding was the bluish black longitudinal pigmentation of nails seen in 14 patients (20.84%), which starts in 2nd phase and disappears by late III phase; earliest melanonychia was seen even with 2 pulses. This also has been reported by Kandan et al.[11] Melanonychia is most probably due to pulse cyclophosphamide. It can cause activation of melanocytes in nail matrix or could be due to drug. It is usually seen in thumb and index fingers. This could be due to the increase frequency of usage of these fingers. Also more in the finger nails compared to toe nails which could be due to the faster growth of finger nails. Dave et al also have reported a peculiar pattern in a female patient who was on DCP therapy involving lateral 2½ fingers.[9] Also generalized hyperpigmentation was seen in 4 (6.24%)

patients which was also reported by others, especially in patients who had prolonged phase I.[7]

To conclude, we have found DCP therapy very effective with minimal and tolerable adverse effects. We would suggest DCP therapy as the first line therapy for pemphigus group of disorders.

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Table 1: Outcome of DCP

	Outcome	No. of patients	Percentage
1.	Phase I	3	4.68
2.	Phase II	7	10.92
3.	Phase III	1	1.56
4.	Phase IV	6	9.36
5.	Cured	25	39
6.	Relapse	8	12.48
7.	Defaultic	2	3.12
8.	Deferred	3	4.68
9.	Lost to follow up	4	6.24
10.	Expired	5	7.80

Table 2: No. of pulses in Phase I Patients

1-3	**28**	**43.68**
4-6	**25**	**39**
7-12	**7**	**10.92**
<12	**4**	**6.24**

Table 3 : Side Effects of DCP – Phase Wise

		Before	I	II	III	IV
I	**Produced by Pulse**					
	A) Infections					
	1) Pyogenic Infection					
	a) Furuncle		5	3		
	b) Abcess		4			
	c) Cutaneous infection					
	i) Staphylococcus		9			
	ii) Pseudomonas aureus		2			
	iii) Klebsiella		1			
	iv) E.Coli		1			
	d) Septicemia		**4**			
	2) Candidiasis – oral	**1**	**9**			**1**
	3) Viral infection:					
	Varicella		**5**			
	Chikungunya		**1**			
	4) Scabies		**2**			
	5) Urinary tract infections		**7**			
	B) Fatigue		**4**			
	Puffiness & flushing of face		**28**			
	Cushingoid habitus		**2**			
	Hiccups		**4**			
	Shivering		**2**			
	C) Metabolic changes					
	DM	**14**	**3**	**1**		
	Ketoacidosis		**2**			
	Hyperglycemia	**3**				
	Weight gain		**3**	**3**		
	HT	**1**	**3**			
	Hypokalemia		**6**	**1**		
	D) Ocular					
	Cataract	**1**	**3**			
	Glaucoma		**1**			
	Fungal endophthalmia		**1**			

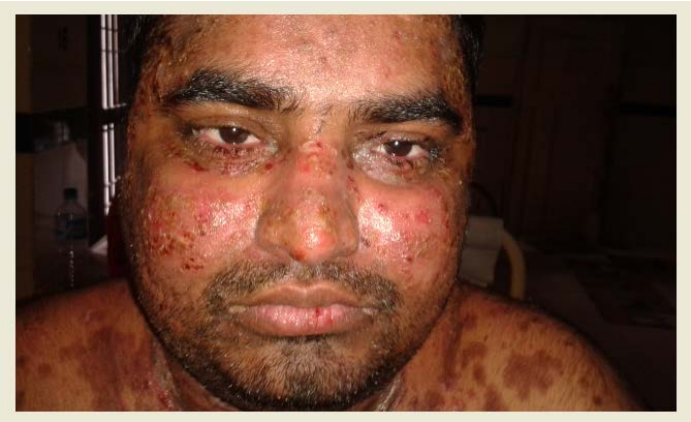
	E) GI side effects					
	Jaundice		**1**			
	Vomiting		**2**			
	Dyspepsia		**2**			
	F) Nail changes					
	Nail-pigmentation		**2**	**12**		
	Nail-onychomadesis		**1**			
	Nail-Beau's lines			**2**		
	G) Musculoskeletal					
	Aseptic necrosis of femur head	**1**	**1**			
	Joint pain		**3**	**2**		
	H) Haematological					
	Anaemia		**7**			
	Leucopenia		**4**			
	I) Genitourinary					
	Amenorrhoea		**3**	**2**	**2**	
	Hematuria		**1**	**2**		
	Renal calculi			**2**		
	J) Cardiovascular					
	Tachycardia		**1**	**1**	**1**	
	Angina		**4**	**4**		
	K) Respiratory					
	Pneumonia		**2**			
	Pleurisy		**1**			
	L) Neurological					
	Seizures		**1**			
	M)Psychiatric					
	Psychosis	**1**	**3**			
	Depression, insomnia		**1**			
	Irritability	**1**				

