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A Study on Efficacy and Safety of Pulse Therapy in Dermatology Among Various Indications

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ABSTRACT

Introduction: The administration of large (supra pharmacologic) doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the possibility of adverse effects related to the daily dosage schedule. **Methodology:** A prospective observational study was conducted for 6 months duration in the Dermatology department in a tertiary care teaching hospital. Demographic details, the reason for hospitalization, past medical history, past medication history, and results of laboratory tests. **Results and discussion:** A total of 113 cases were collected which were all skin infections (pemphigus). All the cases were documented. P-value of the age group and indication category was found to be significant, statistical methods were applied and significance among efficacy and safety of pulse therapy was correlated. **Conclusion:** Pulse therapy is a novel therapy for pemphigus diseases the outcome remission rate of DCP was more when compared to other types of pulse therapy.

INTRODUCTION:

Skin is the outermost layer of the body which is soft and flexible. It is an outermost tissue that covers the body of animals. It has three main functions: Protection, Regulation, and Sensation.[1]Mammalian skin consist of two primary layers: Epidermis and Dermis. The epidermis acts as a barrier and avoids infection due to foreign pathogens, serves as a barrier and Dermis serves as a location for the appendages of skin.

Skin infections [2]:

The largest organ in our body is the skin whose function is to protect our body from infections, but the skin gets infected due to foreign particles such as germs, bacteria, viruses, fungus, parasites, etc. whose symptoms vary from mild to serious. In case of mild infection, the relief from symptoms is easy by using over-the-counter medications and home remedies, whereas the others require special care from health care professionals.

Infection due to autoimmune disorder [3]: Our body reacts in different ways to autoimmune disorders, in which the person's immune system attacks its tissues. Depending upon the severity and condition of autoimmune disorder it can affect a different variety of organs, joints, and muscles or body tissues. The most common tissue that gets affected in autoimmune disorders is the skin, different types of skin-related autoimmune disorders are Scleroderma, Psoriasis, Dermatomyositis, Epidermolysis bullosa, and Bullous pemphigoid.

Bullous pemphigoid [4]: It is a chronic autoimmune disorder in which the patient develops skin blisters that range from mild to severe. In case of mild cases, redness or irritation of the skin is observed whereas in severe case multiple blisters that break open and form ulcers. The symptoms are generally observed in body parts such as arms, legs, or torso, blisters are also formed in the mouth. Few of them even experience itching and bleeding gums. It has been observed in all age groups, among which the elderly age groups are most affected. Both genders are equally at risk for this type of skin infection. It is difficult to report the incidence of this disease because symptoms come and go many patients these conditions disappear after six years.

PULSE THERAPY INTRODUCTION:

The administration of large (suprapharmacologic) doses of drugs in an intermittent manner enhances the therapeutic effect and reduces the possibility of adverse effects related to the daily dosage schedule.[5]

Types:[6]

1. Dexamethasone Cyclophosphamide Pulse (DCP): It consists of giving 100 mg of dexamethasone dissolved in 500ml of 5% glucose as a slow intravenous drip over 2 hours repeated on 3 consecutive days. On the second day, the patient is also given 500mg of Inj. Cyclophosphamide in 500ml of 5% Dextrose. In between the DCPs, the patient receives only 50 mg of Cyclophosphamide orally per day. The DCP regimen is administered in four phases.

2. Dexamethasone Azathioprine Pulse (DAP): Here cyclophosphamide is replaced with 50mg of Azathioprine daily during the first 3 phases.

3. Dexamethasone Methotrexate Pulse (DMP): Here Cyclophosphamide is replaced by 7.5mg of Methotrexate (three doses of Methotrexate 2.5mg at 12hourly intervals) weekly given orally during the first 3 phases of pulse therapy.

4. Pulse Glucocorticoid therapy: Methylprednisolone and dexamethasone are the glucocorticoids most frequently administered in the pulse regimen. Doses of each pulse are usually 10-20mg/kg body weight for methylprednisolone and 2-5mg/kg body weight for dexamethasone. Pulses are usually given daily for 3-5 days.

