COMPARISON OF EFFICACY OF CALCIPOTRIOL AND BETAMETHASONE COMBINATION WITH BETAMETHASONE ALONE IN PLAQUE PSORIASIS

BY

Dr. HARISH . S, MBBS

Dissertation submitted to the

Sri Devaraj Urs Academy Of Higher Education and Research,

Tamaka, Kolar, Karnataka

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

Dr . SARALA . N , MD

Department Of Pharmacology
Sri Devaraj Urs Medical College, Kolar

April 2013

Sri Devaraj Urs Academy Of Higher Education and Research
Tamaka
Kolar

Declaration by the candidate

I hereby declare that this dissertation entitled **"COMPARISON OF EFFICACY OF CALCIPOTRIOL AND BETAMETHASONE COMBINATION WITH BETAMETHASONE ALONE IN PLAQUE PSORIASIS"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr.SARALA. N, MD** Professor and HOD, Department Of Pharmacology Sri Devaraj Urs Medical College, Tamaka, Kolar.

Date : **Signature of the candidate**

Place : **Dr.HARISH . S**

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"COMPARISON OF EFFICACY OF CALCIPOTRIOL AND BETAMETHASONE COMBINATION WITH BETAMETHASONE ALONE IN PLAQUE PSORIASIS"** is a bonafide research work done by **Dr.HARISH. S** in partial fulfillment of the requirement for the degree of **M.D IN PHARMACOLOGY.**

SIGNATURE OF THE GUIDE

DATE:

PLACE:

Dr.SARALA . N , MD

Professor and HOD

Department Of Pharmacology

CERTIFICATE BY THE CO-GUIDE

This is to certify that the dissertation entitled **"COMPARISON OF EFFICACY OF CALCIPOTRIOL AND BETAMETHASONE COMBINATION WITH BETAMETHASONE ALONE IN PLAQUE PSORIASIS"** is a bonafide research work done by **Dr.HARISH. S** in partial fulfillment of the requirement for the degree of **M.D IN PHARMACOLOGY.**

SIGNATURE OF THE CO-GUIDE

DATE:

PLACE:

Dr. SHIVAKUMAR. V, MD

PROFESSOR

DEPARTMENT OF DERMATOLOGY VENEROLOGY

AND LEPROLOGY

ENDORSEMENT BY THE HOD, PRINCIPAL/HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"COMPARISON OF EFFICACY OF CALCIPOTRIOL AND BETAMETHASONE COMBINATION WITH BETAMETHASONE ALONE IN PLAQUE PSORIASIS"** is a bonafide research work done by **Dr. HARISH . S** under the guidance of **Dr.SARALA. N, MD** Professor and HOD, Department Of Pharmacology.

SEAL & SIGNATURE OF THE HOD	SEAL & SIGNATURE OF THE PRINCIPAL
Dr. SARALA . N	**Dr. M.B. SANIKOP**
DATE: PLACE: KOLAR	DATE: PLACE: KOLAR

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the Sri Devaraj Urs Academy of Higher Education And Research, Tamaka, Kolar, Karnataka shall have the rights to preserve, use and disseminate this dissertation in print or electronic format for academic / research purpose.

DATE:
PLACE: KOLAR

SIGNATURE OF THE CANDIDATE
DR. HARISH. S

SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR.

ETHICS COMMITTEE

CERTIFICATE

This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **Dr.HARISH. S**, a postgraduate student in the department of Pharmacology, Sri Devaraj Urs Medical College entitled "**COMPARISON OF EFFICACY OF CALCIPOTRIOL AND BETAMETHASONE COMBINATION WITH BETAMETHASONE ALONE IN PLAQUE PSORIASIS"** to be submitted to the Sri Devaraj Urs Academy of Higher Education And Research, Tamaka, Kolar.

MEMBER SECRETARY **PRINCIPAL**

ACKNOWLEDGEMENT

" No one knows everything and everyone knows something." In the same way I started my dissertation with a drop of knowledge which ended up in bringing out ocean vast of outcomes. This would have not been possible without the help of few kind hearted people. I thank all those who have directly and indirectly contributed their knowledge in bringing out this research work.

No words can express my gratitude to Dr. Sarala N, Professor & HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar. Her everlasting immense enthusiasm in teaching, unimaginable store of knowledge and her graceful blessings will definitely lead towards a bright future for any student. I will be thankful to her for the rest of my career.

The other two wonderful people whom I should not forget for their immense moral as well professional support are Dr. Kumar . T. N and Dr Nagesh Raju. G. Dr Kumar. T. N, former Professor and HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar is a person beyond any comparison. I can only say that he is my role model teacher and I need his blessings throughout my lifetime.

Dr. Nagesh Raju. G, former Professor, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar was instrumental in preparing the synopsis and his excellent views and ideas towards guiding students has impressed me in selecting this work.

I express my humble and sincere respect to my co-guide Dr. Shivakumar . V, Professor, Department of Dermatology, Venerology and Leprology, Sri Devaraj Urs Medical College, Tamaka, Kolar who guided me in completing this dissertation. I also thank Dr Ramesh, former senior resident, Department of Dermatology, Venerology and Leprology, Sri Devaraj Urs Medical College, Tamaka, Kolar for his immense help during my study.

I thank Dr. Girish M Bengalorkar, Associate Professor, Department of Pharmacology for guiding me in making the statistical analysis. And not forget Dr. Bhuvana. K, Associate professor, Department of Pharmacology for sparing her valuable time and helping me in bringing out the final version of this dissertation. I also thank Dr Smitha Rai and Dr Meenakshi, Assistant professors in Department of Pharmacology for their encouragement and support.

I thank my colleagues Dr Balamurali K and Dr Vidhyalakshmi C P who were helping me out at every level in completing my dissertation. I also thank Dr Nandish C, Dr Tejashree T, Dr Dharmistha Patel, Dr Dheepan Nayagam B, Dr Chetan Kumar G, Dr Revathi Ramesh, the postgraduate colleagues in the Department of Pharmacology for their valuable feedback and support. And last but not the least I thank all the non teaching staff of Department of Pharmacology for bearing with me and helping out in carrying out this dissertation.

Finally, I thank my beloved parents and sister for their surplus cooperation and encouragement which resulted in shaping this dissertation work. At the end I thank the Almighty for conferring in me the confidence, skill and ability to make this work a success.

Date:

Place: Kolar Dr. HARISH . S

Dedicated

with

Reverence to my parents

LIST OF ABBREVIATIONS

PSORS	-	Psoriasis susceptibility
MHC	-	Major Histocompatibility complex
PASI	-	Psoriasis Area Severity Index
IL	-	Interleukin
CD	-	Cluster differentiation
HLA	-	Human leukocyte histocompatibility antigen
EGF	-	Epidermal growth factor
APC	-	Antigen presenting cells
NAP	-	Neutrophil activating peptide
cAMP	-	Cyclic Adenosine monophosphate
cGMP	-	Cyclic Guanosine monophosphate
NSAIDs	-	Non steroidal anti-inflammatory drugs
COX	-	Cyclo-oxygenase
NAFLD	-	Non-alcoholic fatty liver disease
AIDS	-	Acquired immunodeficiency
HIV	-	Human immunodeficiency virus

Abstract

Background and Objectives :

Psoriasis is a chronic papulosquamous disorder of skin affecting both genders and all age groups. The disease has an impact on social, psychological and economical parameters. Both topical and systemic therapies are available. Systemic drug administration is associated with poor patient compliance as well increased incidence of adverse effects. Topical therapy is the first line of management in mild to moderate psoriasis.

Objectives of this study are :

1. To study the efficacy of calcipotriol and betamethasone in comparison with betamethasone alone in plaque psoriasis.

2. To study the safety of calcipotriol betamethasone combination with betamethasone in plaque psoriasis.

Materials and Methods:

Study was done on in and out patients presenting to the Department of Dermatology, Sri R. L Jalappa Hospital & Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, from January 2011 to April 2012. Sixty six patients with a clinical diagnosis of plaque psoriasis were recruited for the study. They were divided into two groups, group A constituting 32 patients and were treated with topical calcipotriol 0.005% and betamethasone dipropionate 0.05% combination once daily whereas group B had 34 patients treated with betamethasone dipropionate 0.05% twice daily topically. Evaluation of PASI was done at baseline and at week 2, 4, 6, 8,10 and 12 respectively. During each followup visit patients were clinically examined and the corresponding PASI scores were noted. They were also assessed for any adverse reactions.

Interpretation and Results :

By the end of 12 weeks 30 patients in each group completed the study. In both the groups the PASI scores reduced significantly from the baseline. The clinical response as well as reduction of PASI score in patients receiving calcipotriol 0.005% and betamethasone dipropionate 0.05% combination was statistically significant compared to betamethasone dipropionate 0.05% monotherapy. Also in group A none of the patient complained of any adverse event whereas in group B two of them had adverse effects. Calcipotriol 0.005% and betamethasone 0.05% combination is efficacious and well tolerated compared to betamethasone dipropionate 0.05% monotherapy and therefore this combination is effective and safe in mild to moderate psoriasis.

Key points : Psoriasis; Calcipotriol; Betamethasone.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Introduction :

Psoriasis is a chronic autoimmune disease of skin characterised by increased epidermal proliferation, incomplete epidermal differentiation, vascular changes and inflammation. Etiopathology of psoriasis is not fully understood. Recent evidences implicates the immune system and inflammatory mechanisms, in particular T – lymphocytes and inflammatory cytokines in the pathogenesis of psoriasis. Genetic association has been ascribed to PSORS 1 (psoriasis susceptibility-1) through PSORS 9 locus, which is present on chromosome 6 in MHC.[1]

Psoriasis vulgaris is the most common type of Psoriasis and is characterised by well circumscribed red raised scaly plaques. Lesions usually occur symmetrically on knees, elbows, buttocks, scalp and areas subjected to trauma.[2] Psoriasis is not considered a life-threatening disease, but it is well established that those patients may experience a range of psychological difficulties, including elevated levels of anxiety and depression.[3]

Diagnosis of psoriasis is usually done clinically. Psoriasis is usually graded as mild (affecting less than 3% of the body), moderate (affecting 3-10% of the body) or severe (>10% of body). The Psoriasis Area Severity index (PASI) is the most widely used measurement tool for psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).[4]

Topical therapy is the main stay of treatment for mild to moderate psoriasis. Calcipotriol, a synthetic derivative of 1,25, dihydroxyvitamin

D_3 has been used as topical treatment for psoriasis. Vit D receptors are present on keratinocytes and lymphocytes.[4] Acting through these receptors calcipotriol decreases epidermal proliferation, abnormal keratinisation and angiogenesis. It also decreases the levels of IL-1 and IL-6.[5,6]

Betamethasone a synthetic fluorinated topical steroid improves several markers of inflammation (infiltration, erythema, oedema and hyperproliferation) in psoriasis vulgaris without affecting terminal differentiation. They also inhibit production of cytokines (IL-1, IL-2, IL- 8, tumour necrosis factor – α, interferon-γ) reduce mediators of inflammation (prostaglandins, leukotrienes, nitricoxide) decreases the abnormal CD4:CD8 ratio and the number and activity of Langerhans´ cells.[7] Hence the present study is done using combination of calcipotriol and betamethasone and is compared to betamethasone monotherapy.

