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EVALUATION OF PULSE THERAPY IN PEMPHIGUS

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ABSTRACT

Introduction: In Pemphigus, pulse therapy refers to intravenous (IV) infusion of high doses of steroids for one or more days for quicker, better efficacy, and to decrease the side effects of long-term steroids. **Objective**: To assess the risk benefit ratio of pulse therapy in Pemphigus diseases. **Methodology**: We have conducted a prospective study for a period of 6 months (August 2016 – January 2017) In in-patient Departments of Dermatology, Gandhi hospital, Secunderabad. In this study we have included 45 number of patients. **Results**: In our study we found that the disease was more prevalent in the middle age group of 21-30years. Out of 45 patients 32 patients were given DCP and 13 patients were given DAP. Our study showed that in initial visits safety parameters were found to be high than efficacy but in later visits efficacy increased because patient was prescribed with supportive therapy to monitor safety parameter. **Conclusion**: The disease condition showed remarkable declination regardless of their severity conditionally if patient received regular, rational and complete treatment. Studies with more number of patients and for longer period will help in better management of patient and disease. Hence we conclude that our study provides a hypothesis for future studies which can emphasize on our advantages of Pulsetherapy.

KEYWORDS: Pemphigus, Pulse therapy, long-term steroids, Risk benefit ratio.

KEY MESSAGE

Whats known? – Pulse therapy is dministration of **suprapharmacologic** doses of drugs in an **intermittent** manner to **enhance** the **therapeutic effects** and **reduce** the **side-effects.**

Whats new? - In our study the disease condition showed remarkable declination regardless of their severity conditionally if patient received regular, rational and complete treatment.

INTRODUCTION

Pemphigus is a group of organ specific blistering autoimmune diseases that affect the skin and mucous membranes characterized by the production of auto antibodies to desmogleins.[1] Pemphigus Vulgaris has been reported to occur in the world with an incidence of 0.5-3.2 cases per 100,000 population.[2] The mean age of onset is approximately 50-60 years.[3] Infants with neonatal Pemphigus remit with clearance of maternal auto antibodies.[3] Pemphigus that continues after a patient stops using a drug is referred to as triggered, whereas lesions that clear soon after withdrawal are referred to as induced).[4] It is potentially life-threatening disease, with a mortality rate of approximately 5-15%.[5] The clinical, histological and immune-fluorescence abnormalities of drug-induced Pemphigus are similar to those of the idiopathic variety.[6]

Treatment

The treatment of immune-bullous diseases consists of three phases:

- Control: period of intense therapy given to suppress disease activity until no new lesions appear. The duration of this phase is weeks.
- Consolidation: Drugs and doses are maintained until complete clearance of lesions.
- Maintenance: Medications can be gradually tapered aiming for the lowest dose that prevents new lesions from appearing.
- Relapse may occur at any time, resulting in renewed disease control effort.

Medications[7]

The following prescription medications may be used alone or in combination, depending on the type and severity of your Pemphigus: Corticosteroids, Immunosuppressants [Azathioprine, Mycophenolate mofetil[16], Methotrexate, Cyclophosphamide, Chlorambucil, Intravenous immunoglobulin (IVIG).[8]

Pulse Therapy In Pemphigus

The administration of suprapharmacologic doses of drugs in an intermittent manner is known as "pulse therapy." In Pemphigus, pulse therapy refers to intravenous (IV) infusion of high doses of steroids for one or more days for quicker, better efficacy, and to decrease the side effects of long-term steroids.

DAP is recommended for unmarried patients who have not completed their family.

DMP is recommended for patients not responding to DCP/DAP after 12 pulses inPhase

DMP is recommended for patients not responding to DCP/DAP after 12 pulses in Phase 1

The Entire treatment was divided into four phases as per Pasricha et al. schedule.

Phases Of Dexamethasone -Cyclophosphamide Pulse Therapy[9]

PHASE I: DCP For 3 consecutive days and repeated every 28 days until no new lesions appear between pulses.

- **Day 1** Dexamethasone 100 mg in 500 ml of 5% dextrose IV over 2 hr
- **Day 2** Dexamethasone 100 mg + 500 mg cyclophosphamide in 500 ml of 5% dextrose IV over 2 hr
- **Day 3** Dexamethasone 100 mg in 500 ml of 5% dextrose IV over 2 hr

PHASE II: DCP schedule is given for duration of 9 months.

