A STUDY OF DEXAMETHASONE - CYCLOPHOSPHAMIDE PULSE THERAPY IN PEMPHIGUS PATIENTS

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY OF DEXAMETHASONE-CYCLOPHOSPHAMIDE PULSE THERAPY IN PEMPHIGUS PATIENTS"** submitted by **Dr.V.Seethalakshmi** to The Tamil Nadu DR. M.G.R. Medical university, Chennai is in partial fulfillment of the requirement for the award of M.D. Degree **Branch XII A, M.D., (Dermato Venereology)** and is a bonafide research work carried out by her under direct supervision and guidance.

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CONTENTS

INTRODUCTION

INTRODUCTION

The term "**Pulse Therapy**" has been used for a system of administering drugs in which a very high dose of the drug is given over a very short period for getting a quick result, and then the drug is withdrawn completely till it is needed or used again[1].

Pulse therapy (the big shot)[2] defined as administration of large (supra pharmacological) dose of drugs in an intermittent manner, to enhance the therapeutic effects and to reduce the iatrogenic side effects of drugs.

It is a relatively recent concept; this method has been observed to produce superior therapeutic results which cannot be produced by the conventional methods of giving daily dosages while the side effects of the drugs are reduced very significantly[3].

The list of dermatological indications for pulse therapy is increasing day by day and now it includes pemphigus and other autoimmune bullous diseases, collagen vascular diseases like systemic lupus erythematosus, progressive systemic sclerosis, Dermatomyositis, allergic vasculitis, Pyoderma gangrenosum, Prurigo nodularis, generalized lichen planus, resistant alopecia universalis, sarcoidosis, psoriasis, Darrier's disease, fast spreading vitiligo, airborne contact dermatitis[4].

The auto immune vesiculo bullous diseases are a heterogenous group of diseases. They are classified on the basis of their clinical, histopathological and immuno pathological features. They can be broadly classified histopathologically into epidermal and sub-epidermal blistering dermatoses.Though these disorders are rare in general population, for a given patient the impact of the diseases on the quality of the

life can be devastating. The severity is often variable and the course is unpredictable and may even be fatal.

Pemphigus is the commonest autoimmune vesiculobullous disorder of the Indian subcontinent[5]. The main treatment for pemphigus lies in using corticosteroids and other similar drugs which do help the patient to recover from the disease but whenever an attempt is made to withdraw the drugs the disease tends to became active again. Long term use of these drugs lead to some serious side effects.

The Dexamethasone cyclophosphamide pulse therapy pioneered by Dr.Pasricha et al consists of giving dexamethasone and cyclophosphamide in a very large doses on three consecutive days and repeated at fixed 28 days interval. In this method these drugs are claimed to knock out the disease process so that the patient recovers completely while the side effects are very much reduced and almost insignificant[6]. It is claimed that there is almost no risk of a relapse or recurrence provided the treatment has been taken strictly as per the recommendations[7].

With the ever increasing use of DCP pulse therapy in dermatology there is an increasing necessity for studies to evaluate its efficacy and side effect profile, and this study is an attempt in that direction.

REVIEW OF LITERATURE

HISTORICAL ASPECTS

- 1953 - Walter lever distinguished Pemphigus from Pemphigoid[8]
- 1964 - Beutner and Forder discovered circulatory antibodies against cell surface of Keratinocytes from the sera of Pemphigus patients [9]
- 1969 - Kourtz & cohn[10] to prevent renal allograft rejection-infused methylpredrisolene & heparin & actinomycin-D.
- 1970 - Coburg et al[11] – prednisolone pulse therapy for renal allograft rejection.
- 1971 - Bell et al[12] – prednisolone pulse therapy along with immunosupressants for renal transplantation.
- 1972 - Fedusca et al[13] – first to use the word "pulse" for giving a high dose of methyl prednisolone intravenously for preventing renal allograft rejection.
- 1976 - Cathcart et al[14] – first to use pulse therapy – 1g Methylprednisolone in diffuse proliferative lupus nephritis.
- 1981 - Liebling et al[15] – first to use methyl Prednisolone pulse for rheumatoid arthritis.
- 1981 - Dr.pasricha et al – Dexamethasone pulse therapy for Reiter's disease.
- 1982 - Johnson & Lagarus[16] – first among the foreign workers to use the pulse mode of therapy successfully in a dermatologic disorder – methyl prednisolone pulse therapy for pyoderma gangrenosum.
- 1982 - Synder et al[17] – methyl prednisolone pulse therapy for treating drug induced lichen planus.
- 1982 - Parischa et al Dexamethasone[1] Cyclophosphamide pulse therapy for autoimmune vesiculo bullous disorder.[18]

The term Pemphigus refers to a group of autoimmune blistering disease of skin and mucous membranes that are characterized histologically by intra epidermal blisters due to acantholysis and immuno pathologically by in vivo bound and circulating IgG directed against cell surface of keratinocytes.

Pemphigus is derived from the Greek word, “Pemphix” meaning blister or bubble[19].

Types of Pemphigus:-

1. Pemphigus Vulgaris

   Variant : pemphigus vegetans

2. Pemphigus foliaceus

   Variant : pemphigus herpetiformis

   Variant : pemphigus erythematosus

3. Induced pemphigus (Drugs, radiotherapy, thermal burns, diet)
4. Intercellular IgA dermatosis
5. Paraneoplastic pemphigus

Epidemiology :-

The epidemiological aspects are covered below.

Disease	Incidence	Geographic pattern	Age	M:F	HLA association
Pemphigus vulgaris & vegetans	About 1.3 million/year	Higher in jews and people of Mediterranean origin	Middle age	M=F	DR4(subtype) DQ1, DQB1,0503, DRB1(0402)
Pemphigus foliaceus/ erythematosus	0.3 cases per million per year	Higher in Brazil, Finland and Tunisia	Middle age	M=F	
Fogo selvagum	3.4% on endemic areas of Brazil[20]	Endemic around the rivers of Brazil	Children & young adults	M=F	DR1

In an Indian study by Arya et al[21], pemphigus vulgaris was the commonest vesiculobullous disease comprising 61.4% of the cases studied followed by pemphigus foliaceus. In the study by K.K.Das et al[22], pemphigus vulgaris was the commonest comprising 40.8% of the cases studied.

Etiopathogenesis :-

Disease	Antibody Isotype	Target antigen	Antigen KDa	Epitope	Location
Pemphigus vulgaris/vegetans	IgG(few IgM, IgA)	Desmoglein3 Desmoglein1	130KDa 160KDa	Amino terminal of extracellular domain	Desmosome
Pemphigus foliaceus/ erythematosus	IgG	Desmoglein1	160KDa	,,	,,
IgA Pemphigus	IgA1	Desmocollin1		-	Desmosome
Fogo selvagum	IgG	Desmoglein1	160KDa	Amino terminal of extracellular domain	Desmosome
Paraneoplastic Pemphigus	IgG	Plakins (desmoplakin, envoplakin, BP230, periplakin)	250KDa, 210KDa, 190KDa, 500KDa	Various	Desmosomes, BMZ; Stratified, simple and transitional epithelia.

Clinical Features:-

Disease	Cutaneous distribution	Mucosal involvement	Pattern of skin lesions	Scarring	Disease association

Pemphigus vulgaris	Scalp, face flexures may be generalized	Common Oropharynx, conjunctiva genitalia	Flaccid blisters, erosions show no tendency to heal, nikolsky sign & bulla spread sign +ve, flexural vegetations	-	Other auto immune disease, Thymoma, rarely bullous pemphigoid. may evolve into P.Foliaceus & vice versa.
Pemphigus Vegetans	Flexural	Oral	Vesicles, pustules, erosions, vegetating plaques	-	-
Pemphigus Foliceus	Scalp,face,chest,upperback(seborrheic) may be generalized	-	Scaly papules, crusted erosions, erythroderma	-	-
Endemic pemphigus foliaceus	Head,neck generalized	Uncommon	Flaccid blisters, erosions,verrucous lesions,erythroderma	-	-

Disease	**Cutaneous distribution**	**Mucosal involvement**	**Pattern of skin lesions**	**Scarring**	**Disease association**

Intercellular IgA dermatosis	Axillae, groins, face, scalp, proximal limbs	Uncommon	Flaccid pustules Annular or circinate configuration	-	IgA monoclonal gammopathy.
Paraneoplastic pemphigus	Upper body, Palmo-plantar	Severe mucositis	Polymorphous, Bullae, erosions, 'target lesions'	+	Lympho proliferative disease, castleman's, other malignancies

Diagnosis:

The diagnosis can be made on the basis of clinical criteria and by

1. **Tzanck smear :-**

Rapid preliminary test used in the diagnosis of blistering diseases. A smear is made from the floor of a freshly opened vesicle. It is allowed to dry and flooded with equal quantity of water and Giemsa (or) Leishman's stain. After 30-40 seconds, the slide is rinsed, air-dried and examined for acantholytic cells.

Acantholytic cell :

An acantholytic cell is rounded cell with an enlarged nucleus with peripheral condensation of chromatin and prominent nucleoli. There is a perinuclear halo, with the peripheral parts of the cell staining more darkly. In older cells the nucleus may be pyknotic.