5. Cyclophosphamide pulse therapy: Cyclophosphamide 500mg is dissolved in 25ml of distilled water and added to 500mg of 5% dextrose and given slowly intravenous for 60 minutes. It was followed by 500ml of normal saline. Similar pulses were repeated monthly for 12 months and 2 monthly for further 6 pulses.

6. Dexamethasone-only pulses (DOP): It consists of giving 100 mg of dexamethasone dissolved in 500ml of 5% glucose as a slow intravenous drip over 2 hours repeated on 3 consecutive days.

MEDICATIONS INVOLVED IN PULSE THERAPY.

1. METHOTREXATE:

Methotrexate is a synthetic analog of folic acid that acts as an anti-proliferative and anti-inflammatory drug and as an immune modulator. Considering its immune modifying mechanism, it is also used for the treatment of steroid-recalcitrant inflammatory diseases. There are many studies about the methotrexate efficacy in rheumatic diseases. The use of methotrexate in dermatological conditions except for psoriasis must be explored yet. This study includes the data about the pharmacology of methotrexate and its efficacy in dermatological conditions.

2. **CYCLOPHOSPHAMIDE:**

Cyclophosphamide is a cytotoxic drug and is classified as an alkylating agent. Cyclophosphamide is also used as an immunomodulator. The pharmacology of cyclophosphamide acts by interfering with the malignant cells by cross-linking tumor cell DNA. Cyclophosphamide does not have any specificity for the cell multiplication phase. The cyclophosphamide is metabolized by the liver and forms a metabolite of 4-hydroxy peroxy cyclophosphamide and 4-aldophosphamide.

Cyclophosphamide is given by both oral and IV routes. For the oral route, the dose must be given early in the morning and iv route maximum concentration of cyclophosphamide is 20mg/ml due to its solubility. Infusion of cyclophosphamide is given for 1 to 2 hours.

3. AZATHIOPRINE:

Azathioprine is a synthetic purine analog derived from the 6- mercaptopurine. Previously, the mechanism of azathioprine was thought to be disrupting the nucleic acid synthesis and newly found that azathioprine interferes with the activation of the T-cell. Azathioprine is mostly used for dermatological conditions like immune bullous, generalized eczematous disorders, and photodermatoses.

4. DEXAMETHASONE

Dexamethasone is a very potent, long-acting, and highly selective synthetic glucocorticoid with anti-inflammatory and immunosuppressant properties. The binding affinity of

dexamethasone is 20-30 times more than the affinity for other glucocorticoid receptors of endogenous cortisol.

Phase 1 Description:

DCP	DAP	DOP	DMP
Day 1 Dexamethasone 100 mg (in 5% Dextrose as a IV infusion over 2 hours) +Azathioprine (orally) (Three doses of Methotrexate 2.5mg at 12hourly intervals)	Dexamethasone 100 mg (in 5% Dextrose as a slow IV infusion over 2 hours)	Dexamethasone 100 mg (in 5% Dextrose as a slow IV infusion over 2 hours) weekly given orally	Dexamethasone 100 mg (in 5% Dextrose as a slow slow IV infusion over 2 hours) +7.5mg of 50mg Methotrexate
Day 2 Dexamethasone 100mg (IV)+cyclophosph +Azathioprine amide	Dexamethasone 100 mg (IV) 50me 500 mg (orally)	Dexamethasone 100 mg (IV)	Dexamethasone 100 mg (IV)
Day 3 Dexamethasone 100mg (IV) +Azathioprine 50mg (orally)	Dexamethasone 100 mg (IV)	Dexamethasone 100 mg (IV)	Dexamethasone 100 mg (IV)
Duration leisons are observed.	Until no new leisons are observed.	Until no new leisons are observed.	Until no new leisons are observed.