PHASE III: Monthly pulses are terminated and oral cyclophosphamide (50 mg/dy)is continued for duration of 9 months.

PHASE IV: Treatment is stopped and patients are followed-up for

Phases of Dexamethasone- Azathioprine Pulse Therapy

PHASE I: DCP For 3 consecutive days and repeated every 28 days until no new lesions appear between pulses.

- **Day 1 Dexamethasone 100 mg in 500 ml of 5% dextrose IV over 2 hr**
- **Day 2 Dexamethasone 100 mg + 50 mg Azathioprine 500 mg of 5% dextrose IV over 2 hr**
- **Day 3 Dexamethasone 100 mg in 500 ml of 5% dextrose IV over 2 hr**

PHASE II: DCP schedule is given for duration of 9 months.

PHASE III: Monthly pulses are terminated and oral Azathioprine (50 mg/day)is continued for duration of 9 months.

PHASE IV: Treatment is stopped and patients are followed-up for

Purpose of The Study

- ☞ The study helps in improving the efficacy and patient adherence towards Pulse therapy.
- ☞ It helps to provide information or background for patient care approaches.
- ☞ Improves quality of life.

METHODOLOGY

A prospective observational study was conducted in a tertiary care hospital for a duration of 6 months in Patients who were histologically and cytologically confirmed with Pemphigus disease.

Inclusion criteria

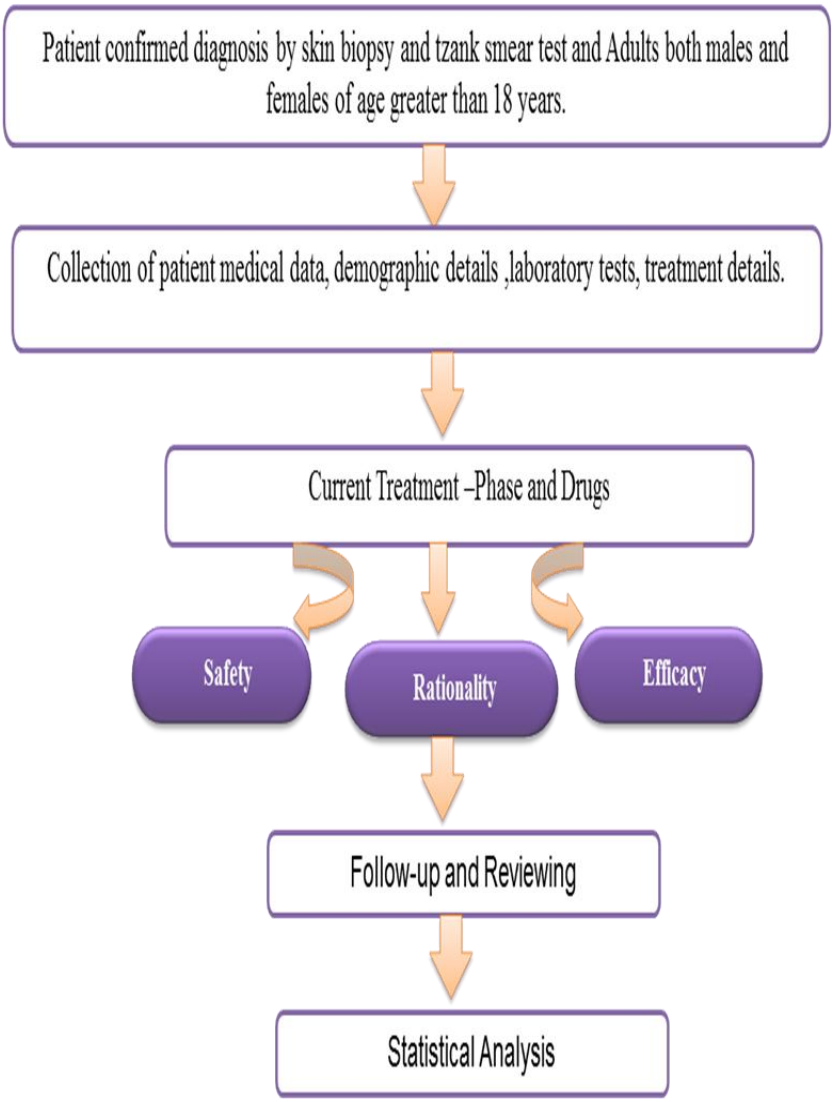
- Adult patients who are >18 years of age of both gender.
- Patients who has been diagnosed with Pemphigus disease.