In pemphigus vulgaris and vegetans typical,rounded acantholytic cells are seen. In pemphigus foliaceus and pemphigus erythematosus, cells tend to be cuboidal, with a small nucleus and more prominent cytoplasm. keratohyaline granules and evidence of keratinisation may be seen. Occasional multinucleated cells may be seen.[23]

2. **Histopathology:**

- **Pemphigus vulgaris:-**

A small early vesicle is preferable. Scalpel biopsy of the intact blister should be done. If punch biopsy is to be done, the lesion should be frozen by refrigerant spray. If no new blister is seen, an old one may be moved to the neighbouring skin by finger. The new cleavage reveals early specific changes.

Early lesions show eosinophilic spongiosis in the lower epidermis. This is the manisfestation of acantholysis, rather than true spongiosis. Developed lesions show clefts and supra basal blisters. Acantholysis extends to the adnexal structures.

The basal keratinocytes are detached from each other, but remain attached to the basement membrane, because the hemidesmosomes are intact. This gives an appearance of "row of tomb stones".

As the blister ages, a mixed inflammatory infiltrate appears in the dermis. There may be epidermal downgrowth or villi.

- **Pemphigus vegetans :**
  - **Neumann type** :

Early lesions have the same histopathology as pemphigus vulgaris. Later there is formation of villi and verrucous epidermal hyperplasia. Eosinophilic spongiosis and eosinophilic pustules are present. Acantholysis may be absent in older lesions.

  - **Hallopeau type :**

Early lesions have suprabasal clefts with plenty of eosinophilis. There are more eosinophilic abscesses than Neumann type.[24]

- **Pemphigus foliaceus :**

There is acantholysis in the granular layer, leading to subcorneal cleft and detachment of stratum corneum. The number of acantholytic cells is small. There may be eosinophilic spongiosis. Dyskeratotic granular keratinocytes are diagnostic.

- **Pemphigus erythematosus :**

Histology similar to pemphigus foliaceus. Interface dermatitis may be seen in rare cases.[25]

- **IgA pemphigus :**
  - SPD type : There are subcorneal vesiculo pustules with minimal acantholysis.
  - IEN type : Has intra epidermal vesiculo pustules with neutrophils.

- **Paraneoplastic pemphigus :**

Variable. EMF-like, LP-like, pemphigus-like and Bullous pemphigoid-like features may be seen. PNP may present with lichenoid interface dermatitis without acantholysis[26].

3. Direct Immunofluorescence:

- A 3-4mm punch biopsy from the inflamed, but unblistered perilesional skin is preferred.
- If there is a delay of more than 24 hrs before processing, the specimen should be kept in Michel's medium, which contains

5% Ammonium sulphate

Magnesium sulphate

N-Ethyl maleimide(K^+ inhibitor)

Citrate buffer (PH 7.25)

- Specimens may be kept in Michel's medium for 2 weeks at room temperature and for several weeks in refrigerator.
- While processing, the specimen is washed, embedded in OCT (Optimized Cutting Temperature) compound, and snap frozen.6μ sections are made, and incubated with anti human IgG, IgM, IgA and C3,which are tagged with fluroscein isothiocyanate. Sections are visualized in fluorescent microscope[27].

DIF Patterns

1. Pemphigus vulgaris

- Squamous intercellular IgG in upto 100%[28], in a chicken wire pattern

- DIF remains positive for many years after the clinical disease has subsided[29].
- False positive tests may be seen in in spongiotic dermatitis, psoriasis and insulation of serum.

2. **Pemphigus vegetans**

Squamous intercellular IgG present in all reported cases[30].

3. **Pemphigus foliaceus**

Two patterns have been described commonly, full thickness squamous intercellular IgG is seen. Rarely IgG may be localized to the upper layers[31].

4. **Pemphigus erythematosus**

Squamous intercellular IgG seen in >75% of cases, along with deposits of IgM (positive lupus band) in the DEJ.

5. **Ig A Pemphigus**

Reveals squamous intercellular IgA throughout the epidermis. Complement and other Immunoglobulins are usually absent. some cases show both IgA and IgG

4. **Indirect immunofluorescence:**

IIF is a semiquantitative procedure in which double immunolabelling is done to evaluate the presence and titre of circulating antibodies, or to specifically localize an antigen in the skin.

Procedure

The serum is serially diluted. The substrates most commonly used are

- Monkey esophagus – pemphigus vulgaris[32]
- Guinea pig esophagus – pemphigus foliaceus[33]
- Human salt split skin – subepidermal blistering diseases

- Murine bladder epithelium – paraneoplastic pemphigus

The serially diluted serum is incubated with the substrate for 30 mins at room temperature and washed. Antibodies bound to the substrate are detected by incubation with FITC-labelled goat antihuman IgA or IgG.

IIF PATTERNS

1. **Pemphigus vulgaris**

   >80% have circulating anti cell surface IgG[34]. there is a positive, but imperfect correlation between the antibody titre and disease activity[35] in pemphigus vulgaris and pemphigus foliaceus.

2. **Pemphigus foliaceus**

   Squamous intercellular IgG deposits seen in 80 – 90% of cases.

3. **Pemphigus erythematosus**

Using monkey esophagus, IIF reveals ICS deposits of IgG in 80% of cases ANA is positive in 30 – 80% of cases.

4. **IgA pemphigus**

   Positive in less than 50% of cases.

5. **Paraneoplastic pemphigus**

   Circulating antibodies that bind to rat bladder epithelium is seen in all cases. Immunoblotting and immunoprecipitation are more sensitive and specific, and at a minimum , antibodies to envoplakin and periplakin should be demonstrated .

OTHER DIAGNOSTIC METHODS

ELISA

In pemphigus, antigen specific ELISA has been shown to be more sensitive and to correlate with disease activity better than IIF.[36]

Immunoperoxidase methods have roughly the same sensitivity as immunofluorescence studies.

Immunoprecipitation and Immunoblotting

They detect antigens as protein bands of diiferent molecular weights separated by electrophoresis. Immunoblotting requires denaturation of substrates, whereas immunoprecipitation does not. The former recognizes antibodies against linear epitopes while the latter recognizes antibodies against conformational epitopes. Immunoblost is easier because immunoprecipitation requires radiolabelling.

PULSE THERAPY REGIMENS

The introduction of Dexamethosone-Cyclophosphamide Pulse (DCP) therapy for the pemphigus group of disorders by Pasricha et al at the All India Institute of Medical Sciences,New Delhi,in 1986 has revolutionized the therapy for pemphigus [37]

The Standard DCP Regimen[38] :

The standard DCP Regimen Consists of 4 phases.

Phase I : In this Phase,100mg of Dexamethasone dissolved in 500ml of 5% Dextrose, given as a slow intravenous infusion over two hours and repeated on 3 consecutive days, combined with 500mg Cyclophosphamide in the same infusion on any one of these three days but preferably on the second day. This constitutes one DCP; such DCP are to be repeated at exactly 4-weeks interval counted from the 1st day of each DCP; in between the DCPs the patient receives only 50mg Cyclophosphamide per day orally;The period during which the patient continues to develop clinical lesions in between the two DCPs till the patient achieves complete clinical remission is designated as Phase I ;The duration of the Phase varies widely in different patients.

Phase II : After the patient achieves clinical remission, the DCP is given at 4 weeks interval and 50mg daily oral dose of Cyclophosphamide are continued for next 6 months; This is called Phase II.This phase is retrospectively calculated;

Phase III: If the patient continues to be in clinical remissions during Phase II, the DCPs are stopped but the oral dose 50mg Cyclophosphamide per day is continued for next 1 year .This is called Phase III.

Phase IV: If the patient still continues to be in remission, even this dose of cyclophosphamide is withdrawn and the patient is followed up without any treatment

to look for any tendency for a relapse(The post treatment follow up period);This is called Phase IV and can be as long as possible .

The dosage of dexamethasone pulse infusion was fixed at 100mg because of the commercial availability of the 100mg pack and the dose of Cyclophosphamide for the pulse was fixed at 50 mg for the sake of convenience and to have reasonably effective dose without producing serious side effects.

The Oral Dose of Cyclophosphamide was fixed at 50mg per day because this dose is almost completely free from side effects, it does not produce leukopenia and thus the patient does not require any monitoring on a day-to-day basis.

The time interval of 4 weeks between the two DCPs was also arbitrary and selected for the sake of convenience; but later on it was realised that it is necessary to administer the next pulse before the immunocompetent cells responsible for producing the auto antibodies start proliferating again.

MECHANISM OF ACTION

Exact mechanism of action not known. It is presumed that supra pharmacologic doses of dexamethasone and cyclophosphamide knock down the auto antibody producing cells and when such doses are repeated at regular intervals before these cells have a chance to proliferate and regenerate themselves more and more of such cells are being progressively destroyed and a stage can possibly be reached when all such cells have been eliminated can virtually inactivated; At that stage there would be no further risk of developing a relapse[39].