OBJECTIVES OF THE STUDY

1. To study the efficacy of calcipotriol and betamethasone in comparison with betamethasone alone in plaque psoriasis.

2. To study the safety of calcipotriol betamethasone combination with betamethasone in plaque psoriasis.

REVIEW OF LITERATURE

HISTORICAL BACKGROUND

Psoriasis is a disease that has existed for centuries since the history of man. It is known for its relapsing nature and variable clinical features. The earliest descriptions of psoriasis were given at the beginning of medicine in the corpus Hippocraticum. This work is edited in Alexandria 100 years after the death of Hippocrates who used the term "psora" and "lepra" for condition that can be recognized as psoriasis.[8] The biblical term "lepra" was applied to various cutaneous disorders including psoriasis, vitiligo, eczema, boils and alopecia areata.[9] The term psoriasis was first introduced by Galen (133-200 AD). He described it as an itchy skin disorder characterized by a scaleness of the eyelids and the scrotum.[10] In 1809, Robert Willian was the first to describe psoriasis and its manifestations. He separated the disease into two entities namely discoid "lepra graecorum" and polycyclic confluent "psora leprosa" . In 1841 Ferdinand Von Habra distinguished the clinical picture of psoriasis from that of leprosy. He clarified Willian's confusion about lepra Graecorum and psora leprosa and he separated psoriasis from leprosy.[8] Heinrich Auspitz (1835-1886) introduced the terms acanthosis and parakeratosis. He showed the presence of bleeding points upon removal of scales, a characteristic sign of psoriasis known today as Auspitz sign.[11] In 1876, Heinrich Koebner described Koebner's phenomenon, which is the occurrence of typical psoriatic lesion in area of trauma.[12,13]

DEFINITION:

Psoriasis is an inflammatory disease of the skin characterized by an accelerated rate of epidermal turnover, with hyper proliferation and defective maturation of epidermal keratinocytes. In the majority of cases psoriasis is a chronic disease which, in its most common form – chronic plaque psoriasis manifests itself as well demarcated, often, symmetrically distributed, thickened, red scaly plaques.[14]

EPIDEMIOLOGY

Psoriasis is universal in occurrence. In the United States, psoriasis affects about 2 % of the population, with approximately 150,000 newly diagnosed cases per year.[8] The incidence of the disease is particularly low in Japanese, Native Americans and American blacks especially those of West African origin.[15] Surveys in UK, USA and Scandinavia have reported that psoriasis is affects 1 and 3 percent of the population respectively. Its prevalence varies from 0.3% or less in Mongoloid ethnic group to more than 2% in parts of Scandinavia.[12,16] In India the incidence of patients with psoriasis attending clinics and hospitals varies from 0.8 to 5.6%. [17,18] Parsis have been found to be more susceptible than Hindus and Muslims.[18]

Age of onset of disease has shown a wide range from birth till the age of 108 years.[19] Psoriasis shows bimodal age distribution with one peak incidence at 22.5 years and a second one at around 55.[20] The incidence of psoriasis in adult men and women is usually reported to be equal.[21,22] But in India, ratio of incidence between males to females was found to be 2.4:1 respectively.[23]

ETIOPATHOGENESIS

The exact cause of psoriasis still remains unknown despite intensive clinical investigations. Many theories have been proposed to explain the pathogenesis but none of them are able to explain all the etiopathological factors. The proposed one's are as follows :

Genetic predisposition

Genetic predisposition to psoriasis has shown increased incidence among monozygotic twins.[24,25] The incidence of psoriasis in siblings was 50% when both parents were affected, 16.4% when one parent was affected and 7.8% when neither of the parent were affected.[25]

Human leukocyte histocompatibility antigen (HLA) studies have demonstrated an increased association of HLA-B13, HLA-B17, CW6, BW38, and B27 with psoriasis.[26] The relative risk of developing psoriasis in CW6 – positive persons vary from 4 to 39% .[27]

PATHOGENESIS

I) Epidermal Proliferation

In 1963 Van Scott and Evel were the first to describe the epidermal proliferation in psoriasis. There is shortening of epidermal germinative cell cycle and epidermal turnover time leading to increase in the number of cells in proliferative pool in psoriatic lesions. In these lesions epidermal proliferation and epidermal growth factor (EGF) receptor expression appears to be increased .[28]

II) Immunological Mechanism

Presence of significant number of activated T cells within the epidermis and dermis determines the immunological mechanism in psoriasis .The predominant changes consist of highly increased, persistent keratinocyte proliferation in conjunction with a characteristic inflammatory pattern. [8]

a) T-lymphocytes dependent mechanisms - T-lymphocyte infiltration into skin is an important feature of psoriatic skin lesions and its role in the pathogenesis of psoriasis is remarkable .[29]

b) Antigen presenting cells (APC) - APC's present antigen to T-cells by binding antigen with the antigen-binding pocket of class II major histocompatibility complex (MHC) molecules. They act as initiators in the cascade of events that result in clinical picture of psoriasis .[30]

c) Keratinocytes - Keratinocytes initiate or maintain the immunological processes that are responsible for pathogenesis of psoriasis . The stem cell population that is resting in normal skin is converted to actively cycling cells and thus produces the hyperproliferative epidermis which is characteristic of this disease.[31]

d) Leucocytes attractants - Attractants are chemical substances released locally from leucocytes and attract other inflammatory cells . The presence of dermal and intra-epidermal neutrophil infiltration in psoriastic lesions suggests that one or more neutrophil attractants are released locally. The neutrophil attractants responsible for psoriatic lesion include leukotrienes B4 (LTB4), monohydroxy arachidonic acid metabolites, eicosatetraenoic acid, ether linked phospholipids, platelet activating factor, interleukin 8 or neutrophil activating peptide (NAP) and complement product C_5.[32]

III) Cyclic Nucleotide Regulation In Psoriasis

Regulation of cyclic nucleotides, particularly cyclic adenosine monophosphate (cyclic AMP) is one of the important components of epidermal homeostasis and a factor responsible for the pathogenesis of psoriasis. Cell proliferation is stimulated either by a fall in cAMP or by an increase in cGMP.[33]

FACTORS INFLUENCING PSORIASIS

Several factors responsible for provoking a new episode of psoriasis or exacerbating pre-existing disease have been identified.[12] The following factors have been identified to precipitate psoriasis :

a) Infection

About 56 to 85 percent of children with acute guttate psoriasis have immediate precedent evidence of streptococcal disease like upper respiratory tract infection. An abnormal group A streptococcal infection may play an important role in exacerbation of psoriasis.[34] The organisms which were identified in case of relapse of chronic plaque psoriasis are S. haemolyticus group A , S. haemolyticus group D, Haemophylus influenzae, M. catarrhalis and C. albicans. Thus in patients with a severe relapse of chronic plaque psoriasis microbial infections should be searched for and, if possible, eliminated.[35]

b) Trauma

Psoriatic lesions may occur at the sites of injury to the skin as " Koebner phenomenon" . Injury may be in the form of physical, chemical, or ultraviolet damage to the epidermis ,thus koebner phenomenon is elicited at sites of sunburn, operation wounds, vaccination, bites (insects, animal) drug reactions, dermatitis, lichen planus, miliaria, vitiligo and herpes zoster.[36] Many theories have been proposed to explain trauma induced keratinocytes proliferation. One of the theories is there is increased release of cytokines from the damaged keratinocytes and these cytokines in turn activate T lymphocytes to produce more cytokines that may amplify inflammation and cause further increase in T-cell and keratinocyte proliferation. A second immunologically based theory is that epidermal Langerhans' cells interact with helper T lymphocytes resulting in the release of cytokines that then activate keratinocytes. Yet another theory proposes that killer T lymphocytes inappropriately attack keratinocytes triggering the effects seen in Koebner's phenomenon. Probably none of these mechanisms is solely involved in psoriasis as several mechanisms may be operating concurrently in the same patient.[37]

c) Endocrine factors

Psoriasis peaks at puberty and at the menopause. Remission of psoriasis may occur during pregnancy but there is exacerbation during the postpartum period.[38] Increased levels of oestrogen relative to progesterone correlate well with psoriatic improvement. Thus it is speculated that low levels of estrogens could be an aetiological factor for the development of psoriasis.[39] Hypocalcemia following accidental parathyroidectomy and dialysis have known to precipitate psoriasis.[40]

d) Psychogenic factor

Psoriasis is one of the most 'stress sensitive' skin diseases . Many stressful events of daily life may exacerbate psoriasis. The disease itself can cause a reactive depression , which could further exacerbate psoriasis.[41] Psoriasis patients commonly report a significant decrease in quality-of-life, and a range of negative psychosocial problems including suicidal thoughts, increased perceived stress levels, social stigmatization, and employment problems.[42]

e) Seasonal variation

Worsening of skin lesions during winter is experienced by many patients. This is attributed to xerosis associated with low humidity in winter months.[43]

f) Alcohol and smoking

The risk for psoriasis is higher in smokers than in patients who never smoked. Cigarette smoke contains more than 4000 toxic as well as non- toxic substances and the adverse effects caused by smoke is due to oxidative damage. High levels of arachidonic acid have been found in psoriatic lesions and smoke causes peroxidation of arachidonic acid which leads to formation of F_2- isoprostanes which plays an important role in oxidative injury. Nicotinic cholinergic receptors are present on keratinocytes, stimulation of which causes calcium influx and increases keratinocyte proliferation. Heavy alcohol consumption may increase the risk for infection or mechanical trauma that in turn may affect psoriasis. Moreover, an effect of alcohol in lymphocyte transformation has been suggested.[44]

g) Acquired immunodeficiency syndrome (AIDS)

Infection with HIV type I may present with two distinct clinical patterns. One is localized, showing either guttate or large plaques. The other is diffuse psoriasiform dermatitis, associated with palmoplantar keratoderma. Presence of HIV in skin leads to immune reaction and release of epidermal growth factor which causes epithelial proliferation and consequently psoriasis. HIV also induces changes in the vascular endothelium and these changes are similar to those occurring in psoriasis during its initial course of development. [45]

h) Drugs

Drug induced or drug exacerbation of psoriasis include administration of lithium, β -adrenergic blocking agents such as propranolol, bisoprolol, metaprolol and oxprenolol.[46] Beta-blockers reduce cyclic AMP level in psoriatic epidermis there by exacerbating psoriasis.[47,48] Rapid withdrawal of corticosteroid therapy in patients with psoriasis may result in precipitation of generalized pustular psoriasis.[46]

NSAIDs like phenylbutazone , oxyphenbutazone, indomethacin and diclofenac were reported to exacerbate psoriasis. NSAIDs inhibit the metabolism of arachidonic acid by the cyclo-oxygenase (COX) pathway leading to accumulation of leukotrienes, which has been postulated to aggravate psoriasis.[47] Other drugs that exacerbate psoriasis are clonidine, potassium iodide, amiodarone, digoxin, trazodone, gemfibrozil, penicillin, and terfenadine.[48]

CLINICAL FEATURES

Clinical classification of psoriasis:[41]

1) Chronic plaque psoriasis
2) Guttate psoriasis
3) Follicular psoriasis
4) Exfoliative psoriasis
5) Pustular psoriasis
6) Mucous membrane psoriasis
7) Psoriasis unguis
8) Arthropathic psoriasis
9) Regional variations in psoriasis: scalp, face, eyes, palms and soles, napkin area.