Exclusion criteria

- Pregnant and lactating women.
- Pediatric Patients.
- Immuno-compromised patients.
- Individuals with uncontrolled hypertension.

Statistical analysis: The obtained data was analyzed by using statistical method mean ± standard error mean (SEM) using GraphPad Prism 5.0 software (GraphPad, San Diego, USA).A unpaired t test was applied to compare the two different levels i.e, lesions and ADR's at each visit. Data was considered statistacially significant between the mean value of the two categorical variables is found to be significant, very significant& extremely significant if P<0.05*, P<0.01** and P<0.001***

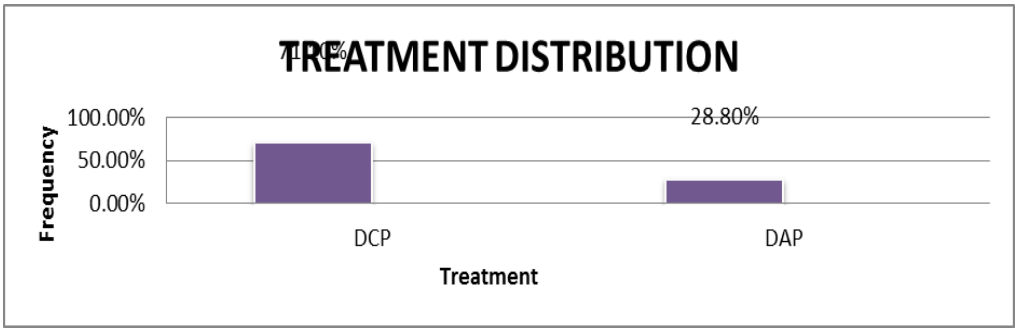
Plan of Work



RESULTS

In dermatology department of a tertiary care hospital during our period of study, 58 patients were diagnosed with Pemphigus out of which 45 patients were treated with pulse therapy. Among them females were predominant constituting for about 64.4% and males were 35.5% Of which 13 patients were between the age group of 21-30 years, followed by 11 patients between the age groups of 41-50 years and 51-60 years each and 3 patients between 10-20 years, remaining 1 was above 61 years, 84.4% of patients were married and 15.5% were unmarried. We found that 77.7% of patients were without any co-morbid conditions, HTN in 8.8% of patients and HTN+DM in 8.8% and remaining 4.4% of patients had DM.

In our study 86.6% of patients were diagnosed with Pemphigus Vulgaris and 13.4 % were diagnosed with Pemphigus Foliaceous.



For statistical analysis we have categorized patients into two categories-

Mild- moderate - (0-2) lesions

Severe - < 2 lesions

DCP

PHASE 1

VISIT1

Table 8.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	6	0.3	0.01	0.0022	P<0.0001 ***
Severe (>2)	47	2.24	1.2	0.2619	

Table 9.

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	20	0.76	0.14	0.0306	P<0.0001 ***
Severe (>2)	3	0.14	0.02	0.0044	

Mean of mild-moderate category of safety was0.95 and mean of mild-moderate category of efficacy was0.3 and its p value was found to be extremely significant.

Mean of severe category of efficacy and safety parameter are 2.24 and 0.14 respectively. Appling unpaired t test to compare two variables (efficacy and safety) P value was found to be extremely significant (P<0.0001) ***

VISIT 2.

Table 10.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	16	0.76	0.14	0.0306	P<0.0001 ***
Severe(>2)	33	1.57	0.5	0.1091	

Table 11.

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	16	0.76	0.14	0.0306	P<0.0001 ***
Severity(>2)	3	0.14	0.02	0.0044	

Mean of mild-moderate category of efficacy and safety were found to be equal (=0.76)

Mean of severe category of efficacy was 1.57 and mean of severe safety parameter was found to be 0.14. Its P value was found to be extremely significant (P<0.0001) ***

VISIT 3

Table 12.