Dexamethasone is a potent, long acting steroid with specific glucocorticoid and nil mineralocorticoid activity with a half life more than 36 hours. The high potency is attributed to its high affinity for the glucocorticoid receptor and long half life. Its metabolized by hepatic microsomal enzymes. It acts by inhibiting transcription factors AP-1, NF-kB while increasing Ik-Bα which is an inhibitor of NF-kB. Along with suppression of pro inflammatory cytokines this forms the crux of its action.[40]

Cyclophosphamide is a pro-drug that is converted by hepatic microsomal enzymes into 4-Hydroxy cyclophosphamide.The half life is between 3 to 10 hours .It is classified as an alkylating agent. These agents are most active in the resting phase of the cells. These drugs are cell cycle non-specific [41.]

MODIFICATION OF THE STANDARD DCP REGIMEN[42]

1. If the patient is already receiving a daily dose of some corticosteroid and/or an immunosuppressive drug,the same dose is continued and the DCP therapy is strated till the patient attains complete clinical remission.after this,daily dose is

progressively reduced at the rate of 10mg prednisolone or 1mg of betamethasone/ dexamethasone at the time of each pulse till the daily dose of corticosteroid and the immunosuppressive drug is completely withdrawn and the patient is receiving only 50mg cyclophosphamide per day in between the DCPs .The patient is considered to be Phase I as long as the patient is receiving any additional dose of corticosteroid/immunosuppressive drug even if he is in clinical remission

2. In case the patient has a concomitant disease such as diabetes mellitus,hypertension, peptic ulceration, tuberculosis,or pyogenic,candidial or dermatophytic infection the treatment of the concomitant disease is to be continued/ started simultaneously without interrupting the DCP therapy.The patients having diabetes mellitus are to be given 8 units of insulin added to each bottle of 500ml glucose and this should be in addition to the treatment given to control the diabetes. In case however, the patient develops herpes simplex,herpes zoster or any other infection which can/has spread dangerously, the pulse therapy has to be interrupted temporarily till the viral infection has been controlled.
3. In case the patient has a cardiac,renal,heptic or neurologic problem,the opinion of the corresponding specialist must be obtained to ascertain that the pulse therapy will not advesely affect the other disease. This is especially necessary in patients having cardiac arrhythmias.
4. In case the skin lesions or mucosal ulcers are heavily infected and there is a risk of dissemination of the infection and toxaemia,the institution of the pulse therapy can be delayed till the infection has been controlled or the first few pulses can be given with dexamethasone alone(without cyclophosphamide).
5. Unmarried patients or those who have not yet completed their family and want to have more children,should be treated with only dexamethasone pulses giving

100mg of dexamethasone on 3 consecutive days, along with 50mg cyclophosphamide orally per day. The high dose of cyclophosphamide is to be withheld because this dose likely to lead to azoospermia/amenorrhoea and therefore infertility. The dexamethasone pulse therapy will be able to make the patient recover from the disease but there is an increased chance of developing a relapse at some time in the future. The patient should complete the treatment as in the standard DCP regimen(without cyclophosphamide pulses) and after the treatment has completed and the drugs have been withdrawn the patient should be advised to get married and have children. In case there is a relapse at any time in the future, the standard DCP therapy regimen can be administered to achieve permanent remission.

6. Patients undergoing DCP therapy are routinely advised to practice contraception during the period of the treatment because corticosteroids and immunosuppressive drugs are well known to lead to foetal developmental abnormalities . In case however, a pregnant patient develops pemphigus,the pulse therapy has to be withheld till the baby is delivered and weaned off. The patient can be treated with daily doses of corticosteroids using as small a dose as possible to control the disease. If pulse has to be used, it should only be a dexamethasone pulse and no cyclophosphamide or any other immunosuppressive drug, and a written advice/permission from the obstetrician must be obtained.

   After the patient has delivered the baby and the child put on artificial feed(weaned) the pulse therapy can be started as per the criteria outlined previously.

7. In case the patient is a child below the age of 12 years, the dose of dexamethasone in the pulse should be reduced to 50mg, and the daily dose of oral

cyclophosphamide should be reduced to 25mg per day. The large dose of cyclophosphamide in the pulse is not to be given, because of the possibility of azoopermia in the males and amenoorrhoea in the females.

8. In case the patients continues to have recurrences in between the DCPs and the duration of Phase I seems to be getting unduly prolonged, the patient can be given additional dexamethasone pulses. An additional dexamethasone pulse consists of two doses of 100mg each administerd on 2 consecutive days in between the two DCPs. Cyclophosphamide is not to be given with the additional dexamethasone pulses because too frequent administration of large doses of cyclophosphamide can lead to excessive immunosuppression and make the patient more prone to develop severe pyogenic or candidial infections.
9. The patients who show a tendency to develop recurrences even earlier than 2 weeks after the DCPs can be given a daily dose of corticosteroids in addition to the 4weekly DCPs with/without additional dexamethasone pulses. The daily dose of corticosteroids should be adjusted to a level which can control the activity of the disease. After the patient attains complete clinical remission. The daily dose of corticosteroid should be withdrawn in a step-wise manner at the time of giving the DCPs and the additional dexamethasone pulses. Phase II should be considered to have begun only after the daily dose of corticosteroid as well as the additional dexamethasone pulses have been completely withdrawn and the patient is receiving only DCPs given at 4-weekly intervals along with the 50mg daily oral dose of cyclophosphamide.
10. Some workers have used azathioprine in a dose of 50-100mg along with dexamethasone in place of cyclophosphamide particularly in unmarried patients

who have not yet completed their family. But azathioprine is expensive and it is potentially hepatotoxic.

INDICATIONS AND CONTRAINDICATIONS:

Since the risk-reward ratio of DCP therapy is claimed to be favourable and because it is said to cure pemphigus it is justified to treat all pemphigus cases with DCP irrespective of the severity of the disease[43] .

There are almost no contraindications. The only contraindication for pulse therapy is pregnancy or if the patient is a lactating mother. This is also not an absolute contraindications. Pulse therapy is only to be postponed till the patient has delivered her baby and stopped feeding the child.

SIDE EFFECTS:

ATTRIBUTABLE TO CORTICOSTEROIDS:

INCREASE IN BODY WEIGHT:

DCP regimen does not lead to an increase in the body weight inspite of the high dose of corticosteroids used during the DCP therapy.[44] Pasricha et al, from their

observations showed that some patients who showed an increase in the body weight during the treatment but most of these patients were those who were also receiving a daily dose of steroids and/ or additional dexamethasone pulses

INFECTIONS :

a.Pyodermic infections:

High incidence of bacterial infection during Phase I may actually be due to the presence of skin ulcers rather than the administration of DCP .[45]

b.Candidosis:

The incidence of candidial infection in the mouth was also extremely high in patients having oral ulcers.

As in the case of bacterial infection of the skin, the candidial infection in the oral cavity also seems to be related more to the presence of ulceration in the mouth rather than the DCP therapy.[45]

c. Dermatophytosis:

Observed in only a few patients especially during Phase I and II but also in the subsequent Phases, and most of the times it is not different from the dermatophytic infection observed in other individual.[45]

d.Tuberculosis:

Reactivation of the tuberculosis during the DCP therapy may occur very rarely.

e.Viral infection:

Patients developing varicella / herpes zoster while receiving the DCP therapy, may be kept under observation and even treated with acyclovir and the pulse administered at the predestined time if there is a reasonable certainity that the viral infection will not spread[46] .Corticosteroid treatment has been suggested as a risk factor

for developing Kaposi's varicelliform eruption,[47] in addition to pemphigus foliaceus itself.[48]

DIABETES MELLITUS:

The incidence of diabetes mellitus in patients receiving DCP therapy has been estimated to be 2%. A diabetic state caused by the administration of corticosteroids is likely to revert back to the normal state after the corticosteroids are withdrawn[49].

HYPERTENSION:

The incidence of hypertension in patients receiving DCP therapy is fairly low[50].

CATARACT:

May be detected during all the 4 phases of the DCP regimen. Almost all patients however are old and could have developed cataract even without the DCP regimen. The risk of developing premature cataract consequent to DCP therapy is practically nil [51].

ACID PEPTIC DISEASE:

More often observed in the patients who were receiving a daily dose of steroids. Rare in DCP therapy .[51]

ASEPTIC NECROSIS OF THE BONES:

A well recognized complication of high dose corticosteroid therapy. In a study by Pasricha et al only one patient out of 250 patients developed this complication.

LEUKOPENIA:

Rare one. Transient and recovers without any special treatment.

GENERAL WEAKNESS AND LETHARGY:

Observed during first few pulses, this side effect tends to disappear as the treatment with the DCP regimen is continued .[51]

PITUTARY ADRENAL AXIS SUPPRESSION:

Occurs in about half of the patient who receive DCP therapy for pemphigus. These patients probably do not require routine replacement therapy with corticosteroid but may need supplementation during periods of stress[52].

MISCELLANEOUS:

- Hiccups[53]
- Transient puffiness, edema, Joint pain and muscle pain[54].
- Hirsutism, facial flushing[55] ,diarrhea.

ATTRIBUTABLE TO CYCLOPHOSPHAMIDE:

The main side effects are leukopenia, hematuria, gonadal failure, generalized pigmentation and hair loss[56].