MORPHOLOGY OF PSORIATIC LESION

Psoriasis is characterized by the development of erythematous, well-defined, dry, scaly papules and plaques from pinhead to palm sized or larger. The scales are abundant, loose, dry and silvery white.[41] "Woronoff's ring" - A zone of hypo pigmentation may be seen around the plaque after treatment with ultraviolet radiation or topical corticosteroids.[48]

When the scales are completely scrapped off, the basement membrane is exposed and is seen as a moist red surface (membrane of Bulkeley), through which dilated capillaries are seen as red spots. On further scraping capillaries at the tip of the elongated papillae are torn leading to multiple bleeding points, known as Auspitz sign.[12] Each psoriatic lesion starts as a papule and extends peripherally to form nummular or discoid plaque. Many discoid lesions coalesce to form large plaque. The

plaque extends peripherally; the central part undergoes clearing forming annular lesions. Many incomplete annular lesions join to form gyrate lesions.[41]

CLINICAL VARIANTS

1) Chronic plaque psoriasis

This is the most frequent clinical pattern.[8] It manifests as coin-shaped to large palm-sized well-distributed erythematosquamous plaques distributed bilaterally. If palm sized lesion predominates, it is known as psoriasis geographica, where as if coin sized lesions predominate, it is called nummular psoriasis. Lesions initially appear as papules and eventually coalesce to form plaques. Plaques are well demarcated and covered by a silvery scale. Plaques exhibit the Auspitz sign (bleeding after the removal of scale) and the Koebner phenomenon (lesions induced by trauma).[50] The lesions are stable and remain unchanged for a longer period than in guttate psoriasis. The extensor surface of the body, the elbow and knees, lumbosacral area and back is commonly involved.[41]

2) Guttate psoriasis

This is seen in children and young adults following streptococcal infection. Pinhead, raindrop like erythematous papules erupt abruptly, distributed over the trunk and proximal part of limb. Lesions size varies from 2 or 3 mm to 1cm in diameter, round or oval. The prognosis is good.[41]

3) Follicular psoriasis

This is a morphologic variant with follicle-oriented papules. Two clinical forms are described, an adult type, seen in females where follicular lesions occur on the thigh. In Childhood type, follicular lesions are seen over the trunk, extends to form isolated plaques.[51]

4) Exfoliative psoriasis (Psoriatic erythroderma)

It is a generalized form of the disease and is characterized by universal erythema and scaling. Two forms exist, in one form the chronic lesions may evolve gradually into an exfoliative phase or may occur as an initial manifestation of the disease. The second form is part of spectrum of "unstable" psoriasis seen in Arthropathic psoriasis. Pustular psoriasis may revert to erythrodermic state. It can be precipitated by infection, hypocalcemia, antimalarials, tars and corticosteroids.[41]

5) Pustular psoriasis

Neutrophilic accumulation in the epidermis is a characteristic histological feature of all types and patterns of psoriasis, but in clinical practice the term 'pustular psoriasis' is reserved for those forms of the disease in which macroscopic pustular lesions appear.[13] A convenient classification is localized pustular psoriasis (chronic palmoplantar, acrodermatitis continua) and generalized pustular psoriasis (acute, infantile, circinate).

6) Mucous membrane in psoriasis

Mucosal lesions are involved in pustular and exfoliative forms.[52] Various lesions have been described including grey, yellow, white or translucent plaques or annular forms, diffuse areas of erythema and the geographic tongue. About 2% of psoriasis has a lesion on the glans penis, usually a solitary patch.[53]

7) Psoriasis unguis

Nail changes are present in 25-50% of cases. The common changes include pitting of the nail plate, onycholysis, subungal hyperkeratosis, crumbling of nail plate, grooves and ridges on the nail plate, yellowish discolouration and splinter haemorrhage. Pits, ridges and grooves are due to psoriasis of nail matrix, where as onycholysis, subungal hyperkeratosis and splinter hemorrhages are attributable to disease of the nail bed or hyponychium.[54] Circular areas of discolouration of the nail bed and hyponychium may resemble an "oil drop" below the nail. Histologically these are areas of psoriatic changes in hyponychium.[55]

8) Arthropathic psoriasis

Psoriatic arthritis is an inflammatory arthritis associated with psoriasis with a negative test for rheumatoid factor. Incidence is 5-10% of patients. HLA studies showed that B27, DR4, A26 and B38 haplotypes are associated with psoriatic arthritis. Psoriatic arthritis is common in the age group of 30 to 55 years. Five clinical patterns are – (i) Classic psoriatic arthritis (ii) Rheumatoid type of psoriatic arthritis, (iii) Arthritis mutilans, (iv) oligoarticular arthritis and (v) Psoriatic spondylitis.[56]

9) Regional variation in psoriasis

a) **Scalp:** The well defined nature of the plaques of psoriasis is retained on the scalp in most cases, but diffuse involvement may occur if there is associated seborrhoeic dermatitis . Often a band of corona of psoriasis, 2-5cm wide projects beyond the hairline on the forehead called 'corona psoriatica' .[41]

b) **Face:** The face is rarely involved in psoriasis, usually in children or when the disease becomes erythrodermic. Facial lesions are less thick and scaly but more erythematous than those elsewhere.[41]

c) **Eyes:** These include blepharitis, conjunctivitis, keratitis, xerophthalmia and symblepharon.

d) **Palms and soles:** Lesions on the palms and soles are well defined scaly and surface shows fissures. A sharply defined edge at the wrist or forearm and absence of vesiculation help to distinguish from eczema of hands. There may be relationship to trauma or occupational irritants.[13]

e) **Napkin area:** In infants and children, psoriatic lesions are sometimes localized to the napkin area. The exact cause for such localization is not known. About 17% of such children develop typical psoriasis in later life.[41]

COMPLICATIONS OF PSORIASIS

1) Infection

Staphylococcus aureus was the commonest organism causing secondary infections of skin lesions this was attributed to the antiphagocytic effect of protein A released from this organism.[57] Guttate psoriasis in children is mostly

complicated by S. pyogenes superantigen. Isolation of opportunistic pathogens from psoriatic lesions like non anthrax type Bacillus species and Staphylococcus epidermidis was thought to reduce local defense factors in the lesion due to local and systemic immunosuppressant drugs like cytotoxic drugs and corticosteroids used for the treatment of psoriasis. Anaerobic bacteria were also isolated from few cases . The recovery of multiple organisms from psoriatic lesions of patients illustrated the polymicrobial nature of secondarily infected psoriasis .[58]

2) Exfoliative dermatitis

Psoriasis is the most common cause of exfoliative dermatitis amongst the dermatologic disorders. However in children it is the second most common cause of the disease.[59] It usually develops gradually or acutely during the course of chronic psoriasis. The mean age of patients at the onset of erythroderma is 48-55 years, and males outnumber females.[60]

3) Hepatic failure:

Abnormalities of liver function occur in erythrodermic or pustular psoriasis and are likely related to drugs, alcohol intake and oligaemia.[19] Non-alcoholic fatty liver disease (NAFLD) is frequent in patients with chronic plaque psoriasis affecting up to nearly half of these patients and is strongly associated with psoriasis severity. So, early recognition of NAFLD by radiological imaging tests in this group of patients is adviced . [61]

4) Nephritis and renal failure:

Mesangioproliferative glomerulonephritis, AA amyloidosis and membranous nephropathy are described in association with psoriasis. Glomerulonephritis in psoriasis is mainly of a mesangioproliferative type with fixation of IgA and C3 on the mesangium and basal membranes of glomerular capillaries. Amyloid nephropathy in psoriasis has all the morphological features of acquired amyloidosis.[62] The exact relationship of psoriasis and nephropathy remains unclear, but an autoimmune mechanism most likely links the two. Renal failure occurs either due to acute tubular necrosis or from oligaemia, after loss of albumin from the skin in acute pustular psoriasis.[63]

5) Amyloidosis:

It is a rare sequel of arthropathic and generalized pustular psoriasis. It is an additional cause of renal failure with psoriasis and may follow an aggressive course.[64] Generalized pustular psoriasis may predispose to the development of secondary amyloidosis, either by prolonged stimulation of the reticuloendothelial system or through abnormal immunoglobulin synthesis. [65]

MANAGEMENT

Management of a patient with psoriasis is a challenging task to the clinician. The patients should be explained that psoriasis is not a contagious disease and there is less likelihood that the patients general health will be affected. Reassurance and emotional support are valuable, stressing the benign nature of disease, possibility of spontaneous remission and the availability of a wide range of therapeutic options for all psoriatic patients. Various forms of treatment have been developed in the past several decades. They have mostly been developed empirically, and since the exact aetiology is not known new regimens are being tried constantly.[1]

GENERAL AND NON-SPECIFIC MEASURES

Attention should be given to the patient's general, physical and psychological health. A weight reduction is helpful in the management of flexural psoriasis in over weight patients and patients should be advised to have a balanced diet, to avoid excessive weight gain.[8]

Excessive scratching and sun or UVL exposure should be avoided to prevent Koebner phenomenon. In palmar psoriasis, occupation and hobbies have to be investigated to expose a source of local trauma to the volar skin.[8]

Pharmacological approach

Topical therapy

1) Keratolytics

Keratolytics remove the excessive abnormal scale formed in psoriasis and other diseases. Salicylic acid probably dissolves the intercellular cement

substance of the keratocytes. Salicylic acid 2-10% ointment is used as monotherapy.[66] In concentrations of 5 to 10 % it is compounded either with petrolatum or acid mantle cream or topical corticosteroid which can be used twice daily for several weeks on thick keratotic plaques. 20 % salicylic acid can be applied for about two weeks to remove the thick scale so as to enable other topical therapies to penetrate the skin.[67]

Systemic absorption of salicylic acid can lead to "salicylism" especially in children when applied over a large surface area . Other topical agents having possible keratolytic effect are α-hydroxy acids such as lactic acid, tartaric acid, pyrumic acid, glycolic acid and urea containing preparation.[66]

2) Emollients and moisturizers

Mineral oils are the most frequently used emollients and other agents are urea, glycerine, petrolatum and lanolin.[67] These products are usually bath oils, soap substitutes, and skin creams and act by producing an occlusive film that limits evaporation of water from the skin and allowing the stratum corneum to rehydrate itself. These products will moisturize, lubricate, and soothe the dry and flaky skin. They are particularly valuable in dry skin and skin dryness aggravated by frequent bathing and sun exposure. With increased hydration, the stratum corneum swells and assumes a more normalized flat contour as well scaling is decreased. These products are often used as pre-treatment measures for psoriatic plaques. They can be applied all over the exterior surface of the body three times a day. Two adverse effects seen with these products are contact dermatitis and folliculitis.[66]

4) Coal tar therapy

Coal tar contains 48% hydrocarbon, 42% carbon and 10% water.[68] Goeckerman popularized its use in treatment of psoriasis in 1931. The exact mechanism of action of this agent in psoriasis is not known, but it is found to depress DNA synthesis.

