

OUR TEN YEARS' EXPERIENCE WITH PULSE THERAPY IN PEMPHIGUS- A RETROSPECTIVE ANALYSIS OF 194 CASES

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ABSTRACT

BACKGROUND

Pemphigus is a group of autoimmune disease that affect skin and mucous membranes clinically manifested by flaccid blisters because of acantholysis. Pulse therapy was initiated in 1981 to treat the cases of pemphigus, which has reduced the mortality to a great extent. Various regimens of pulse therapy Dexamethasone-Cyclophosphamide (DCP), Dexamethasone-Azathioprine (DAP), Dexamethasone-Methotrexate (DMP) and Dexamethasone only are used.

The aim of the study is to study the efficacy and various side effects associated with pulse therapy.

MATERIALS AND METHODS

Patients were put on DCP, DAP and DOP are used depending on the age and completion of family.

RESULTS

194 patients were started on pulse therapy. 63 males, 131 females (M:F-1:2). Age ranged from 9 years to 68 years. Majority of the patients were in the age group of 31-40 years (29.4%). 184 cases were diagnosed as Pemphigus Vulgaris (PV), 1 case as pemphigus vegetans (P veg) and 9 cases as Pemphigus Foliaceus (PF). DCP was started in 147 cases, DAP in 38 cases and DOP in 9 patients. Out of 194 patients, 137 (70.6%) patients were on regular treatment, 12 (6%) were irregular, 38 (19.5%) were defaulted and 7 (3.6%) patients were died. Relapse was seen in 3 patients in phase II, 5 patients in phase III, 4 patients in phase IV and 5 patients after pulse therapy.

CONCLUSION

Though side effects are more with DCP, it is most effective in reducing the morbidity, mortality and relapses as compared to DAP and DOP.

KEYWORDS

Pemphigus, Pulse Therapy.

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BACKGROUND

Pemphigus is an autoimmune disease associated with high mortality.¹ With the introduction of pulse therapy, mortality was reduced to a great extent. Dexamethasone Cyclophosphamide (DCP) pulse therapy was used to treat pemphigus cases since 1981.^{2,3,4,5,6,7} DCP was effective in treating the cases of pemphigus, but because of its side effects, various modifications were done like Dexamethasone-Azathioprine (DAP), Dexamethasone-Methotrexate (DMP) and Dexamethasone Only (DOP) Pulse therapy. Azathioprine was used in the reproductive age group.

Pulse therapy was started in our institution since 2007.

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AIM- To study the efficacy and various side effects associated with pulse therapy.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Dermatology, Venereology and Leprosy for a period of 10 years (2007-2017). Data was collected from the records of the patients available at the Department of Dermatology, Venereology and Leprosy of our institution. Data was analysed thoroughly and results were noted.

Inclusion Criteria

All the clinically-diagnosed cases of pemphigus were included in the study, irrespective of their age and sex.

Exclusion Criteria

Patients who were unfit for pulse therapy and who were unable to come regularly were excluded.

All clinically-diagnosed cases of pemphigus were confirmed by histopathology and direct immunofluorescence. They were started on pulse therapy after thorough investigations and getting fitness from

cardiologist. Patient's demographic profile and a detailed history regarding the onset, duration, associated comorbid conditions, drug history, family history, marital status, children and menstrual history (in case of females) was taken. Thorough general examination was done. Vitals were recorded. Investigations done were- complete haemogram, complete urine examination, liver and renal function tests, serum electrolytes, ECG, ultrasonography of abdomen, chest x-ray, stool examination for occult blood and ova and cyst, upper gastrointestinal endoscopy and 2D echocardiogram. Pus and blood were sent for culture and sensitivity wherever necessary. Pregnancy test was done in case of females. Baseline blood pressure and weight recording was done. All the above investigations were repeated every month along with weight recording before starting the pulse therapy. Indirect immunofluorescence was not done as the facilities were not available. Semen analysis was not done in male patients who were on DCP as they had completed their families.

After taking informed consent from the patients, they were started on pulse therapy. DCP was started in patients who had completed their families as cyclophosphamide has adverse effects on gonads causing azoospermia and ovarian failure. DAP was started in those patients who had not completed the families.⁸ DOP was started in patients who were below 18 years.