HEMATURIA:

Well known complication of cyclophosphamide therapy due to the stagnation of acrolein in the urinary bladder, a metabolite of cyclophosphamide. In the study of

Pasricha et al only 2% of the patients developed hemorrhagic cystitis. Cyclophosphamide should be taken in the morning so that major part of the drug is excreted out during the day and there is no accumulation of the drug in the bladder during the night time . Hemorrhagic cystitis usually occurs after a cumulative dose of 85gm of cyclophosphamide [57]. Cystitis can be reduced in intensity or prevented by parenteral administration of MESNA- a sulfhydryl compound that readily reacts with acrolein in the acid environment of the urinary tract.[58]

GONADAL FAILURE:

Cyclophosphamide interferes with oogenesis and spermatogenesis and it may cause infertility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide , duration of therapy and the state of gonadal function at the time of treatment.

Amenorrhoea occurs in about 50% of the female patients treated with DCP regimen [59]; In the study by McDermott et al the incidence of premenopausal ovarian failure was 54% and the incidence of pre mature menopause (occurring before 40 years of age) was 41% after treatment with cyclophosphamide pulse therapy.[60] Cyclophosphamide induced sterility may be irreversible in some patients[61]. Incidence of azoospermia is estimated to be same as amenorrhoea in females that is 50%[62]

PIGMENTATION:

General darkening of complexion[63] and a peculiar pattern of nail pigmentation[64] have been documented .

HAIR LOSS:

Diffuse hair loss is observed in a very high proportion of the patients mainly during Phase I and Phase II; Anagen defluvium is a known complication of cyclophosphamide therapy.[65]

Leucopenia and Thrombocytopenia: rare[65]

AIM OF THE STUDY

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This study of Dexamethasone Cyclophosphamide Pulse therapy in Pemphigus patients was undertaken

1. To find out the clinical efficacy of DCP therapy in Pemphigus patients.
2. To find out the various side effects of the regimen.

MATERIALS AND METHODS

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The material for this study was from the patients attending the skin OPD, Government Rajaji Hospital, Madurai Medical College, Madurai with pemphigus, during the period of June 2005 – June 2007.

Inclusion Criteria:

1. Above 18 years of age
2. The patients with pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus registered during the period from June 2005 –June 2007 and whose diagnosis was confirmed by Histopathological examination and Direct immunofluorescence.

Exclusion Criteria :

1. Age below 18 years.
2. Uncontrolled diabetes mellitus/ Hypertension. However diabetic and hypertensive patients were included, if their disease was under control with appropriate therapy. The routine antidiabetic and antihypertensive drugs were continued in the same dose along with DCP. However six units of insulin was added to counter the effect of 5% dextrose in diabetic patients.
3. Severe systemic diseases where high dose steroids are contra-indicated.
4. Pregnant and lactating mothers.
5. Patients on long term systemic steroids therapy.
6. Pemphigus patients in whom the diagnosis could not be confirmed by DIF.
7. Patients who had not completed their family.

After applying the criteria mentioned above, 26 cases of pemphigus enrolled for pulse therapy and followed up from June 2005 – June 2007. After their informed consent they were hospitalized and thorough general, systemic and dermatological examinations were done. Relevant Baseline investigations like complete haemogram,

routine blood biochemistry, urine examination, electro-cardiography, chest X-ray, semen analysis, baseline Fitzpatrick skin typing were done.

Dexamethasone Cyclophospamide pulse therapy was administered to each patient, strictly adhering to the prescribed guidelines. Due importance was given to patient education regarding the disease process and the treatment regimen.

During every pulse, complete blood count, urine analysis especially for red blood cells, electrocardiogram, blood sugar, blood urea, serum electrolytes, liver function tests, stool examination for occult blood, ophthalmic examination for cataract, blood pressure recording and weight charting were done.

OBSERVATIONS & RESULTS

OBSERVATIONS AND RESULTS

In this study, 26 cases of Pemphigus patients from the outpatient Department of Dermatology, Government Rajaji Hospital, Madurai were treated with

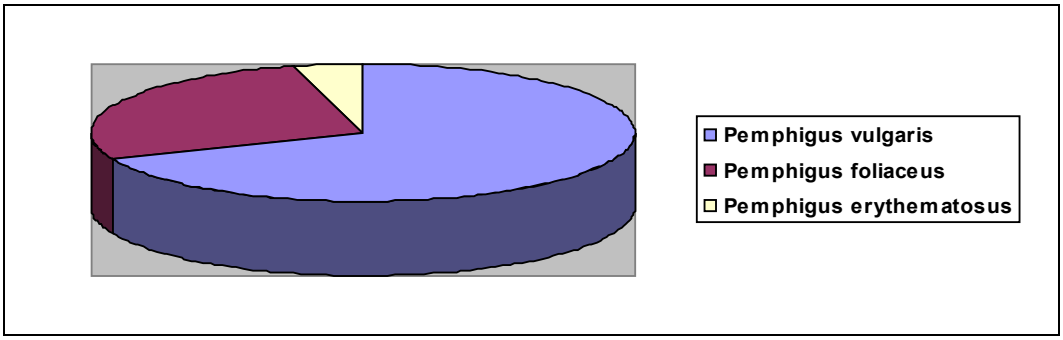
Dexamethasone Cyclophosphamide pulse therapy and observed during the period of June 2005 – June 2007; The following observations were made.

Type of Pemphigus:

Of the 26 pemphigus patients 18(70%) patients had pemphigus vulgaris, 7(26%) patients had pemphigus foliaceus, and 1 (4%) patient had pemphigus erythematosus. Thus pemphigus vulgaris is by far the most predominant type of pemphigus requiring DCP therapy.

Table I

Disease	No. of patients	Percentage (%)
Pemphigus Vulgaris	18	70
Pemphigus Foliaceus	7	26
Pemphigus Erythematosus	1	4



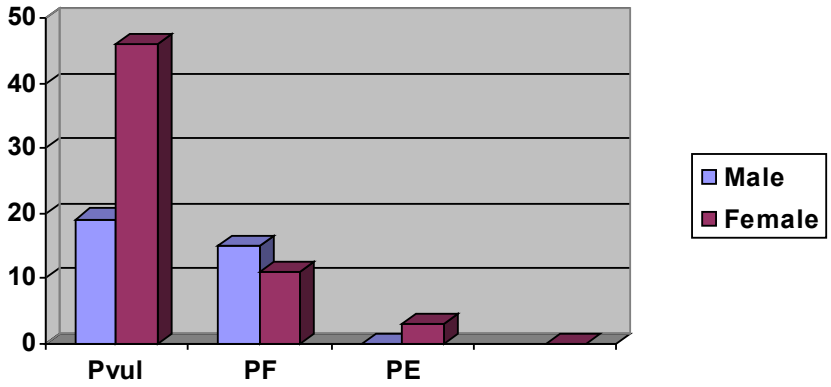
Sex ratio:

In our study 16 patients were females while 10 patients were males. In our study the male: female ratio was 1:1.6

Table II

Type of Pemphigus	Total	Male	Female	M:F
Pemphigus Vulgaris(PVul)	18	6	12	6:12

Pemphigus Foliaceus(PF)	7	4	3	4:3
Pemphigus Erythematosus(PE)	1	-	1	0:1
Total	26	10	16	5:8

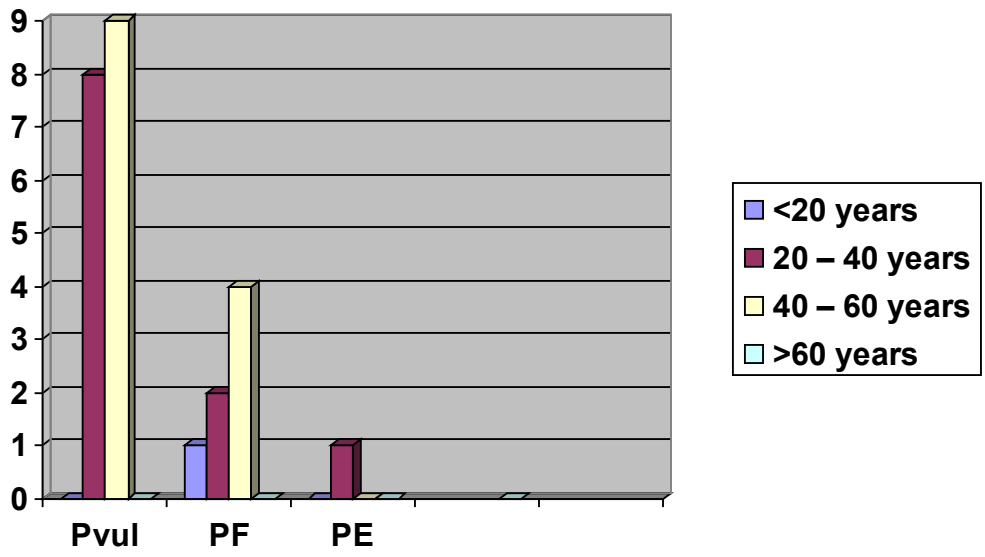


Age Distribution:

The age at recruitment in various types of pemphigus is shown in Table III. Most of the patients were between the ages of 20 to 60 years when the disease started.