Goeckerman used coal tar ointment containing 1-5% crude tar, zinc oxide and petroleum. After its application the ointment was allowed to stay for 24 hours, the patients were exposed to an air - cooled quartz lamp (phototherapy), in order to produce tanning. This was followed by bathing with soap and water. Many modifications have been done in the above treatment, which includes a series of progressive stronger ultraviolet –B (UVB) treatment along with the local application of tars to sensitize the psoriatic skin to the ultraviolet radiation.[8] Folliculitis is the commonest side effect with this regimen and is also known to cause skin cancer and stain clothes.[66]

5) Dithranol (Anthralin)

Dithranol is 1,8 – dihydroxy – 9 - anthrone, also known as cignolin. After a coal tar therapy, scales and the previous topical applications are removed, suberythema UVB is given and the lesions are covered with dithranol paste in the concentration of 0.05% to 0.1% increasing upto 0.25% or 0.5% according to response avoiding irritation to normal skin. [69] Dithranol inhibits DNA synthesis in epidermal cells. It also binds to mitochondrial DNA and inhibits various enzymes.[70] The reactive oxygen species (ROS) produced by anthralin is responsible for the antipsoriatic and proinflammatory effects elicited by dithranol.ROS is responsible for activation of c-junc-N-terminal (JNK)cascade. JNK cascade is responsible for regulation of proliferation and apoptosis of epidermal cells. [71]

Most common side effects are irritation of skin and staining of clothes, skin and furniture. It is highly irritable if introduced into the eyes. Allergic contact dermatitis is extremely rare but has been reported.[72] Attempts to reduce these side effects include a short-contact regimen (topical therapy applied to skin daily for a period of 5 to 30 minutes then washed off) , heat-sensitive preparations, and use of triethanolamine to prevent staining. However these variations have not reduced the effectiveness of the treatment.[73]

6) Capsaicin

In a study capsaicin 0.025% was applied topically four times a day for 6 weeks in patients with pruritic psoriasis, these patients showed significant improvement in the global evaluation and pruritus. [74]

7) Corticosteroids

Topical corticosteroids are of established value in psoriasis. They remain the mainstay of treatment for psoriasis despite introduction of newer, nonsteroidal agents.[75]

MECHANISM OF ACTION OF CORTICOSTEROIDES

Corticosteroids effects involve interactions with intracellular receptors that belong to super family of receptors that control gene transcription. Corticosteroids after entering the cells bind to specific receptors in the cytoplasm which are found in virtually all tissues. After interaction with the steroid receptor they get activated by undergoing conformational change which exposes a DNA-binding domine. The steroid-receptor complexes form dimers, then move to the nucleus and bind to steroid -response elements in the DNA. This results in either repression (prevent transcription) or induction(initiate transcription) of particular gene. Repression is

brought about in part by inhibition of the action of various transcription factors such as AP -1 and NF-KB. These transcription factors normally switch on the genes for COX-2, various proinflammatory cytokines and the inducible form of nitric oxide synthase These transcription factors also have broad actions on the regulation of growth factors. Thus it mediates greatly antiinflammatory, immunosuppressive and anti-growth effects of glucocorticoids.

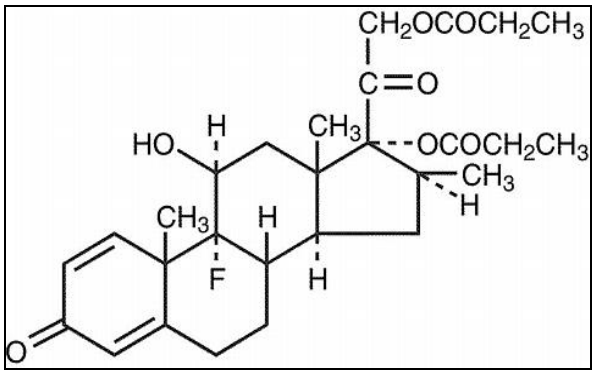
Induction involves the formation of specific messenger RNAs, which direct the synthesis of specific proteins e.g. the cyclic AMP-dependent kinase. The inflammation, which is mediated by a complex series of interactions with cell adhesion molecules, particularly those on endothelial cells, is inhibited by glucocorticoids.[76]

Glucocorticoids also inhibit the functions of tissue macrophages and other antigen presenting cells thereby limit their ability to phagocytose and kill microorganisms as well limit their ability to produce TNF-α(tumor necrosis factor-α), IL-1 (interleukine-1), metalloprotienases and plasminogen activator. They also decrease the inflammatory responses by reducing the prostaglandins, leukotrienes, (IL-1 to IL-6) and platelet activating factor synthesis that result from activation of phospholipase A2.[77]

The mechanisms by which topical steroids are believed to act in psoriasis are – 1) Vasoconstriction- leading to reduced erythema, 2) Slowing cellular proliferation- decreased cell turnover and 3) Anti- inflammatory action - inhibiting phospholipase A_2 and thus inhibits arachidonic acid pathway.

In this study betamethasone dipropionate is used and hence details regarding its topical use is being mentioned

Structure of betamethasone dipropionate



PHARAMCOKINETICS

The mean maximal uptake of betamethasone dipropionate 0.05% cream into the stratum corneum was linear over a treatment duration of up to 2 h in six healthy volunteers. No further significant increase occurred beyond this time although mean maximal uptake was at 6 h. A second dose-response assessment using different drug concentrations found that increasing the concentration of topical preparation of betamethasone dipropionate from 0.02 to 0.05% significantly increased the maximum concentration in the stratum corneum from 0.05 to 0.17 μg/cm^2 . Uptake did not increase further at the highest tested concentration of 0.063%. No significant change in maximal uptake resulted from increased film thickness or surface area.[78]

Potency rating of topical steroides

The preferred way to determine the potency of topical steroids is the vasoconstrictor assay- which classifies steroids based on their ability to cause cutaneous vasoconstriction ("blanching effect") in healthy persons. This is a useful but imperfect method for predicting the clinical effectiveness of steroids. A ranking system that compares clinical outcomes or an effectiveness-to-safety ratio may be of greater benefit, but does not currently exist.[79]

A simplified classification of topical steroids based on their clinical efficacy is given below. They have been classified into seven groups ranging from ultra high potency (group I) to low potency (group VII).[80]

Potency (group)	**Medication**
Ultra high (I)	Clobetasol propionate 0.05% Diflorasone diacetate 0.05% Halobetasol propionate 0.05%
High (II)	Betamethasone dipropionate 0.05% Fluocinonide 0.05% Halcinonide 0.1%
Medium to high (III)	Fluticasone propionate 0.005% Triamcinolone acetonide 0.5%
Medium (IV and V)	Desoximetasone 0.05% Fluocinolone acetonide 0.025% Hydrocortisone butyrate 0.1% Hydrocortisone probutate 0.1%

	Hydrocortisone valerate 0.2% Mometasone furoate 0.1%
Low (VI)	Alclometasone dipropionate 0.05% Desonide 0.05%
Least potent (VII)	Hydrocortisone 1%, 2.5%

Side effects

Side effects of topical corticosteroids, include cutaneous atrophy, development of striae, formation of telangiectasia, and a host of other local cutaneous effects such as the formation of an acneiform eruption known as perioral dermatitis on the face. Hypothalamic–pituitary–adrenal (HPA) axis suppression can occur with prolonged use of excessive quantities of topical corticosteroids, particularly if they are occluded or if superpotent corticosteroids are used continuously over large areas of the body.

One of the most troubling features of topical corticosteroid is that patients develop tachyphylaxis, a phenomenon whereby medications that are highly effective initially, lose efficacy with prolonged use. To avoid tachyphylaxis and the other side effects of topical corticosteroids, regimens have been developed in which superpotent corticosteroids are applied twice daily for two weeks, after which they are applied on weekends only. Strong topical corticosteroids should also be avoided on the face and intertriginous sites, areas that are more prone to steroid side effects. The quantity of strong topical corticosteroids applied should be limited to 50 or 60 g per week, and

occlusion should be avoided except on the scalp, palms, and soles. Strong corticosteroids should be avoided or used cautiously in children.[81]

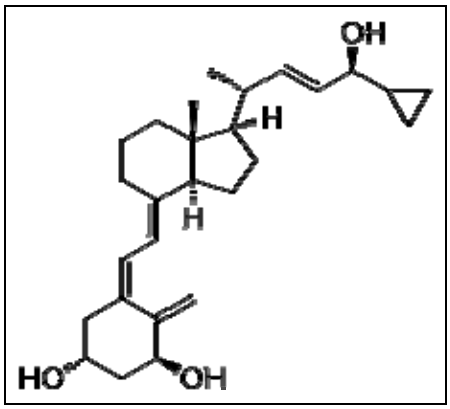
Combination therapy of steroid with other antipsoriatic drugs are found to be efficacious than monotherapy. A combination of topical clobetasol propionate, dithranol and UVB is superior to UVB and dithranol alone in clearing psoriasis.[82] Other drugs used in combination with topical steroids include oral and topical retinoids, psoralens, and cyclosporine.

8) VITAMIN D3 ANALOGUES

Topical vitamin D_3 analogues have become an effective and safe treatment options for the treatment of psoriasis. Studies with topical vitamin D_3 analogues have demonstrated efficacy with both monotherapy and combination therapy, with the latter approach found to be more applicable in the clinical setting. Topical vitamin D3 was approved by U.S. Food and Drug Administration (FDA) for treatment of plaque psoriasis in 1994. Calcipotriol, calcitriol and tacalcitol are the most recent of this class of agents.[83] Calcitriol is a natural topical vitamin D3 analogue with both short- and long-term studies demonstrating its efficacy and safety. Tacalcitol is indicated in vitiligo as well.

Calcipotriol, a synthetic derivative of 1, 25, dihydroxy vitamin D_3 is used as topical treatment for psoriasis. It has antiproliferative, anti-inflammatory and immunomodulatory effects and is preferred over calcitriol for topical application because of lower incidence of hypocalcaemia and it is rapidly metabolised in the skin.[84]

Structure of calcipotriol [85]



Mechanism of action

Calcipotriol binds to the Vitamin D Receptors (VDR) which are mainly present in the nucleus of target cells and acts as a heterodimer with the retinoid X receptor (RXR). It induces terminal differentiation and inhibit epidermal proliferation as well angiogenesis seen in psoriasis. It also induces apoptosis in inflammatory cells and causes a shift from Th1 cytokines to Th2 cytokines. By decreasing the levels of interleukin-1 (IL-1) and IL-6 and by reducing the CD45 RO and CD8+ T cells it modulates inflammatory process in psoriasis. Moreover, it increases the levels of transforming growth factor-β1 (TGF-β1) and β2, which inhibit the epithelial cell growth. It changes antimicrobial peptide (AMP)-cathelicidin expression in the keratinocytes of psoriatic lesions, which is produced in macrophages triggered by bacterial, viral, and fungal infections. AMPs act as proinflammatory mediators and play a role in the pathogenesis of psoriasis thus, targeting their expression might be beneficial in treatment of this disease. [85]

Pharmacokinetics

When applied topically the absorption rate of calcipotriol varies from 1-6% . But this absorption rate is different for different anatomical sites and this rate is least when applied at the back. The absorption estimate was based on radioactivity recovery and on the radioactivity of its metabolite. The rapid clearance of calcipotriol may be a result of extensive hepatic metabolism to its metabolites (MC 1046 and MC 1080), which have reduced pharmacological activity.[86]

In vitro experiments have shown that calcipotriol is metabolised by a variety of cells, including human keratinocyte to less active metabolites. Thus, calcipotriol when applied topically is probably subjected to local metabolism which may explain its negligible effects on calcium homeostasis. It has also been suggested that calcipotriol is initially metabolised by non-specific enzymes including 24-oxidoreductase and 22,23 - reductase and later the subsequent steps of 23-hydroxylation and side chain cleavage occurs.[87]

Dosage and precautions

In psoriasis vulgaris, calcipotriol ointment 50 μg /g (no more than 100 g per week) should be applied to affected areas (≤30% of the body surface) twice daily for a period of 4 weeks, after that it can be applied once daily. Calcipotriol/betamethasone dipropionate (calcipotriol 50 μg/g and betamethasone 0.5 mg/g) is a fixed-dose combination available in both ointment as well as gel form and can be applied once a day.[85] Because of the risk of facial dermatitis, calcipotriol should not be applied to the face, and patients should wash their hands thoroughly after ointment application to prevent unwanted transfer from hands to face.