Phases of all types of cycles:

	DCP	DAP	DOP	DMP
PHASE 1	DCP Cycle until no new lesions are observed.	DAP Cycle until no new lesions are observed.	DOP Cycle until no new lesions are observed.	DMP Cycle until no new lesions are observed.
PHASE 2	DCP Schedule given for a fixed duration of 9	DAP Schedule is given for a fixed duration of 9 months	DOP Schedule is given for a fixed duration of 9	DMP Schedule given for a fixed duration of 9 months
PHASE 3	Only oral Cyclophosphamide 50 mg/day is given for 1 year	Only oral Azathioprine 50 mg/day is given for 1 year	Patient is given oral dexamethasone based on need.	7.5mg of Methotrexate (three doses of Methotrexate 2.5mg at 12hourly intervals) weekly gave orally
PHASE 4	All the drugs are withdrawn, and the patient is followed up (observed).	All the drugs are withdrawn, and the patient is followed up (observed).	All the drugs are withdrawn, and the patient is followed up(observed)	All the drugs are withdrawn, and the patient is followed up (observed).

AIM:

To access the therapeutic benefit of pulse therapy in the dermatology department.

OBJECTIVES:

1. To study the efficacy and safety of pulse therapy in various indications.

2. To study management of co-morbidities during pulse therapy.

3. To reduce the need for long-term use of systemic steroids.

METHODOLOGY:

Study design: A Prospective Observational Study.

Study duration: 6 months.

Sample size: 113.

Study period: September (2019) – February (2020)

Inclusion criteria:

- Patient or Patient caretaker was able to communicate adequately.
- Patient(s) hospitalized in Dermatology department.
- Patient with a known case of pemphigus vulgaris psoriasis and other related cases.

Exclusion criteria:

- Patients admitted with the herbal medicine-related problem.
- Outpatients consulting for allergies reactions and other hypersensitive reactions.
- Pediatrics patients were excluded.
- Patients, who discontinued the pulse therapy in between.

STUDY PROCEDURE:

1. **Review of a patient**: The cases from the departments included in the study are reviewed.

2. **Enrollment of patient**: based inclusion and exclusion criteria.

3. Collecting the data from the patient: The case sheets of patients with past medical history are considered and assessed for the impact of the medication used in the past on the current complaints and if the DRP is observed, the case will be considered for further study by documenting necessary information in documentation forms. A data collection form was

designed and found applicable to the participating departments. The following data were recorded for each patient: age, gender, the reason for hospitalization, past medical history, past medication history, and results of laboratory tests.

4. Evaluate the efficacy and safety: Efficacy based on severity and size of lesions and safety based on the severity of ADR occurrence.

5. Severity was classified as:

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with not more than one small inflammatory lesion
2	Mild severity; greater than grade 1; some non-inflammatory lesions with not more than a few inflammatory lesions (papules/ pistules only, no nodular lesions)
3	Moderate severity; greater than grade 2; up to many non-inflammatory lesions, but not more than one small nodular lesion
4	Severe, greater than grade 3, up to many non-inflammatory and inflammatory lesions, but not more than a few nodular lesions

RESULTS:

A total of 113 cases were collected which were all skin infections (pemphigus). All the cases were documented.

Table: 1 Categorization of data based on gender.

Gender	**No.**	**Percentage (%)**
Male	57	50
Female	56	50

The above result indicates that both genders are similarly exposed to pemphigus diseases.

Table 2: Categorization of data based on age.

Age Group (Years)	No.	Percentage (%)
11-20	2	1.7
21-30	26	23
31-40	39	34.5
41-50	33	29.2
51-60	11	9.7
61-70	2	1.7

The above table shows that the age group 31-40years is the highest to get infected with this disease. The P-Value is <0.05, Hence the variables are found to be significant.

Table: 3 Categorization of data based on the type of cycle.