Table III

Age at onset(years)	Pemphigus Vulgaris	Pemphigus Foliaceus	Pemphigus Erythematosus	Total
<20	-	1	-	1(4%)
20 – 40	9	2	1	12(46%)
40 – 60	9	4	-	13(50%)
>60	-	-	-	-



Distribution of lesions

Involvement of skin and mucous membrane:

In 9 patients, the disease was limited to skin only. In the remaining 17 patients both the skin and the mucous membranes were involved.

Table IV

	Pemphigus Vulgaris	**Pemphigus Foliaceus**	**Pemphigus Erythematosus**	**Number of patients**	**Percentage (%)**
Involvement	2	7	1	10	39

of skin only					
Involvement of both skin and mucous membranes.	16	0	-	16	61

Table V

Order of involvement	**Pemphigus Vulgaris**	**Pemphigus Foliaceus**	**Pemphigus Erythematosus**	**Number of patients**	**Percentage (%)**
Mucosa first	14	-	-	14	54
Skin first	2	7	1	10	38
Simultaneous involvement	2	-	-	2	8

The mucosal involvement was severe in all patients with pemphigus vulgaris and preceded the skin lesions by a mean duration of 2 months. A detailed analysis of the involvement of various mucous membrane in 26 patients revealed involvement of oral mucosa in 18 patients, nasal mucosa in 3 patients, genital mucosa in 5 patients, conjunctival mucosa in 1 patient and anal mucosa in 1 patient. 3 patients had palms and soles involvement as their presenting feature.

Table VI

Mucous membrane	**Number of patients**	**Percentage (%)**
Oral mucosa	18	70
Genital mucosa	5	19
Nasal mucosa	3	12
Conjunctival mucosa	1	4
Anal mucosa	1	4

RESPONSE TO THE DCP REGIMEN

❖**Adherence:**

Of the 26 patients, only 3 (12%) were lost to follow up. Strict adherence to the regimen was offered by all the patients who completed the study.

Table VII

Total patients	**26**
On DCP	20 (76%)
Left out	3 (12%)
Died	3(12%)

❖**Patients lost to follow up:**

A total of 3 patients (12%) could not continue the treatment for the following reasons.

Table VIII

Presumed reason	Number of Patients
Due to long distance	2
Due to haemorrhagic cystitis	1

❖**Cause of Death** :

A total of 3 patients died in our study. All the deaths were due to septicaemia.

Table IX

Disease	Number of patients	Cause of death	Phase
Pemphigus vulgaris	2	Septicaemia	I
Pemphigus foliaceus	1	Septicaemia	I

❖**Number of DCP required to achieve complete clinical remission** :

Response to DCP regimen was gradual in our study but remission was achieved in all the treated patients.

Table X

Number of DCP	Pemphigus vulgaris	Pemphigus foliaceus	Pemphigus erythematosus	Number of Patients
1-6	-	-	-	-
7-12	-	-	-	-
13-24	11	3	1	15
25-36	5	-	-	-
37-48	-	-	-	-

The average number of pulses required to achieve remission in Pemphigus vulgaris and Pemphigus foliaceus was observed to be 20 and 16 respectively in our study.

❖**Phase wise distribution of cases at the end of study period:**

Out of the 26 patients, a total of 11 patients were in phase III, 7 patients were in phase IV, 2 patient relapsed during phase IV, 3 patients could not continue the treatment with us for a variety of reasons and 3 patients had died.

Table XI

	Male	**Female**	**Total**
Phase I	-	-	-
Phase II	-	-	-
Phase III	3	8	11
Phase IV	4	3	7

❖**Relapse rate** :

Out of the 26 patients 2 patients relapsed during phase IV. These 2 patients had persistent oral ulcers during phase I. There was no obvious cause for relapse.

Side effects :

Table XII

Side effects	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	**Total**	**Percentage (%)**
Weight gain	-	2	-	-	2	8
Pyodermic infections	2	1	-	-	3	12
Dermato phytosis	1	1	-	-	2	8
Candidosis	2	1	-	-	3	12
Kaposi'svaricelliform eruption	1	-	-	-	1	4
Hypertension	-	-	-	-	-	-
Diabetes mellitus	3	-	-	-	3	12
Catatract	-	-	1	1	2	8
Hematuria	1	-	-	-	1	4
Menstrual abnormalities	4	2	-	-	6	38
Defective spermatogenesis	-	-	3	4	7	70
Skin pigmentation	4	3	1	-	8	30
Nail changes	2	-	-	-	2	8
Diffuse hair loss	2	3	-	-	5	20
Teeth loss	-	1	-	-	1	4
Bone pain	2	-	-	-	2	8
Periodontitis	-	1	-	-	1	4
Pedal edema	1	-	-	-	1	4
Hiccups	1	-	-	-	1	4

The following was a brief account of the side effects observed in our patients and the measures taken to deal with the side effects :

1. **Weight gain :-** {more than 10% of baseline body weight}

Out of the 26 patients 2 patients (8%)showed weight gain in phase II.

2. Infections :-

- Pyodermic infections :

  In our study 3 patients (12%) showed pyodermic infections. Gram stain, culture and sensitivity done for these patients which showed staphylococcus aureus. These patients were treated with appropriate topical and systemic antibiotics.

- Dermatophytosis :

  Dermatophytic infection of the skin was observed in 2 patients (8%) especially during phase I and II. In these patients extensive dermatophytic infection was noticed.

- Candidosis :

  In our study oral candidosis was observed in 3 patients (12%) mainly during phase I and they are treated with topical anti candidal agents.

- Kaposi's varicelliform eruption :

  One male patient with Pemphigus foliaceus developed vesicular eruption over the face during phase I, which was diagnosed to be Kaposi's varicelliform eruption and confirmed by Tzanck smear and Histopathological examination. He was treated with oral acyclovir 200mg X 5 times a day for 7 days and he recovered completely.

3. Diabetes mellitus :

During phase I, 3 patients were discovered to have diabetes mellitus. These patients were given appropriate treatment to control their disease and in

addition each patient was given 8 units of insulin along with every bottle of 500ml of 5 % dextrose used for the infusion.

4. Hypertension :

In our study none of the patient developed systemic hypertension during or after DCP therapy. Only one patient had preexisting hypertension and his blood pressure was within normal limits with antihypertensive drugs.

5. Cataract :

Cataracts were detected in 2 patients (8%) in our study. These patients however were old and they were above 50 years of age. They could have developed cataract even without the DCP regimen. There was no patient who could be considered to have developed premature cataract.

6. Hematuria :

A 55 year old male patient who was administered DCP for pemphigus vulgaris developed hematuria after the 3rd pulse. Cystoscopy revealed the presence of haemorrhagic cystitis confirming that the hematuria was being caused by cyclophosphamide. The cystitis subsided with oral intake of plenty of fluids. He, however was lost to follow up since then.

7. **Menstrual abnormalities :**

Out of the 16 female patients in our study, 6 patients (38%) developed amenorrhoea at the end of phase I. None of the patient regained her menstrual cycle after the cessation of pulse therapy. Ultrasound revealed ovarian atrophy in 2 patients. One patient developed menorrhagia during phase I. She

responded to symptomatic treatment and she regained her normal cycles during phase III.

8. Abnormalities of spermatogenesis:

Defective spermatogenesis was observed in 7 patients (70%) out of 10 male patients. All patients showed more than 50% reduction in their sperm count. They also showed profound inhibition of sperm motility, however there were no significant morphological abnormalities. These changes were observed mainly during phase III.

9. Pigmentation :

Generalized Pigmentation was observed in 8 patients (30%)

10. Diffuse Hair loss :

Diffuse loss of hair was seen in 5 patients (20%) mostly during phase I and II, when the patient was receiving high doses of cyclophosphamide. In all these patients the hair re-grew to their original profusion after the completion of Pulse therapy.

11. Teeth loss :

A 35 year old male patient - a case of pemphigus foliaceus had a sudden unexplained loss of multiple teeth at the end of phase I.

12. Osteoporosis :

2 female patients (8%) developed low back ache during pulse therapy. Their X-ray showed osteoporotic changes of the spine.

13. Periodontitis :

Observed in one patient which subsided with appropriate antibiotic therapy.

14. Hiccups :

One patient developed intractable hiccups during phase I and he responded well to chlorpromazine. Then he was put on prophylactic chlorpromazine, during subsequent pulses.

15. Nail changes :

Hyperpigmentation of nails was observed in 2 patients (8%) in our study.

16. Other side effects :

- Several patients complained of generalized weakness, lethargy and lack of desire to do anything for 3 – 4 days following each pulse which subsided during phase III.
- Transient puffiness of face was observed in few patients for 2 – 3 days after each pulse which subsided without treatment.

DISCUSSION

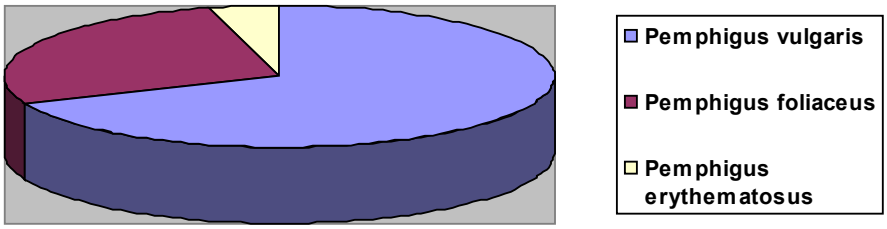
DISCUSSION

The study was conducted during the period of June 2005 – June 2007 at the Department of Dermatology , Government Rajaji Hospital, Madurai Medical College, Madurai. 26 Pemphigus patients were treated with Dexamethasone Cyclophosphamide Pulse therapy during the period of study.