Side effects

Skin irritation is the most common side effect seen with calcipotriol therapy. Hypercalcemia can occur rarely, especially if a maximum dose of 100-120 gm/week is exceeded. Other minor adverse reactions include mild to moderate erythema, xerosis, itching, local irritation, contact dermatitis, perioral dermatitis and photosensitivity.[88]

Contraindications

Calcipotriol is contraindicated in hypercalcemia, hypercalciuria, urolithiasis, parathyroid disease, disorders of calcium metabolism, lactation and concomitant use of vitamin D or calcium or any other drug that can affect calcium homeostasis. It is also contraindicated in patients who are allergic to calcipotriol or other calcium preparations as well in pregnancy.[88]

SYSTEMIC THERAPY

METHOTREXATE

In 1951, Guber and co-workers used the first systemic folic acid antagonist aminopterin and is presently replaced by a stable analogue methotrexate for the treatment of psoriasis. Methotrexate (4 - amino - 10 - methyl pteroyl glutamic acid, MTX) was introduced several decades ago for the treatment of psoriasis and is still one of the most effective therapies.[89]

Mechanism of Action

Methotrexate is a synthetic analogue of folic acid thus binds extracellularly to dihydrofolate reductase and prevents conversion of dihydrofolate to tetrahydrofolate. Tetrahydrofolate is a co – factor required for normal functioning of

thymidilate synthetase which helps in purine synthesis. Thus methotrexate inhibits DNA synthesis and to a lesser extent RNA synthesis. It targets, therefore cells in the S-phase of the cell cycle. Kinetic studies in psoriasis indicated that more keratinocytes are in the S-phase than in normal skin and since this process can be reversed by methotrexate, epidermal proliferation is normalized in psoriasis. Methotrexate is indicated in disease not responsive to other regimens such as systemic administration of retinoids or PUVA , especially in patients with associated arthropathy. Contraindications are significant abnormalities of the liver or renal function, severe anemia, leukopenia or thrombocytopenia, gastritis , active infectious diseases and excessive alcohol consumption.[90]

Dosage and schedule of administration

There are two most popular schedules of methotrexate therapy.[91]

(i) A single oral dose of 25 to 35 mg of methotrexate given once a week or 25 - 35 mg methotrexate given as intramuscular injection once in a week.

(ii) 5-7.5 mg given at 12h intervals for three doses per week.

The incidence of hepatic damage is less if the total cumulative dose is less than 1.5-2 g.

Side effects

Mild side effects of nausea, anorexia and fatigue can be seen immediately after methotrexate therapy. Toxic effects on bone marrow include leucopenia, thrombocytopenia and rarely anemia. Drug induced hepatic fibrosis and cirrhosis also has been noted.

Contraindications

These include pregnancy or those who desire to get pregnant, moderate to severe renal or hepatic compromise, blood dyscrasia and acute peptic ulcer.

PHOTOCHEMOTHERAPY

Types of phototherapy –

a) Broad-band UVB irradiation (290-320) : For choosing the initial UVB dose the patient's minimal erythema dose (MED) has to be determined.MED is defined as the lowest UVB dose that causes uniform erythema with distinct borders 24 h after exposure. Eruptive types of psoriasis respond more rapidly to broad-band UVB irradiation as compared to chronic plaque-type psoriasis. As a rule, nearly 20-35 sessions are required to clear psoriasis.

b) Narrow-band UVB therapy(311-313 nm): Narrow-band UV phototherapy has been shown to be superior to conventional broad-band UVB with respect to clearing and remission times . Narrow-band UVB has been used successfully in several combination regimens, such as with dithranol , vitamin D derivatives or tazarotene .

c) PUVA photochemotherapy: PUVA is the combination of oral psoralens with subsequent irradiation with long-wave UV (UVA). In the presence of UVA psoralens crosslink the cellular DNA , and generate reactive oxygen species inducing cell damage. Different psoralens are used: 8-methoxypsoralen (8 - M O P) , 5 - methoxypsoralen (5-MOP), and 4,5,8-trimethylpsoralen (TMP).

Dose: The most commonly employed dose is 8-MOP 0.6 mg/kg body weight, on alternate days followed by 2 hours later by exposure to UV rays.

Side effects:

Acute side effects include nausea, lethargy, headache, hypertrichosis of face, phototoxic reactions, pruritus and reactivation of lupus erythematosis.

Long-term effects include ophthalmologic effects such as dense central corneal opacification, immunologic changes and neoplastic changes like squamous cell carcinoma.

RETINOIDS

Retinoid acid, also known as tretinoin or all- transretinoic acid, is the acid form of vitamin A. The action of vitamin A analogues is exerted through hormone like receptors in both cytoplasm and nucleus.

Retinoic acid receptor effect

The biology associated with retinoids is very complex. A major factor contributing to this complexity is the multiplicity of retinoid receptors. Two families of retinoid nuclear receptors have been identified, retinoid acid receptors (RARs) and retinoid X receptors (RXRs) each of which include three subtypes (α,β,δ) encoded by distinct genes.[92]

Mechanism of action

Activated retinoid receptor complex can regulate transcription of genes in two distinct ways. It can bind directly to promoter regions of specific genes and directly regulate gene transcription. It is generally believed that most of the differentiation inducing actions of retinoids is associated with this type of mechanism. Alternatively, the activated retinoid receptor complex can block the transcriptional effects of other nuclear transcription factors such as AP-1. AP-1 is an oncogenic protein, which is highly over expressive in a variety of hyperproliferative and inflammatory conditions. It is believed that primarily this type of general mechanism mediates the antiproliferative and anti- inflammatory activities of retinoids.

CLASSIFICATION OF RETINOL:

The retinoids depending on the aromatized α -ionic ring in the chemical structure are divided into three generations.

First generation non-aromatic retinol. e.g. Tretinoin, Isotretinoin.
Second-generation mono-aromatic retinol. e.g. Etretinate, Acitretin.
Third generation polyaromatic retinol. e.g.: Arytenoids, Adapalene, and Tazarotene.

Materials And Methods

This study was conducted by departments of Pharmacology and Dermatology at Sri R. L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka Kolar. Duration of the study was from January 2011 to April 2012. The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from all the patients willing to participate in the study. Sixty six patients who were clinically diagnosed as plaque psoriasis were recruited and randomly divided into two groups. It was a open label study.

Inclusion criteria

- Patients of both gender aged between 18-70 years
- Those with mild to moderate plaque psoriasis (<10% of body involvement)

Exclusion criteria

- Patients with severe psoriasis, scalp psoriasis and pustular psoriasis
- Patients receiving antipsoriatic drugs (vitamin D_3 analogues, corticosteroids, coal tar, anthralin, photochemotherapy, immunosuppressants)
- Who had received calcium/vit D_3 analogues in the past 2 months before recruiting to the study
- Patients with severe illnesses involving heart, liver, kidney and lung
- Pregnant and lactating women
- Patients with history of allergy to calcium and vit D analogues

During first visit name, age, gender, occupation and full address were recorded. A detailed history of psoriasis like age on onset, duration of illness, site of onset, seasonal variations, aggravating factors, family history, past modality of treatment of psoriasis and other associated systemic diseases were recorded. Sixty six patients were recruited for the study out of which thirty two patients were assigned to group A and thirty four patients to group B .

Group A -----Received combination of calcipotriol (0.005%) and betamethasone ointment (0.05%) once daily as topical therapy.

Group B ----- Received betamethasone ointment (0.05%) alone twice daily as topical therapy.

Evaluation was carried out at baseline and every 2 weeks for 12 weeks. During each visit patients were examined and PASI score was done and were assessed for any adverse reactions.

Psoriasis Area And Severity Index (PASI)

The assessment of the effectiveness of new treatment for psoriasis is limited by the lack of any objective measure to determine the disease severity. Though PASI has a limitation of entirely being objective method of assessment it remains the gold standard to measure psoriasis severity .The PASI score is calculated as follows –

$$\mathbf{PASI = 0.1 (E_H + S_H + I_H)A_H + 0.2 (E_U + S_U + I_U) A_U + 0.3 (E_T + S_T + I_T) A_T + 0.4 (E_L + S_L + I_L) A_L}$$

Where,

E = Erythema or redness

S = Scaling

I = Induration

A = Area of involvement

H = Head

U = Upper limb

T = Trunk

L = Lower limb

Area of extent of lesion is classified on a 7-point scale as

0 – No involvement

1 – Less than 10%

2 – 10-29%

3 – 30-49%

4 – 50-69%

5 – 70-89%

6 – 90-100%

The severity of lesions (erythema, scaling, induration) are classified on a 5-point scale-

0 – Complete lack of involvement

1 – Mild involvement

2 – Moderate involvement

3 – Severe involvement

4 – Severest possible involvement

STATISTICAL ANALYSIS

Descriptive data were expressed as mean ± standard deviation. Continuous data post treatment changes compared to baseline was analyzed by paired Student t-test and between groups by unpaired t-test. For PASI score, non-parametric test (Wilcoxon rank score test, Mann-Whitney test) were used.

Wilcoxon Signed Ranks Test was used to compare the PASI scores between baseline and their respective follow up weeks. Mann-Whitney U test was the statistical method used to compare the mean PASI scores between the groups at their respective follow up weeks. Categorical data was analyzed by Chi-square test. p-value of 0.05 or less was considered statistically significant.

Taking into consideration a power of 85%, an α error of 5%, and to detect a difference of 0.5 in the PASI score considering a drop rate of 10%, the sample size was calculated to be 32 per group.

Results

Sixty six patients who satisfied the inclusion criteria were recruited and divided into Group A (n=32) which received combination of calcipotriol (0.005%) and betamethasone ointment (0.05%) once daily and Group B (n=34) betamethasone ointment (0.05%) alone twice daily. Both medications were applied topically. Thirty patients in each group completed the study. Two patients in group A and four in group B were lost to follow up and did not complete the study.

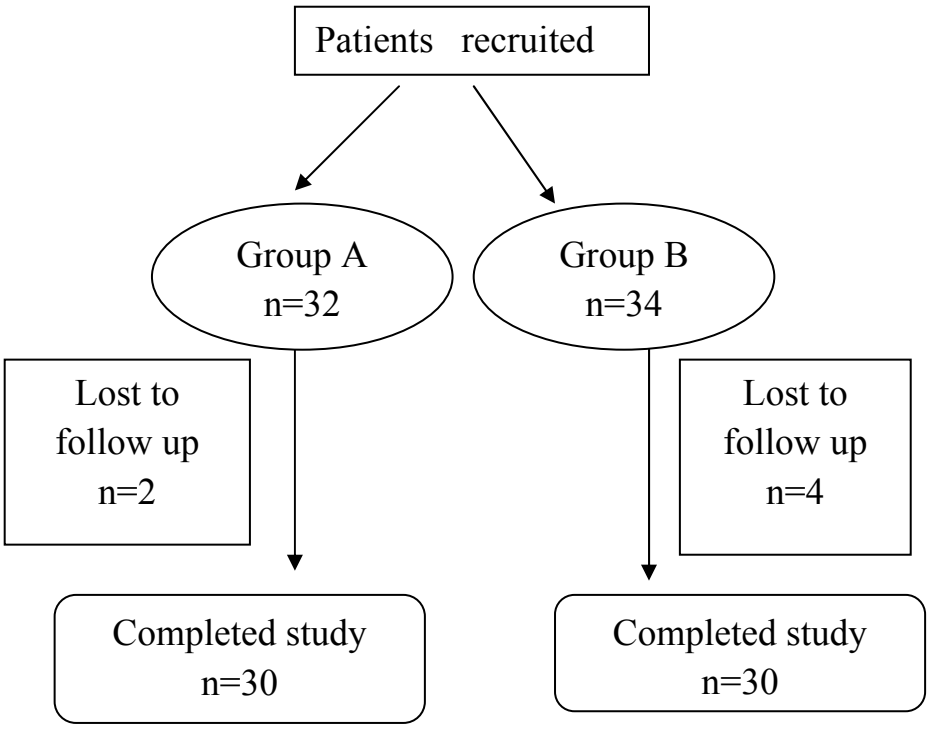


Fig 1: Flow chart showing patient recruitment

Table 1 : Gender distribution

	Group A (n=32)		**Group B(n=34)**	
	No	**%**	**No**	**%**
Female	9	28.1	11	32.4
Male	23	71.9	23	67.6
Total	32	100.0	34	100.0

There were 46 males and 20 females in the present study. In group A, there were 71.9 % and 28.1% males and females respectively and in group B 67.6 % and 32.3%.