Table 4: Comparison of Outcome of DCP Therapy

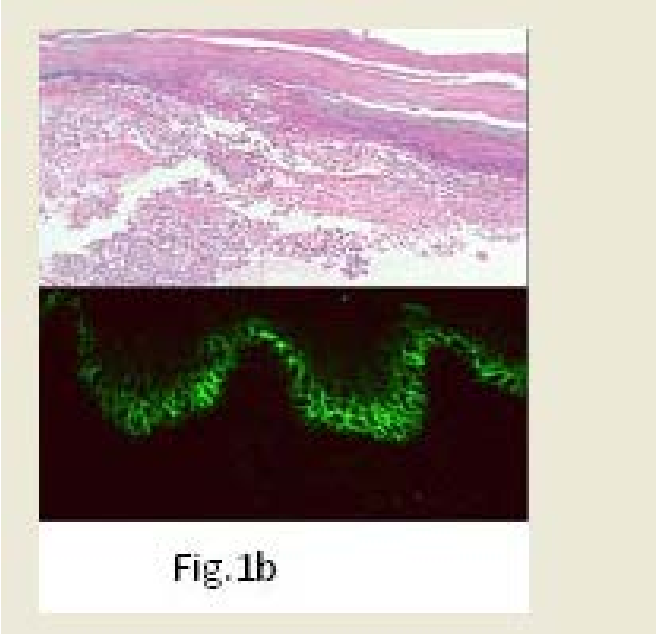
	No. of patients	Cured	Relapsed	Died
Pasricha[6]	300	190/227(84%)	59/227(26%)	12
Masood[8]	30	12	-	1
Sachidanand[10]	50	41 (82%)	2 (4%)	1 (2%)
Kandan[11]	65	6(9.78%)	4 (6.52%)	5 (7.7%)
Zivanovic[12]	72	43	13	7
Present study	64	25 (39%)	8 (12.48%)	5 (7.8%)

Figure Legends:

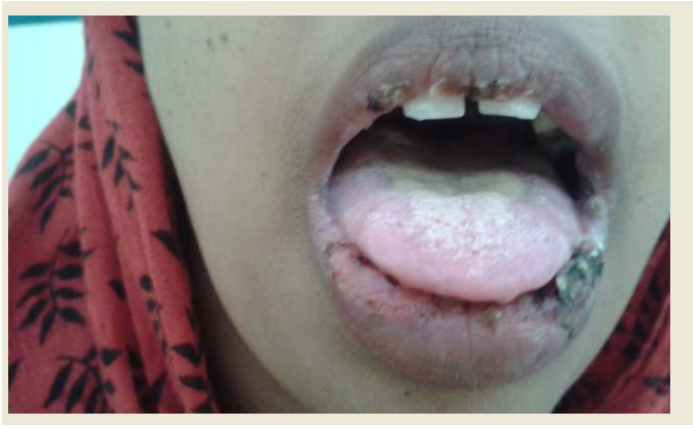
1. Fig. 1a showing extensive vesicles and crusted erosions in a patient with pemphigus vulgaris.



2. Fig. 1b showing suprabasal cleavage on biopsy and fish net pattern on DIF in a patient with pemphigus vulgaris



2. Fig. 2 showing predominant oral and lip lesion in a patient with pemphigus vulgaris.



3. Fig. 3 showing melanonychia in a patient of pemphigus vulgaris on DCP