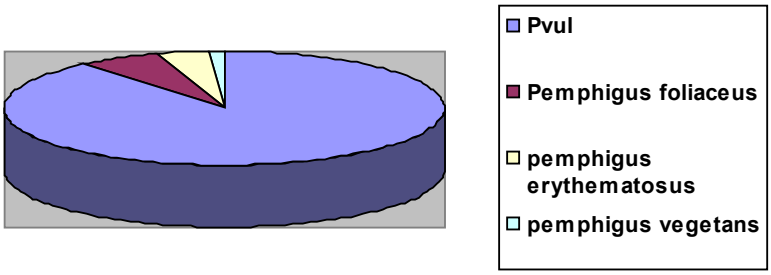
Case distribution :

Of the 26 patients who completed our study 18 patients (70%) had pemphigus vulgaris, 7 patients (26%) had pemphigus foliaceus,and 1 patient (4%) had pemphigus erythematosus .In the study by Pasricha et al out of 500 patients 89% had pemphigus vulgaris. However pemphigus foliaceus patients comprised only 6% . This may be due to geographic variations in the incidence pattern of these diseases or exclusion of pemphigus foliaceus by Pasricha et al in their study .

Our Study

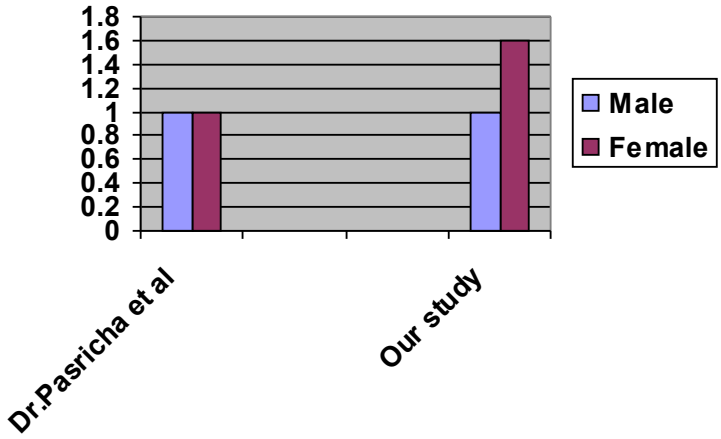


Dr.Pasricha et al Study



Sex distribution :

In our study the male:female ratio was is **1:1.6.** In the study by Pasricha et al the ratio was 1:1. The female preponderance in our study tends to reflect the overall sex distribution of pemphigus in our centre.32 cases of autoimmune bullous diseases were diagnosed in about 1,92,750 patients who attended the skin OPD during the period of study and the male:female ratio was approximately 2:3.



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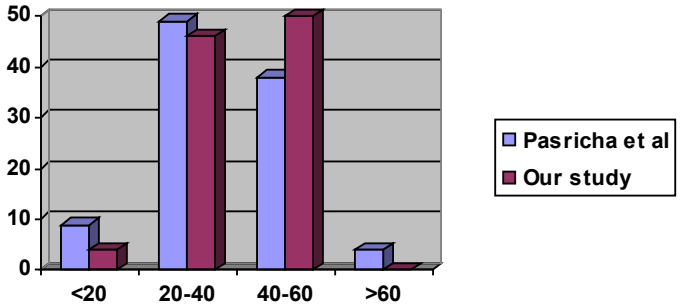
Age Distribution:

Majority of our patients (96%) were between 21 – 60 years of age. This was in concordance with the study by Pasricha et al who recorded 88% in that age group.



Involvement of the skin and mucous membrane:

Involvement	Our study (%)	Pasricha et al (%)
Skin alone	37	27
Mucous membrane only	-	25
Both skin and mucous	65	52.4

Our results were comparable with Pasricha et al study except that the skin is involved in some point of the course of the disease and none of our patients had exclusive mucous membrane involvement whereas 25% had the same in Pasricha et al study.

Number of pulses required to achieve remission:

Number of DCP required	Our study (%)	Dr.Pasricha et al (%)
1 – 6	-	66
7 – 12	-	9
13 – 24	75	13
25 – 36	25	3
37 – 48	-	1

In our study majority of patients (75%) required an average of 16 pulses to achieve remission whereas in the study by Pasricha et al even with 6 DCP they were able to achieve remission in 66% of patients. It is obvious that there is gross variation between these studies. Hence an universally acceptable clinical scoring or grading system to objectively assess the severity of the disease process and to monitor the clinical progress may allow for a fair comparison between reports from different centres. This is particularly important because Indirect immunofluorescence titres bear only an imperfect correlation with clinical activity[66].

Simultaneous multicentric studies are another possible method to circumvent this problem. We also observed that the average number of DCP required

to achieve remission in Pemphigus vulgaris (20) is higher than that required in Pemphigus foliaceus(16).

Patients lost to follow up :

3 patients (12%) out of 26 patients did not complete our study. Out of these 3 who were lost to follow up, inability to travel long distance was the reason in two cases and the development of hemorrhagic cystitis was the reason the other. In the study by Pasricha et al 16% of patients did not complete the study.

Cause of death :

3 out of 26 patient (11%)in our study died during the study period. All the deaths(100%)were attributed to septicaemia. In the study by Pasricha et al 3% of patients died during the study period and the most common cause of death in his study also septicaemia. In the study by Royrenu et al study, 11% of patients died during the study period and the major cause of death was found to be septicaemia.

Relapse rate and cause of relapse :

In our study 2 patients (8%) showed relapse in phase IV. There was no attributable cause for their relapse. In Pasricha et al study 14% showed relapse mostly due to irregularity of pulses and incomplete phase II. The lower rate of relapse (8% vs 14%) during phase IV in our study may be due to better adherence of our patients to the prescribed regimen. However, careful follow up of the patients for a longer period of time is essential to ascertain the efficacy of DCP as a curative treatment.

Side effects:

- Significant weight gain (more than 10% from the baseline) was observed in 2 patients (8%) in our study whereas it was 3% in the study by Pasricha

et al study. Retention of sodium and water could be the possible explanation of weight gain.

- While Kaposi's varicelliform eruption was observed in one patient a case of pemphigus foliaceus in our study, no such manifestation was observed by Pasricha et al and Roy renu et al in their study. However Kaposi's varicelliform eruption is one of the well known complication of steroid therapy and pemphigus foliaceus itself.
- In our study 3 patients (12%) developed diabetes mellitus whereas in Pasricha et al study it was 1% only. The variation can be attributed to the small sample size of our study.
- Menstrual irregularities: Amenorrhoea was observed in 6 patients(38%) in our study, as compared to 50% in the study by Pasricha et al . None of the patients regained her menstrual cycle even after one year of cessation of the pulse therapy.
- Defective spermatogenesis was observed in 7 patients(70%) in our study. Count and motility were the parameters affected significantly. Marginal recovery of spermatogenesis was observed in 5(72%) of the 7 patients. No improvement in spermatogenesis could be detected in the other two.
- Generalised skin pigmentation was observed in 8 patients(30%) in our study where as it was 1% in pasricha et al study. This disparity could be possibly due to the higher baseline pigmentation(Fitzpatrick skin type IV-VI) in south Indian patients as compared to their North Indian counterparts.
- Sudden simultaneous unexplained loss of teeth was observed in one patient with pemphigus foliaceus after six pulses of DCP. There was no pre

existing dental pathology that could be held responsible for this phenomenon.

- Osteoporosis was observed in 2 female patients(8%) in our study. It is a well known complication of high dose steroid therapy. Avascular necrosis, a rare complication noted in 0.4% of patients in the study by Pasricha et al was not encountered in our study.

CONCLUSION

CONCLUSION

1) Pemphigus vulgaris is by far the commonest epidermal autoimmune vesiculobullous disorder that requires Dexamethasone cyclophosphamide pulse therapy.

2) An overwhelming majority of patients requiring DCP for Pemphigus are in the reproductive age group.
3) DCP significantly improves patient compliance by reducing the duration of hospital stay.
4) The average number of pulses required to achieve clinical remission is significantly higher than the figures mentioned in the available literature.
5) Septicaemia is the commonest cause of death in patients receiving DCP.
6) Metabolic side effects attributable to long term steroid therapy are significantly lower in patients treated with DCP.
7) An universally acceptable clinical grading of Pemphigus is needed to objectively assess the baseline severity and subsequent improvement. It would also allow for a fair comparison of the results reported by different centres.
8) Potentially irreversible gonadal suppression appears to be the most important side effect against which the benefits of DCP have to be weighed.
9) Ways and means to reduce the gonadal toxicity of DCP need to be explored, as DCP therapy is likely to stay as the treatment of choice in autoimmune vesiculobullous diseases.