Table 2:Age distribution

	Males	Age yrs ±SD	Females	Age yrs ±SD
Group A	23	39.7 ± 13.0	9	39.3 ± 3.0
Group B	23	40.0 ± 10.0	11	35.1 ± 8.6

The mean age of males in group A was 39.7% and in group B it was 40 %. Whereas in females it was 39.3% and 35.1% respectively.

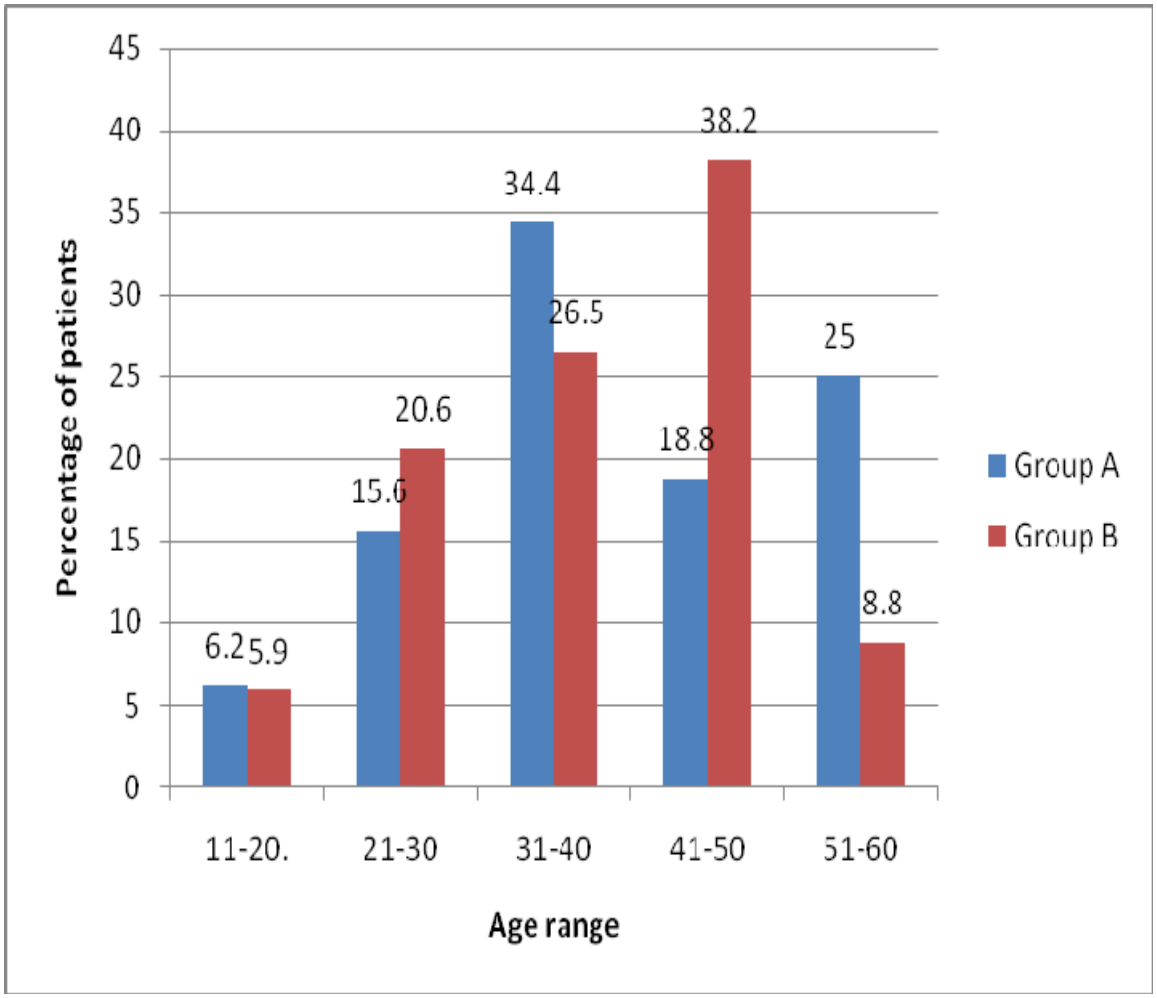


Fig 2: Percentage of patients in different age groups

In this study 30.3% of patients were in the age group of 31 – 40 years, with 34.4 % in group A and 26.5 % in group B. In group A the youngest patient was 18 and eldest was 60 years whereas in group B it was 20 and 58 years respectively.

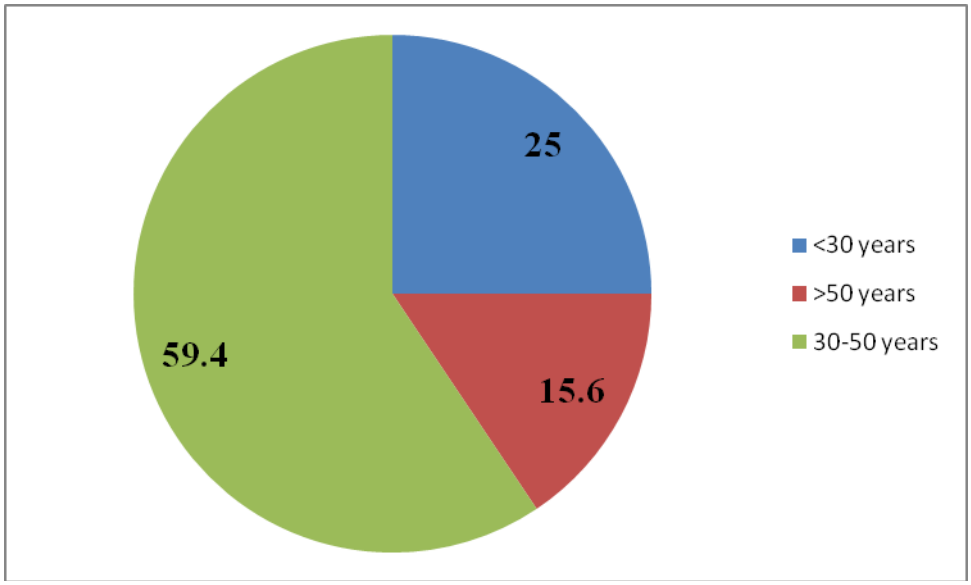


Fig 3 :Percentage of patients with age of onset of psoriasis in Group A

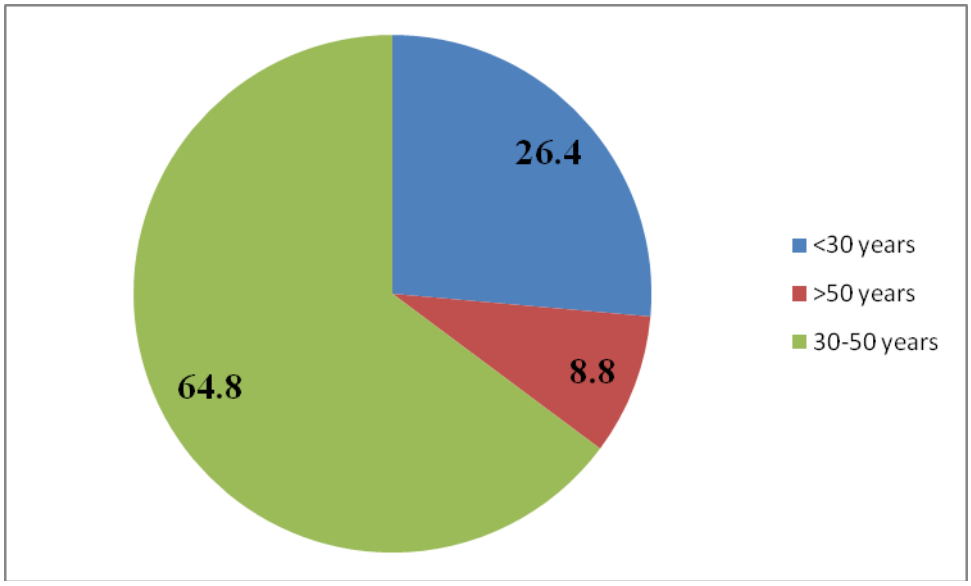


Fig 4 : Percentage of patients with age of onset of psoriasis in group B

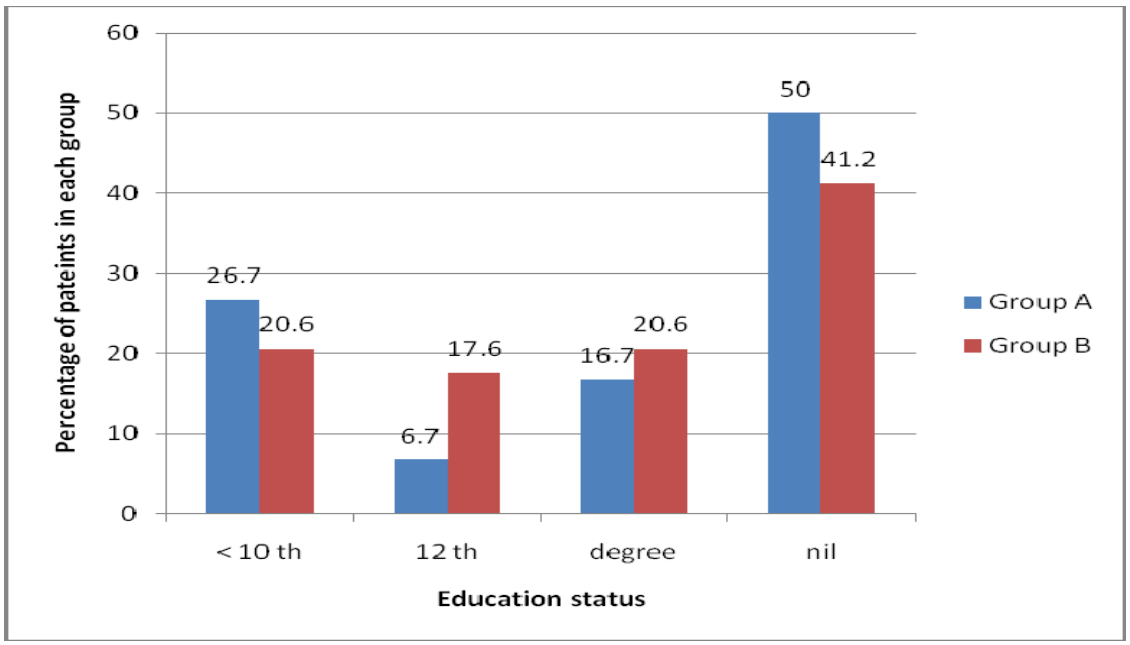
The age of onset of psoriasis was between 30- 50 years in most of the patients in both the groups. It was 59% in group A and 65 % in group B .

Table 3 : Duration of psoriasis

	Group A		Group B	
	No	%	No	%
< 6 months	4	12.5	2	5.9
6 months – 1 year	2	6.2	4	11.8
1 – 2 years	7	21.9	6	17.6
>2 years	19	59.4	22	64.7
Total	32	100.0	34	100.0

From the table 3 it is clear that most of the patients suffered from psoriasis for more than 2 years followed by 1-2 years duration.

Fig 5: Educational status of patients with psoriasis in both the groups



Out of 66 patients 44 were uneducated accounting for 66.6 % of all the patients.