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	18	0.86	0.06	0.0131	P<0.0001 ***
Severe(>2)	3	0.14	0.02	0.0044	

Table 13.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	11	0.52	0.09	0.0196	P<0.0001 ***
Severe(>2)	30	1.43	0.6	0.1309	

Mean of mild-moderate category of safety and efficacy was found to 0.86 and 0.52 respectively. Its P value was found to be extremely significant (P<0.0001) ***

Mean of severe category of efficacy was 1.43 while mean of severe safety parameter was 0. Appling unpaired t test to compare two variables (efficacy and safety) P value was found to be extremely significant (P<0.0001) ***

PHASE2

VISIT 1

Table13.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	2	0.2	0.07	0.0221	P<0.0001 ***
Severe(>2)	4	0.4	0.09	0.0285	

Table 14.

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	6	10	0.6	-	-
Severe(>2)	-	10	-	-	-

Mean of mild-moderate category of safety is 0.6 and mean of mild-moderate category of efficacy is 0.2 Its P value was found to be extremely significant (P<0.0001) ***

Mean of severe category of lesions couldn't be compared statistically as numerical data of this parameter was not available.

VISIT 2

Table 15.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	4	0.4	0.07	0.0221	P = 1
Severe(>2)	4	0.4	0.09	0.0285	

Table 16.

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	8	10	0.8	-	-
Severe(>2)	-	10	-	-	

Mean of mild-moderate category of safety was found to be 0.8and mean of mild-moderate of efficacy was 0.4 But mean of severe category of lesions couldn't be compared statistically as numerical data of this parameter was not available.

VISIT 3.

Table 17.

SEVERITY	Cumulative frequency of lesions	Cumulative frequency of ADR
MILD- MODERATE (0-2)	2 mean(0.4)	4 mean(0.2)
SEVERE (> 2)	-	-

Mean of mild-moderate category of safety is 0.4 and mean of mild-moderate of efficacy is 0.2 Mean of severe category of lesions couldn't be compared statistically as numerical data of this parameter was not available.

PHASE 3.

Table 18.

SEVERITY	Cumulative frequency of lesions	Cumulative frequency of ADR
MILD- MODERATE (0-2)	2	4
SEVERE (> 2)	-	-

Mean of two variables (efficacy and safety) couldn't be compared statistically as numerical data of this parameters was in sufficient.

DAP

PHASE 1.

VISIT 1.

Table 19.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	5	0.42	0.08	0.0231	P = 0.0091**
Severity(>2)	32	2.66	1.5	0.4330	

Mean of mild-moderate category of safety was found to be 0.58 and mean of mild-moderate of efficacy was 0.42. Its P value was found to be very significant (P<0.0001)**

Table 20.

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	7	0.58	0.07	0.0202	P<0.0001 ***
Severity(>2)	3	0.25	0.08	0.0231	

Mean of severe category of efficacy was 2.66 and mean of severe safety parameter was 0.25. Appling unpaired t test to compare two variables (efficacy and safety) P value was found to be extremely significant (P<0.0001)***

VISIT 2

Table 21.

Severity	Cumulative frequency of lesion	Mean	SD	SEM	P value
Mild To moderate(0-2)	15	1.25	0.78	0.2252	P = 0.1780
Severity(>2)	21	1.75	0.97	0.28	

Table 22

Severity	Cumulative frequency of ADR	Mean	SD	SEM	P value
Mild To moderate(0-2)	8	0.66	0.09	0.026	P<0.0001 ***
Severity(>2)	6	0.5	0.07	0.0202	

Mean of mild-moderate category of efficacy was found to be higher(1.25) than mean of mild-moderate category of safety (0.66) and its P value was found to be very significant(P<0.0001)**

Mean of severe category of efficacy is 1.75 and mean of severe safety parameter is 0.5. Its P value was found to be extremely significant (P<0.0001)***

VISIT 3

Table 23.

SEVERITY	Cumulative frequency of lesion	Cumulative frequency of ADR
MILD- MODERATE (0-2)	3	7
SEVERE (> 2)	-	-

Mean of two variables (efficacy and safety) couldn't be compared statistically as numerical data of this parameters was not available.

PHASE2

Table 24.

SEVERITY	Cumulative frequency of lesion	Cumulative frequency of ADR
MILD- MODERATE (0-2)	3	7
SEVERE (> 2)	-	-

Table 25.