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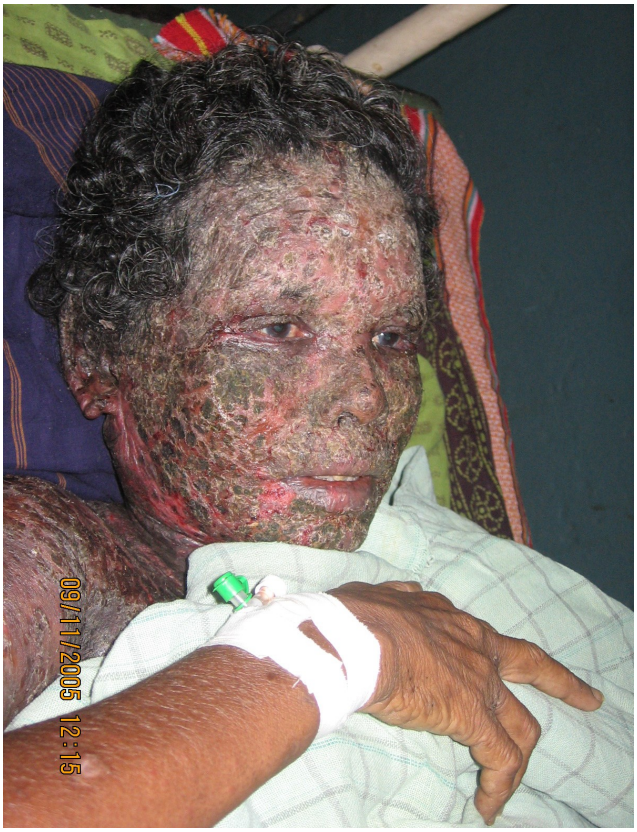


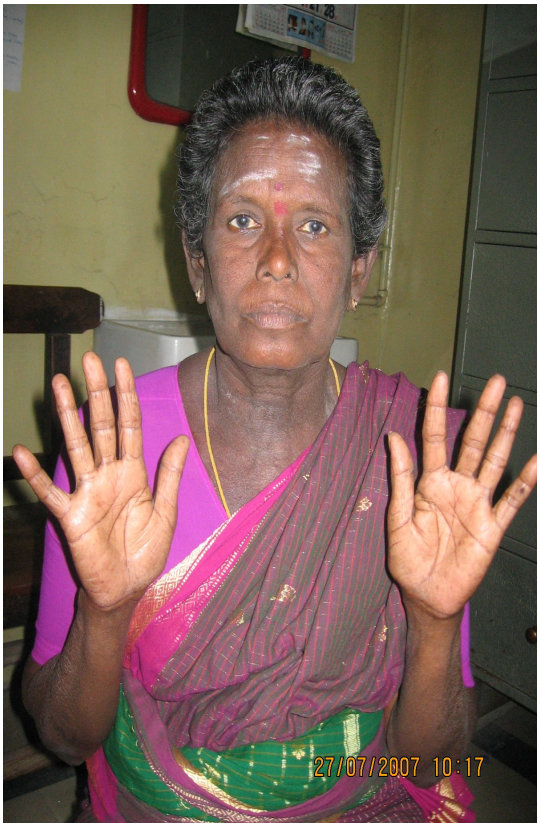
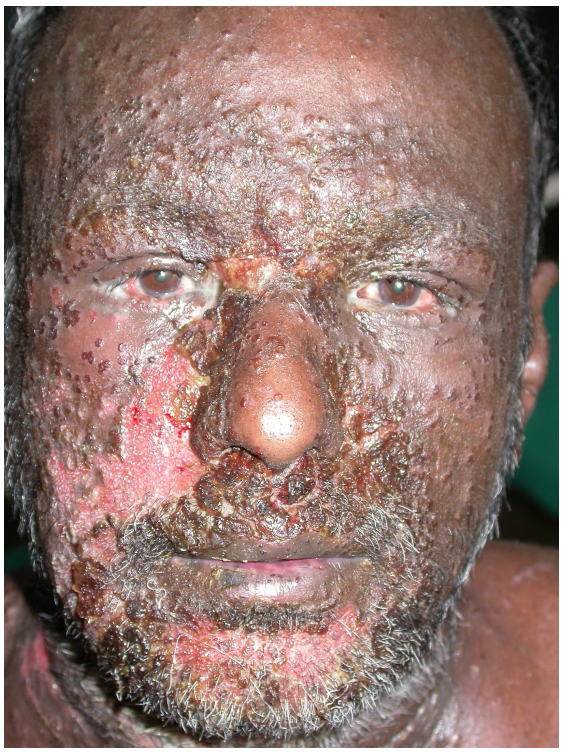