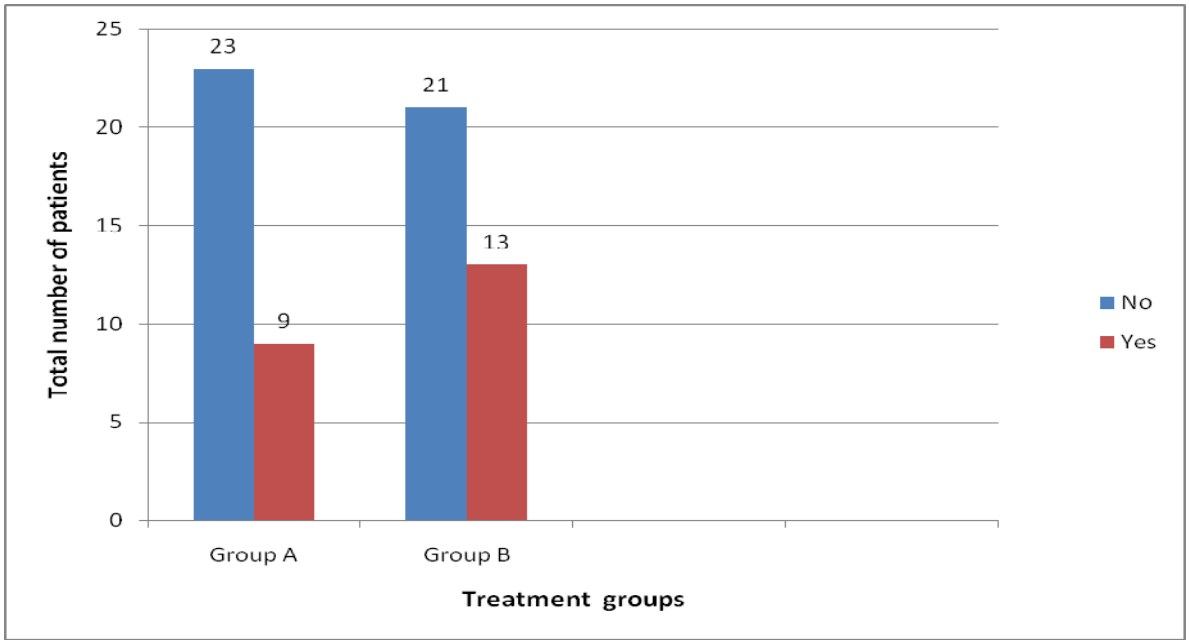


Fig 6 : History of smoking in psoriasis patients

History of smoking was present in 23 patients in group A and 21 in that of group B

.

Table 4 : History of alcohol consumption in patients with Psoriasis

	Group A		Group B	
	No of patients	Percent	No of patients	Percent
No	30	93.8	28	82.4
Yes	2	6.2	6	17.6
Total	32	100.0	34	100.0

Number of patients consuming alcohol were more in group B

Table 5 : Presenting symptoms in both the groups

	Group A		Group B	
	Frequency	Percent	Frequency	Percent
Itchy scaly	28	87.5	31	91.2
Scaly	4	12.5	3	8.8
Total	32	100.0	34	100.0

Itchy scaly lesions were the most common presenting complaints among both the groups as shown in the above table. Few patients also complained of only scaly lesions.

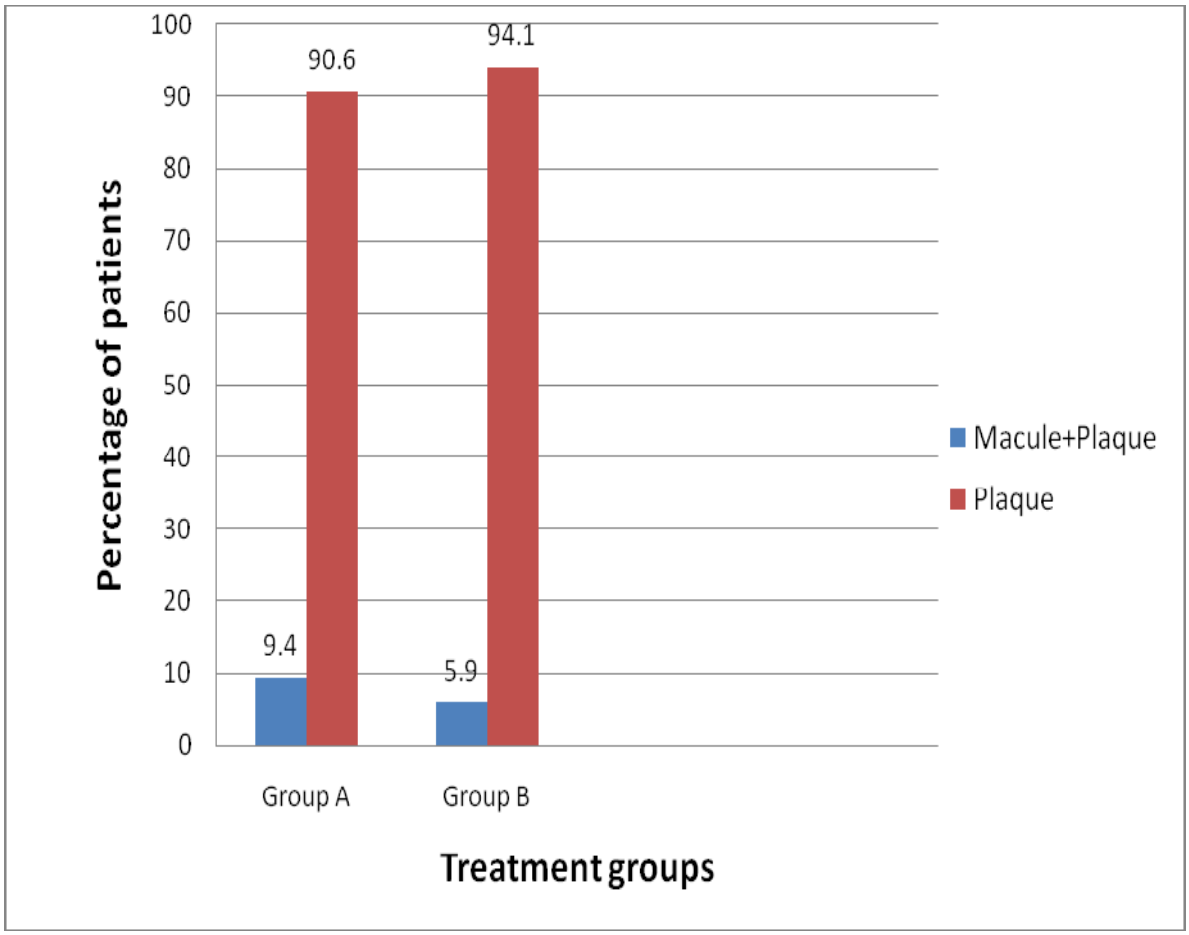


Fig 7: Type of lesions

In both the treatment groups plaques were the most common type of lesions observed. In group A plaques were observed in 90.6 % of patients whereas in group B it was seen 94.1 % of patients.

Table 6 : Area of involvement in psoriasis patients

	Group A		Group B	
	No of patients	Percentage	Frequency	Percentage
U	4	12.5	4	11.8
T + U	7	21.9	6	17.6
T + L	4	12.4	4	11.8
T + U + L	5	15.6	1	2.9
L	6	18.8	13	38.3
U + L	6	18.8	6	17.6

L = Lower limb, T= Trunk , U = Upper limb

From table 6 it is clear that the lesions were most commonly present on extremities in both the groups. In group A 33.3 % of patients had lesions either in upper or lower limb alone where as it was 53.3 % in group B. In the rest of patients the lesions were present in combinations at different sites including upper limb , lower limb and trunk .

Table 7: Comparison of PASI score between baseline and follow up in Group A

	Baseline	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
Mean	4.63	2.46	0.95	0.12	0	0	0
SD	1.75	1.20	0.61	0.20	0	0	0
P-value		0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

In group A there was a significant difference in mean PASI scores between baseline and respective follow up weeks. All the patients had a PASI score of 0 by 8 th week .

Table 8 : Comparison of PASI score between baseline and follow up in Group B

	Baseline	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks
Mean	3.85	3.08	2.24	1.37	0.70	0.24	0.08
SD	1.62	1.28	1.04	0.75	0.46	0.24	0.12
P-value		0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

In group B also there was a significant difference in mean PASI scores between baseline and the respective follow up weeks. But most of the patients were not completely recovered even at 12 week follow up.

Table 9 : Comparison of baseline PASI score between groups

	Mean PASI score ± SD	P- value
Group A	4.63±1.75	0.079
Group B	3.85±1.62	

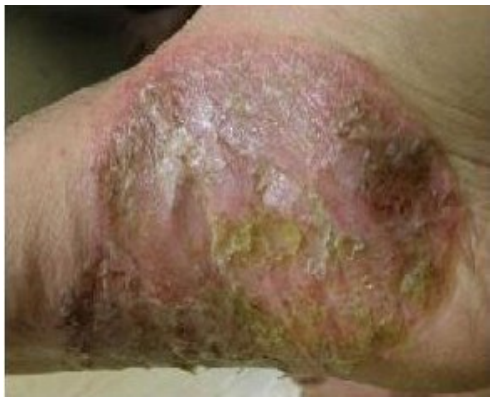
As depicted in table 9, there is no significant difference in the mean PASI score between two groups at baseline.

Table 10 : Comparison of PASI score between two groups

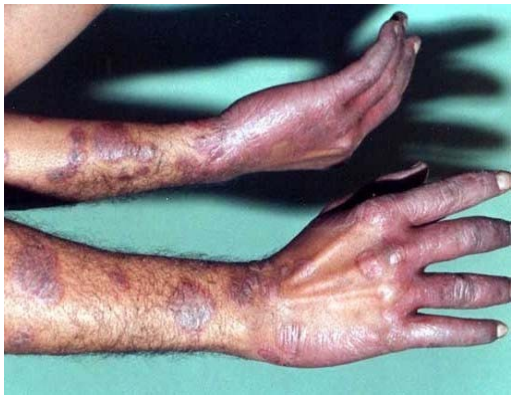
		Weeks					
		2	4	6	8	10	12
Mean ± SD	Group A (Calcipotriol and Betamethasone)	2.46± 1.20	0.95 ± 0.61	0.12 ±.20	0	0	0
	Group B (Betamethasone)	3.08±1.28	2.24 ±1.04	1.37 ±0.75	0.70 ±0.46	0.24 ±0.24	0.08 ±0.12
P – value		0.064	0.0001	0.0001	0.0001	0.0001	0.0001

In comparing the mean PASI scores between group A and group B there was no significant difference in the scores at week 2 but there was a significant difference at 4, 6, 8, 10 and 12 week follow up.

Fig 8a : Photographs showing psoriasis in calcipotriol and betamethasone combination group at week 0.