SEVERITY	Cumulative frequency of lesion	Cumulative frequency of ADR
MILD- MODERATE (0-2)	3	7
SEVERE (> 2)	-	-

Mean of two variables (efficacy and safety) couldn't be compared statistically as numerical data of these parameters was not available.

DISCUSSION

Out of the 45 patients included, disease was more prevalent in the middle age group of 21-30years which was correlating with the studies conducted by J. S. Pasricha *et al*., (2008) and Poonam *et al*.,(2008).[22] But this was found contradicting to the studies conducted by Kailash Bhatia *et al*., (2016) and Chitra S. Nayak *et al*.,(2014) which showed that the age ranged between 11 to 78 years.[18][19]

We found that females (64.4%) were predominant than males (35.5%) which was similar to the study conducted by Kailash Bhatia *et al*., (2016).[18] Finding of a female predominance among pemphigus patients is attributed to the immunopathogenesis of the disease that makes women more susceptible to this and other autoimmune disorders because androgens, the male hormones, are anti-inflammatory and depress immunity, while estrogens, the female hormones, enhance it. The result is that women have a greater immune response to external agents.[30]

Amongest the patients included in the study most of them were married (84.4%).

We found that out of the total patients included in the study majority of them were diagnosed as Pemphigus Vulgaris (86.6%) and remaining with Pemphius Foliaceae (13.4%) which was correlating with studies conducted by Chitra S. Nayak *et al*.,(2014) and Somshukla Ray *et al*., (2014).[19]

Out of the people included in the study, patients who have not completed their family life were give with DAP(28.9%) and the rest were given DCP(71.1%) which was correlating with the studies conducted by J. S. Pasricha *et al*., (2008) and Poonam *et al*., (2008).[22] The use of cyclophosphamide is relatively contraindicated in patients who wish to conceive children as the patient may be rendered infertile by the drug.[31]

In DCP Phase 1 of our study, Visit 1&3 showed that in mild-moderate category the safety was comparatively extremely significant than efficacy but the mean of the severe category signified that efficacy of therapy outrated the safety.

In the Visit 2 the efficacy and safety of the mild-moderate category was equal which signifies a balanced risk benefit ratio and the efficacy of the severe category shows extreme significance over the safety of the therapy.

In DCP Phase 2 of our study mild-moderate category of the study reveals that safety was stastically extremely significant than the efficacy in all the 3 Visits. The severe category cumulative frequency of lesions was 4 and there were no ADR's reported.

In DCP phase 3 of our study cumulative frequency of both lesion and ADR was found to be 2 in mild–moderate category. In severe category there was no lesion and ADR reported in both.

In DAP phase 1 of our study, Visit 1 showed that safety was very significant than efficacy of the mild -moderate category which was vice versa in severe category and in Visit 2,3 therapy seems to be beneficial than risk in the both the categories.

In DAP phase 2, our study shows that in Visit 1&2 the cumulative frequency of lesion was found to be 2 in mild-moderate category. There were no ADR reported in Visit 1&2 in severe category.

In our study, out of the 45 patients treated with Pulse therapy (both DCP and DAP) most commonly identified adverse reactions were weight gain (30.5%), alopecia(18.8%), facial puffines(14.1%), fever with chills(12.9%), pedal edema(10.5%), joint pains(10.5%), teary eyes(1.17%) dyspepsia(1.17%).

Our study showed that in initial visits safety parameters were found to be high than efficacy but in later visits efficacy increased because patient was prescribed with supportive therapy to monitor safety parameter. Supportive therapy may include - Mouthwashes containing antiseptic or local anaesthetic, Wound care treatments such as dressings help to heal raw areas, Antifungal medication helps if thrush infects the mouth, throat or gullet area.

All are patients have showen good response to DCP/DAP irrespective of disease activity and severity which is similar to the studies conducted by Kailash Bhatia *et al*., (2016). Satguru Dayal *et al*.,(2016).[18]

CONCLUSION

In our study it was noted that the patients had showed betterment in their health condition irrespective of certain side effects.

The disease condition showed remarkable declination regardless of their severity conditionally if patient received regular, rational and complete treatment.

Studies with more number of patients and for longer period will help in better management of patient and disease.

Hence we conclude that our study provides a hypothesis for future studies which can emphasize on our advantages of Pulsetherapy.

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