Dexamethasone 100 mg was given intravenously in 5% of dextrose for three consecutive days in DCP, DAP and DOP. In DCP pulse therapy, cyclophosphamide 500 mg was added to 5% dextrose on 2nd day of pulse therapy. Patient was given T. cyclophosphamide 50 mg daily on non-pulse days. T. Azathioprine was given to the patients on DAP. In DOP patients, no additional treatment was given. Interval steroids were given to the patients to control the disease activity in between the pulse therapies. Interval pulse therapy was given to the patients with severe disease activity. Antibiotics and antifungals were given wherever necessary.

Diabetics were managed as per endocrinologist's advice and 8 U of insulin was added to 5% dextrose at the time of pulse therapy. Blood pressure, pulse rate and respiratory rates were monitored every 30 minutes while on pulse. Injection vitamin D and calcium supplements were given after pulse therapy. Serum electrolytes and ECG recording was done after pulse therapy.

RESULTS

A total of 194 patients were started on pulse therapy, out of which 63 males, 131 females (M:F 1:2).

Age ranged from 9 years to 68 years, majority of them were in 31-40 (57 patients - 29.3%), followed by 21-30 years (50 cases - 25.7%) (Table 1).

Distribution of cases given in the table (Table 2).

Duration of the disease varied from 2 weeks to 7 years. Four patients gave the history of intake of herbal medication prior to the onset of the disease. 102 patients were on oral corticosteroids and 10 patients had a history of pulse therapy from outside for 1-3 cycles. 4 patients were on azathioprine,

3 were on cyclophosphamide, 1 patient was on methotrexate and 1 patient was on dapsone.

12 patients were diabetics, 13 were hypertensive, 1 patient had a past history of miliary tuberculosis, 2 had a history of pulmonary arterial hypertension and 1 patient had coronary artery disease. Pulse therapy was started in these patients after taking fitness from cardiologist.

Out of 194 patients, 158 had completed their families. Out of 131 females, 2 had not attained menarche, 89 had regular menstrual cycles, 9 had irregular cycles and 31 had reached menopause.

DCP was started in 147 cases, DAP in 38 cases and DOP in 9 cases (Table 3).

Out of 194 patients, 137 were on regular treatment (following 28 days cycle), 12 were irregular but completed the treatment, 38 patients defaulted and 7 patients died.

Phase I- 48 patients had prolonged cycles, while others had 6-9 cycles. Phase II was fixed to 9 months (Table 4).

Oral corticosteroids were given in 48 cases for 2-7 months. Interval pulse therapy was given in two patients who were on DCP (2 cycles in 1 patient, 1 cycle in 1 patient). 3 patients were shifted from DCP to DAP (two patients developed haemorrhagic cystitis and one patient developed anaemia). In one patient, pulse was stopped because of severe hypertension. Mycophenolate mofetil was given for 4 months in two cases who were having persistent lesions, but there was no response. One patient became pregnant while on pulse in spite of counseling, she aborted and pulse restarted after 3 months.

New lesions occurred in 3 patients in phase II (DCP-2 cases, DAP-1 case), in 5 patients in phase III (DCP-4, DAP-1), in 4 patients in phase IV (DCP-2, DAP-2). 5 patients relapsed (DCP-1, DAP-2, DOP-2) after completion of 4 phases. Gap was 6 months to 2 years 8 months. One patient relapsed as pemphigus vegetans. One female patient of 45 years, a case of pemphigus foliaceus had developed relapses even after two pulse therapies of DCP. Persistent oral lesions were seen in 5 patients (DCP-2, DAP-3) (Table 5).

Complications were more with DCP. They are shown in the table (Table 6).

ECG changes seen were - T inversions (5 cases), flat T waves (2 cases), prolonged PR interval (2 cases) and left axis deviation (2 cases).

Weight gain was seen in 66 patients (2-5 kg in 41 cases, 5-10 kg in 16 cases and >10 kg in 9 cases). Amenorrhoea was seen in 48 females. It was seen with 2 cycles to 18 cycles of pulse therapy. 3 patients complained of menorrhagia and one complained of polymenorrhoea who were on DCP.

7 patients died during pulse therapy (4 patients with septicemia, 2 with pneumonia and 1 patient with electrolyte imbalance).