Type of cycle	No.	Percentage (%)
DCP	94	83
DAP	10	9
DOP	9	8

Most cases documented were DCP (83%), followed by DAP (9%), followed by DOP (8%). The P-Value is <0.001, Hence the variables are found to be significant.

Table: 4 Categorization of data based on comorbidities:

Comorbidities	No.	Percentage (%)
Hypertension	18	15.9
Diabetes Mellitus	10	8.8
Hypothyroidism	1	0.8
None	84	74.3

The maximum no. of cases documented had no comorbidities (74%), rest Hypertension (15%), DM (8%). The P-Value is <0.001, Hence the variables are found to be significant.

Table: 5 Categorization of data based on social habits:

Social habits	No.	Percentage (%)
Smoker	21	18.5
Alcoholic	20	17.7
Other (gutka and pan chewing)	5	0.4
None	67	59.2

From the cases documented most of them had no social habits (59%), were smokers (18%), alcoholics (17%). The P-Value is <0.001, Hence the variables are found to be significant.

Table: 6 Categorization of data based on Indications:

Indication	No.	Percentage (%)
Pemphigus. vulgaris	98	86.7
Pemphigus.foliceous	9	7.9
Pemphigus.bollous	4	3.5
Another pemphigus	2	1.7

The majority of cases documented were *P.vulgaris* (86%), followed by *P.foliceous* (7.9%), followed by *P.bollous* (3%). The P-Value is <0.05, Hence the variables are found to be significant.

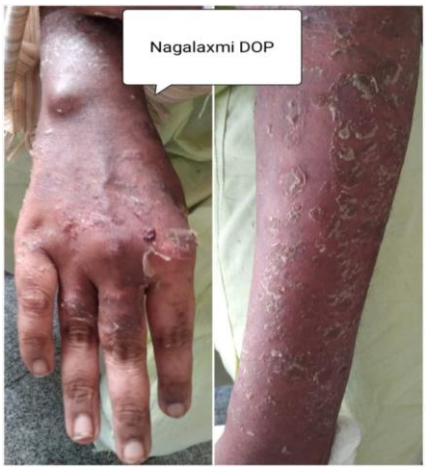
Table:7 Outcome of CYCLEs:

Type of cycle	Total no. Of patient	No. of discontinuation	No. Of deaths	Pulse stopped	No. Of attained remission	No. the Patient relapsed	Remission rates (%)
DCP	94	0	0	0	91	3	96%
DAP	10	1	0	1	9	1	90%
DOP	9	0	0	0	9	0	100%

The remission rate of DCP was found to be 96%, DAP 90%, DOP 100%. Deaths were 0, discontinuation of therapy 1, relapse was 4.

DOP cycle:

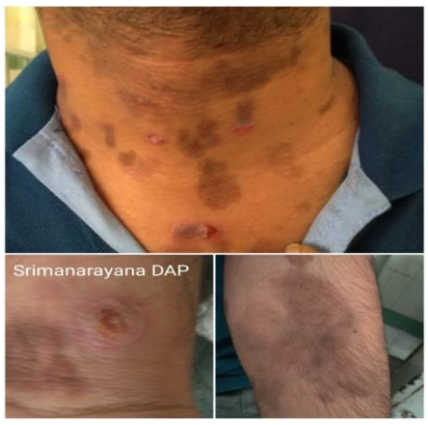
Phase 1 Cycle 2: Multiple scaly plaque and crusting are observed over upper limbs.



DAP cycle:

Phase 1 Cycle 4:

Newer lesions over neck and limbs.