Figure 1: A case of pemphigus foliaceus before and after DCP

Figure 2:A case of pemphigus vulgaris before and after DCP



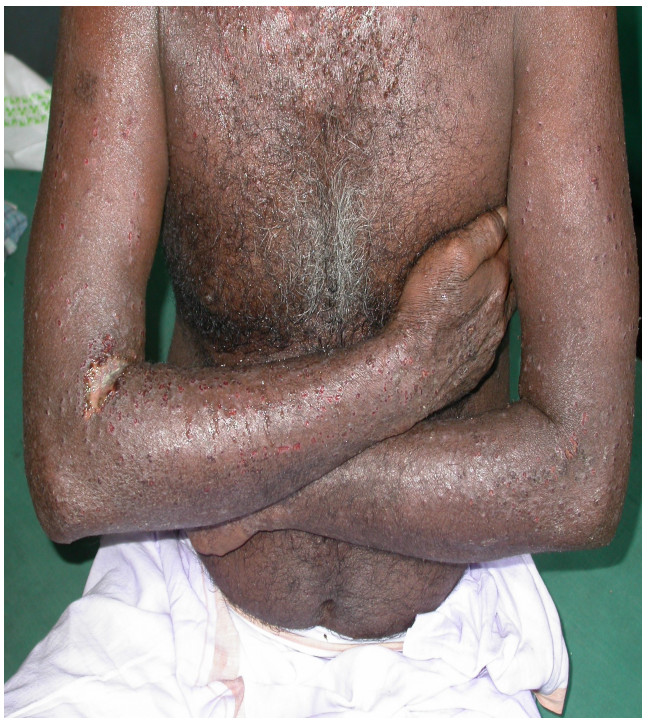


Figure 3: A case of pemphigus foliaceus with kaposi's varicelliform eruption

Figure 4: A case of Pemphigus foliaceus with loss of teeth

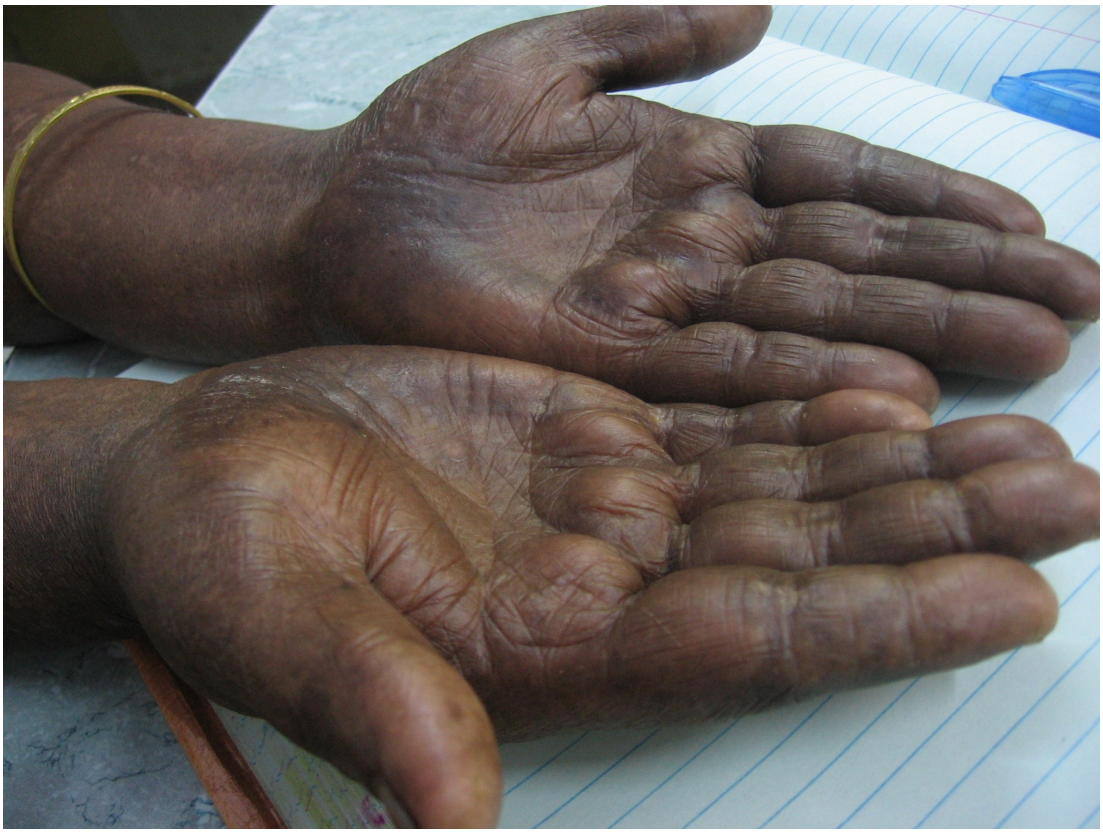


Figure 5: A case of Pemphigus vulgaris with pigmented palms after DCP

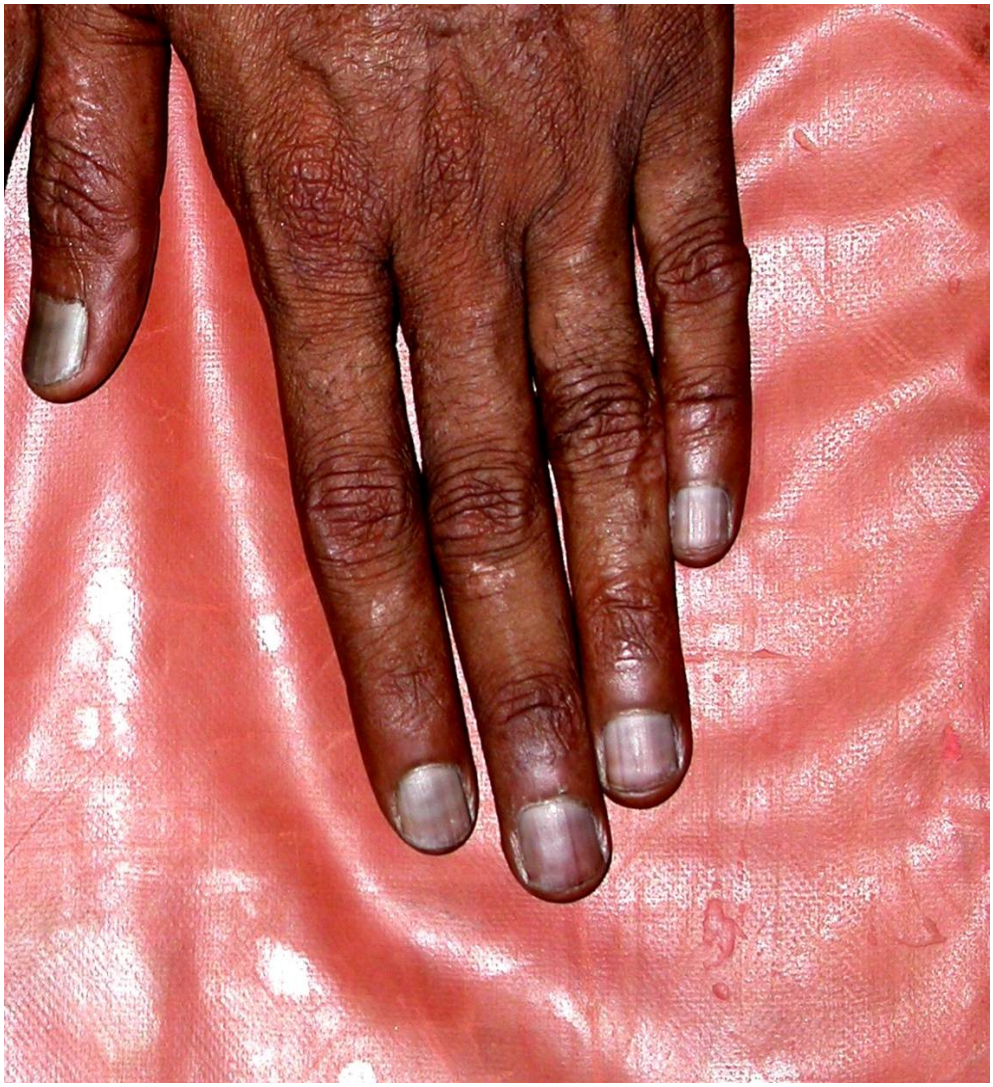


Figure 6: A case of Pemphigus vulgaris with diffuse pigmentation of nails after DCP

PROFORMA

Name : Age / Sex : Occupation : Income : S/E status :	Address :

General history

- HT / DM :
- PT / Heart disease :
- Malignancy :
- Smoking / Alcohol :
- Precipitating factor :
  - Drugs :
  - Infection :
  - Diet :
  - Trauma :
  - Sweating :
  - Sun exposure :
- Oral / Genital herpes :
-

Family History

- Marital status :
- Children :
- Obstetric history :
- P / S done or not :
- Menstrual history :
- H/O other auto immune disease in the patient :
- H/O auto immune diseases in relatives :

H/O Vesiculobullous disease

- Date of onset :
- Site of first lesion (mucosal / skin) :
- Morphology of first skin lesion and its evolution :
- Treatment received :
- Date of registration at GRH :
- Number of exacerbations :

Onset	Duration	PPt. factors	Treatment

Conditions on first visit

- **General condition**
  - Wt :
  - CVS :
  - RS :
  - Abd :
  - Others :
- **Oral lesion**
- **Active skin lesions**
  - Number of bullae :
  - Distribution – groups / discrete/ Along lines of trauma :

- Tense / flaccid :
- Contents – clear / pustular / Hemorrhagic :
- Nikolsky sign & Bulla spread sign :
- Are of erosions :
- Symptoms :

➢ **Healing skin lesions**

- Hyper / hypo pigmentation :
- Milia :
- Scarring :
- Peripheral extension :

Investigations

LFT	
RFT	
Sr. Electrolytes	
Hemogram	
ECG	
Tzanck smear	
Biopsy and DIF	
Semen analysis	
USG abdomen	

Ophthal examn	
Others	Chest X-ray, Stool examination for occult blood, Baseline fitz Patrick skin typing.

Name																	
Date	Comp laints	New lesions Skin / mucous	Persistent lesions Oral/scalp /skin	Wt.	BP	Urine ASD	TC	DC	Hb	Blood USC	LFT/ Tzanck	HPE /DIF	Semen analysis	Menstrual history	No. of DCP in phase I	Blister free period	Ophthal examn.

Master Chart

Name	Age / Sex	Diagnosis	No.of Dcp req for remission	Wt. gain	Bacterial infection	Dermatophytosis	Candidosis	KVCE	HTN	DM	Cataract	Hematuria	Amenorrhoea	Defective spermatogenesis	Skin pigmentation	Nail changes	Hair loss	Teeth loss	Hiccups	Periodontitis	Pedal edema	Osteoporosis	Remarks
Banu	30/f	PV	14	P	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A	A	A	
Indu	35/F	PV	26	A	A	A	A	A	A	A	A	A	P	A	P	A	P	A	A	P	A	A	Ovarian atrophy
Valli	45/F	PV	13	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A	A	A	A	A	Cataract
Baby	33/F	PE	18	A	A	P	A	A	A	A	A	A	P	A	A	A	P	A	A	A	A	A	
Andichi	50/F	PV	16	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	A	P	
Mumtaj	42/F	PV	14	A	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	DM
Ramu	57/F	PF	18	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A	Skin pigmentation
Ramathilagam	40/F	PV	30	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A	A	A	Ovarian atrophy
Pattanichi	42/F	PV	17	A	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	
Rakha	18/F	PF	16	A	P	P	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	Died-septicaemia
Latha	38/F	PV	13	P	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A	P	P	
Vanaja	42/F	PV	12	A	P	A	P	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	Died-septicaemia
Muthulakshmi	42/F	PV	16	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	
Manohari	44/F	PV	30	A	P	A	P	A	A	P	A	A	A	A	A	A	A	A	A	A	A	A	Died-septicaemia
Muthu venkat	53/F	PV	16	A	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A	
Suresh	30/M	PV	24	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A	A	
Dekolin	28/M	PV	28	A	A	A	A	A	A	A	A	A	A	P	A	P	A	A	A	A	A	A	Pigmented nail
Vijay	25/M	PF	16	A	A	A	A	P	A	A	A	A	A	P	A	A	A	A	A	A	A	A	KVCE
Arumugan	48/M	PV	13	A	A	A	A	A	A	A	P	A	A	P	P	A	A	A	A	A	A	A	
Anbu	35/M	PF	14	A	A	A	A	A	A	A	A	A	A	P	A	A	A	P	A	A	A	A	Teeth loss
Karthik	23/M	PV	26	A	A	A	A	A	A	A	A	A	A	P	A	A	A	A	A	A	A	A	
Karupiah	50/M	PF	12	A	A	A	A	A	A	P	A	A	A	A	P	A	A	A	A	A	A	A	Left-long distance
Raja rathnam	58/F	PF	5	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	Left-long distance
Siva	55/M	PF	3	A	A	A	A	A	A	A	A	P	A	A	A	A	A	AA	A	A	A	A	Left-hemorrhagic cystitis
Selvaraj	38/M	PV	14	A	A	A	A	A	A	A	A	A	A	P	P	A	A	A	A	A	A	A	
indrani	28/F	PV	29	A	A	A	A	A	A	A	A	A	P	A	P	A	P	A	A	A	A	A	

KEY TO MASTER CHART

PV= pemphigus vulgaris

PF= pemphigus foliaceus

PE= pemphigus erythematosus

P= present

A= absent

HTN= hypertension

DM= diabetes mellitus

KVCE= Kaposi's varicelliform eruption.