The complications associated with DCP pulse therapy were- anaemia (2 patients), leucopenia (2 case, 1 patient had persistent leucopenia for 4 months and treated with GM-CSF), thrombocytopenia (1 case), convulsions (1 case), furuncles (4 cases), folliculitis (6 cases), perianal abscess (1 case), cellulitis (2 cases), pelvic inflammatory disease (1

case), herpes simplex (1 case), herpes zoster (1 case), haemorrhagic cystitis (2 cases), raised serum creatinine (1 case), raised liver enzymes (1 case), coronary artery disease

(1 case), bradycardia (2 cases) and myocardial infarction (1 case).

Age	0-10	11-20	21-30	31-40	41-50	51-60	61-70
Number of cases	1 (0.5%)	10 (5.1%)	50 (25.8%)	57 (29.4%)	44 (22.7%)	23 (11.9%)	7 (3.6%)

Table 1. Age Wise Distribution of the Cases

Type of Disease	Number of Patients
Pemphigus vulgaris	184 (94.8%)
Pemphigus vegetans	1 (0.5%)
Pemphigus foliaceus	9 (4.6%)

Table 2. Distribution of the Cases

Type of Pulse Therapy	Number of Patients	Males	Females
DCP	147 (75.7%)	46	101
DAP	38 (19.6%)	17	21
DOP	9 (4.6%)	-	9

Table 3. Type of Pulse Therapy

Number of Cycles	10-15	16-20	>20	Total
DCP	23	2	2	27 (18%)
DAP	10	6	-	16 (42%)
DOP	5	-	-	5 (55%)

Table 4. Phase I Prolonged Cycles

New Lesions	Phase III	Phase IV	After Pulse Therapy	Total
DCP	4	2	1	9 (6%)
DAP	1	2	2	6 (15.7%)
DOP	-	-	2	2 (22%)

Table 5. Relapse Cases

Complications	DCP (Number of Patients)	DAP (Number of Patients)	DOP (Number of Patients)
Diabetes mellitus	12	1	-
Hypertension	20	6	-
Oral candidiasis	15	7	-
Tinea corporis	4	3	-
Weakness	18	12	-
Cushingoid features	2	2	-
ECG changes	8	3	-
Chills	7	1	-
Entamoeba cysts in stools	1	4	-
Avascular necrosis of femur	1	2	-
Amenorrhoea	48	2	-
Hypokalaemia	4	-	1
Weight gain	49	14	3
Cataract	4	1	-
Death	6	1	-

Table 6. Complications Associated with Pulse Therapy

DISCUSSION

In our study, females were more affected than males, which was also similar to the study done by Iffat Hassan et al⁸ and Javidi Z et al.⁹

Most common age group affected was 31-40 years. Youngest was 9 years old female. In the study of Devinder Thappa et al, bimodal pattern was seen.¹⁰

Though side effects are more with DCP^{9,10,11,12,13} than DAP or DOP, it was more effective. DCP was associated with shortened phase I cycles, faster response, even in extensive disease and low relapse rate (6%). Relapses were more with DOP (22%), followed by DAP (15.7%).⁸ Relapses were managed with oral corticosteroids except in one who needed pulse therapy.

Persistent oral lesions were seen more with DAP.

Mycophenolate mofetil was given to 2 patients for 4 months who were not responding to DCP, but we did not find any significant improvement.

Pemphigus foliaceus cases were difficult to treat. One 45-year-old female patient relapsed even after 2 pulse therapies. Three cases were having persistent oral lesions. One patient relapsed after pulse therapy.

Cardiac patients can be given pulse therapy without any adverse effects with close monitoring under cardiologist's guidance.

Patients with uncontrolled diabetes mellitus were treated under the guidance of endocrinologist.

Weight gain was more in phase I followed by phase II. Majority of them gained 2-5 kg weight.

One patient had persistent leucopenia and treated with GM-CSF.¹⁴

Amenorrhoea was more common with DCP¹⁵ in few females. It was seen with 2nd cycle of pulse therapy.

Cataract developed in patients who were above 40 years. It may be due to age-related changes or corticosteroids is not known.

Bacterial, fungal, viral and protozoal infections treated accordingly.

CONCLUSION

Though side effects are more with DCP, it is most effective in reducing the morbidity, mortality and relapses as compared to DAP and DOP.

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