RESULTS:

	Age group	Gender	Type of cycle	Social habits	Comorbidities	Indication
p-value	<0.05		<0.001	<0.001	<0.001	<0.05
Mean	39	56.5	37.67	28.25	28.25	28.25
Median	39	56.5	10	20.5	14	6.5
Standard Deviation	9.71	56.33	56.33	38.75	55.75	28.25
Range	47	1	85	62	83	96
Minimum	20	56	9	5	1	2
Maximum	67	57	94	67	84	98
Sum	4407	113	113	113	113	113
Count	113	2	3	4	4	4
Sample Variance	93.45	0.25	15.86	5.4	10.72	16.28
Kurtosis	-0.025994					
Skewness	0.418829					
Confidence Level (95.0%)	±4.6%	±18.4%	±27.6%	±25.3%	±36.4%	±18.4%

DISCUSSION:

- Pulse therapy is found to be a major reason for admission into the dermatology department. A total of 120 patients participated in our study (all from the dermatology department). Out of which 113 patients were included and 7 were excluded based on inclusion and exclusion criteria. the cases were documented, analyzed, and interpreted by the dermatology department during the study period (September 2019 to February 2020).

- Gender distribution of collected cases has shown: Male 57(50%) and female 56(50%). This indicated prevalence is similar in both males and females.

- Collected cases have shown that age (31-40years) 34.5%, this denotes that age group 31-40 years are more prevalent to pemphigus disease. Our finding was like a study conducted **by Rao. et.al, Varalas. et.al, Haneef NS et.al and Hassan I et.al.** However, **Kandan et.al** reported a higher age group with the majority of the patient between 40-59years. As pemphigus affects the young and middle-aged population it has a significant impact on the socio-economic condition of the family.

- 94cases (83.1%) on DCP, 10cases (9%) on DAP, 9cases (8%) on DOP. Our result indicates that DCP therapy is efficacious than DAP therapy in pemphigus patients. Azathioprine is an alternative regimen for a patient who has to complete their family. A study conducted by Yemen reported 8out of 11 pemphigus patients were treated with Azathioprine. Our finding of DCP being more effective over DAP is like that of **Varala S et.al, Hassan I et.al, Yemen** Etc.

- About 8 cases (15.9%) had hypertension, 10 cases (8.8%) had diabetes mellitus, 1case had hyperthyroidism, and 84cases (74.3%) had no other comorbidities. With this statement, we say that such factor is governing the risk of pemphigus disease. **By Hassan I et.al and Mundakkat V et.al.**

- 21 smokers (18.5%), 20 alcoholics (17.6%), 5 other social habits (4%), 67 no such social habits (59.2%). Hence no additional worsening of the condition due to any social habit, similar finding by **Mundakkat V. et.al.**

- A different variant of pemphigus- 98cases of pemphigus vulgaris (86.7%), 9cases of pemphigus foliaceous (7.9%), 4cases of pemphigus bullous (3.5%), 2cases of another pemphigus. By **Hassan I. et.al.**

- The outcome of cycles: 96% remission rate of DCP, 90% remission rate of DAP, 100%remission rate of DOP. Deaths were 0, discontinuation of therapy -1, relapse were 4, Study by Rao et.al showed 96% of remission rate with DCP. Pasricha et.al showed a 100%remission rate in 103 pemphigus patients. Similar by **Varala S et.al.**

CONCLUSION:

Pulse therapy is a novel therapy for pemphigus diseases. A lot of work has been done on pulse therapy in India. Pemphigus vulgaris is the major cause for the administration of pulse

therapy – DCP (Dexamethasone cyclophosphamide pulse) in specific rather than DOP or DAP. The latter one is also preferred in special cases. The outcome remission rate of DCP was more than DAP. It is also known that no comorbidity or any social habit can develop or worsen the condition.

BENEFITS OF OUR STUDY:

1. To get quicker and stronger efficacy and decrease the need for long-term use of steroids.

2. To understand the correlation between P. vulgaris and choice of DCP (Pulse therapy).

3. To attain maximum remission rate in Pemphigus disease with the use of DCP (pulse therapy).

STUDY LIMITATIONS:

1. Pediatrics were not being examined in this study.

2. 4 relapse cases and 1 discontinuation of the therapy.

3. A clear statement about the correlation between social habits, comorbidities, and pulse therapy could not be established.

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