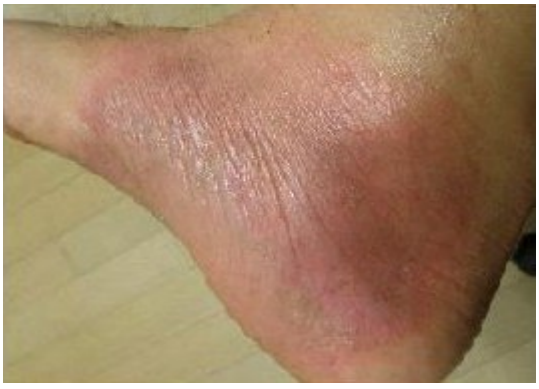


Right ankle region

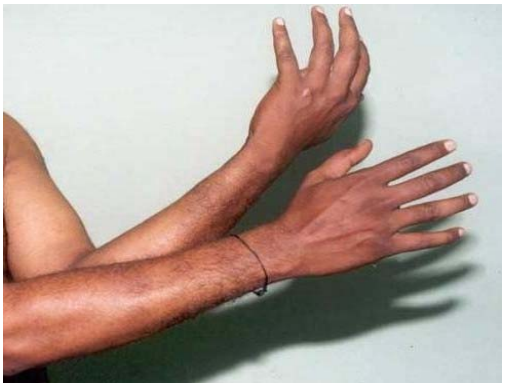


Both hands dorsal aspect

Fig 8b: Photographs showing improvement after calcipotriol and betamethasone combination therapy at 12 weeks

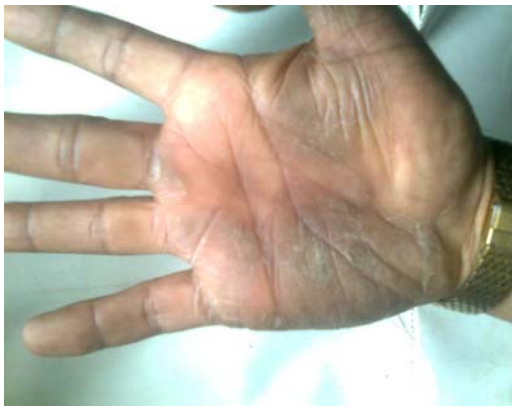


Right ankle region

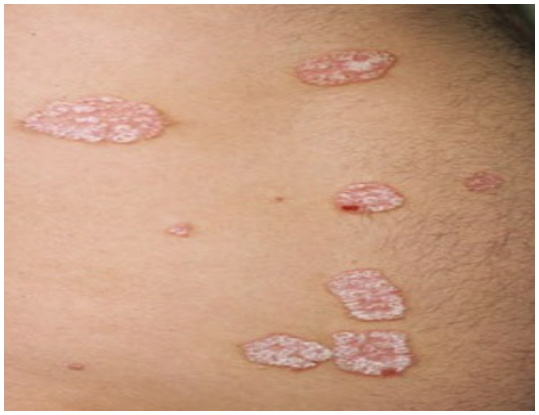


Both hands dorsal aspect

Fig 9a : Photographs showing clinical improvement after treatment with Betamethasone alone

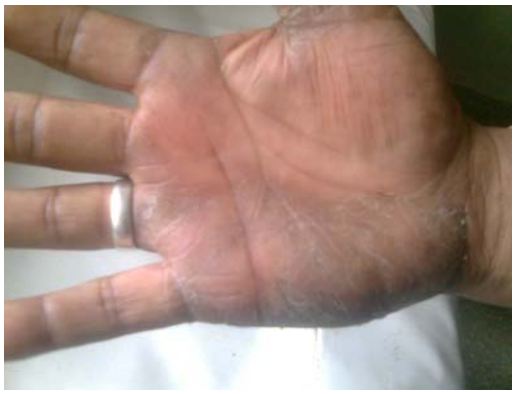


Right hand – palmar region

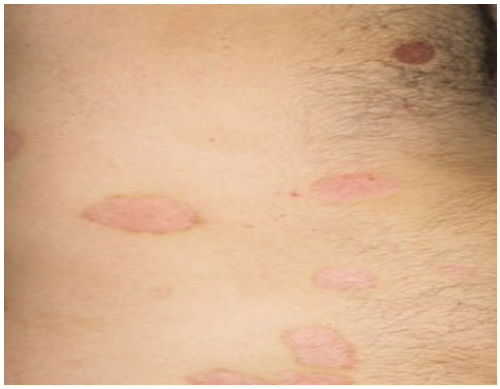


Anterior aspect of trunk

Fig 9a: **Photographs showing clinical improvement after treatment with Betamethasone alone at 12 weeks**



Right hand – palmar region



Anterior aspect of trunk

Discussion

Psoriasis is a itchy chronic inflammatory disease of skin affecting keratinocyte turn over and is characterised by erythematous, sharply demarcated papules and rounded plaques covered by silvery scales. Psoriasis has the ability to cause cosmetic disfiguration as well stigmatization. Visible skin changes in psoriasis may arouse fear, aversion, and few of them may be afraid of the possible contagious character of the disease.[93] Thus early diagnosis and treatment play a major role in improving the quality of life in patients with psoriasis. Among all the classified types, psoriasis vulgaris is the most common one. The exact cause is not known and hence a wide range of treatment options have been tried.[8] Management of psoriasis includes - topical application of drugs like anthralin, coal tar, corticosteroids etc, PUVA therapy and systemic therapy with methotrexate and other immunosuppressants. Topical application is the most widely practiced method of management.

Vitamin D_3 analogues are recently emerging effective and safe drugs for topical therapy in psoriasis. Calcipotriol, a vitamin D_3 analogue has shown to be effective as monotherapy in treatment of psoriasis vulgaris as compared to other topical monotherapies.[94] Topical application of steroids was the main stay of treatment before calcipotriol came into use. Betamethasone dipropionate is a highly potent steroid used as topical treatment in psoriasis. Since both these drugs act by different mechanisms combination of these two drugs may be more efficacious than monotherapy.

Hence, in our study we have compared calcipotriol 0.005% and betamethasone dipropionate 0.05% combination (Group A) once daily topical application with betamethasone dipropionate 0.05% monotherapy (Group B) twice

daily in the treatment of patients suffering from mild to moderate psoriasis vulgaris.

There were 46 males and 20 females in the present study accounting for 69.7% and 30.3 % respectively. This finding correlates with the higher incidence of psoriasis in males as per Indian statistics.[95] Male : Female ratio observed in our study was 2.3:1 which is similar to a previous study with a ratio of 2.4 :1.[96] It is also observed that psoriasis affects females more commonly in younger age group.[97] But in our study out of 20 female patients only three of them were in younger age group.

Our observation is that we had patients in the age group of 18-60 years , but with higher occurrence of psoriasis in their fourties (Table 2). Bedi et al also observed that the incidence of psoriasis was highest in third and fourth decade of life.[98] Duration of psoriasis in majority of the patients was more than 2 years in both the groups (Table 3) but duration of disease did not affect the outcome of therapy in any of these groups.

We have observed that the occurrence of psoriasis was more among uneducated population (Fig 5). Non smokers were more in our study (Fig 6). Smoking has been implicated in both pathogenesis as well as progression of psoriasis but conclusive data of its role is still lacking.[99]

In the present study number of patients with history of alcohol intake were more in Group B (Table 4) but overall there were more number of non alcoholics. Alcohol consumption is directly associated with development of psoriasis and the extent of involvement of body surface area depends on average alcohol intake.[100] Alcohol has been associated with disease severity and treatment failure.[99] In our study

no difference was observed in alcoholic patients with respect to either disease occurrence or improvement with treatment.

There was no family history of psoriasis in the patients recruited and seasonal variation was seen in nine patients of which six had history of exacerbation in winter and three in summer. These findings correlated with those observed in a study where the prevalence of psoriasis was more in cooler than warmer areas.[99]

Itchy scaly lesions were the most common presenting complaints in both the groups. Only seven (10.6%) had history of scaly lesions alone. Naldi L and Gambini D also noticed in 2007 that plaques were one of the commonest clinical manifestations. The lesions initially start as pin point papules which soon evolve to form scaling.[101] Majority of our patients (92.4%) also had plaque type of clinical manifestation.

Psoriasis preferentially affects the extremities including elbows and knees. The other less common sites are lumbosacral and intergluteal areas. In our study 43.3% of patients presented with lesions in the extremities which was in par with the other study.[101] Parslew and Traulsen used combination of calcipotriol 0.005% and betamethasone 0.05% for 4 weeks and found that the mean reduction in PASI score was 67.8% in patients below 60 years compared with 72.6% in those above 60 years. Combination therapy was found to be effective and well-tolerated in the treatment of psoriasis vulgaris, regardless of age group.[102] In our study all the patients were below 60 years of age and the mean reduction in PASI score from baseline to the end of the study was 100% in calcipotriol and betamethasone combination group.

At baseline the PASI scores between the two groups were comparable with no significant difference in their mean scores. While on treatment, in group A there was a significant(p=0.0001) reduction in the PASI scores at each follow up week compared to baseline. The lesions were cleared in all the patients by eighth week and the PASI score was 0 till the end of the study (Table 8). Even after complete clearance of the lesions topical therapy with calcipotriol and betamethasone combination was continued till the end of the study to observe for adverse effects. Kragballe K et al used the combination of calcipotriol 0.005% and betamethasone 0.05% for 8 weeks and found a reduction in PASI score of 73.3% from baseline to eighth week.[103]

In betamethasone monotherapy group also there was a significant (p=0.0001) reduction in PASI scores at each follow up weeks compared to baseline. But the lesions were cleared completely in only two patients by week eight while 10 patients still had lesions to be cleared at the end of 12 weeks (Table 9).

When PASI scores were compared between the groups there was no significant difference at second week (p=0.064) while there was a difference (table 10) in the scores from week four onwards till the end of the study.

Tolerability and safety are the important factors to be considered while treating psoriasis patients because it is a chronic disease and thus requires long term treatment. In the present 12 week study none of the patients receiving calcipotriol and betamethasone combination presented with any adverse effects but two of them receiving betamethasone monotherapy presented with mild itching around the lesions after 2 weeks of application of topical betamethasone.

Conclusion :

- Psoriasis affects males commonly than females and most of the patients were in their fourties.
- Age of onset is between 30-50 years with a mean duration of disease of more than two years.
- It showed seasonal variation with exacerbations occurring during winter in majority of patients.
- Although genetic factors play a role in the pathogenesis of psoriasis, none of the patients had a family history of psoriasis.
- The lesions were seen on the extremities and the commonest type was plaques.
- The baseline PASI scores were comparable between the calcipotriol 0.005 % and betamethasone dipropionate 0.05% combination and betamethasone dipropionate 0.05% .
- Treatment of mild to moderate psoriasis with combination therapy showed better clinical response and also reduction in PASI score.
- Thus combination of calcipotriol 0.005 % and betamethasone dipropionate 0.05% is effective and safe compared to betamethasone 0.05% monotherapy in the treatment of mild to moderate psoriasis.

Summary

- A total of 66 patients with plaque psoriasis were recruited of which 60 completed the study.
- There were 46 males and 20 females. With a ratio of 2.3 : 1.
- Most of the patients were in the age group of 31-40 years (30.3 %) .
- In 41 patients the duration of psoriasis was for more than two years while only six patients had a duration of less than six months.
- Uneducated patients accounted for 66.6% . History of smoking was present in 44 patients while that of alcohol was observed in eight of them.
- Six patients showed exacerbations in winter while three of them in summer.
- None of them had a family history of psoriasis.
- Itchy scaly lesion was the common (89.3 %) presenting symptom and plaque was the common type of lesion observed on the extremities.
- Group A received calcipotriol 0.005% and betamethasone dipropionate 0.05% combination once daily and group B received betamethasone dipropionate 0.05% twice daily as topical application for 12 weeks .
- Baseline PSAI score was similar with no significant difference between both the groups ($p = 0.079$)
- There was a significant decrease in PASI score from baseline to successive follow up weeks in both the groups.
- The reduction in score was highly significant in calcipotriol 0.005% and betamethasone dipropionate 0.05% combination group compared to betamethasone dipropionate 0.05% monotherapy group ($p < 0.0001$).

- No adverse effects were noticed with combination therapygroup but only two patients in betamethasone group presented with mild itching.
- Thus calcipotriol 0.005% and betamethasone dipropionate 0.05% combination is more effective and can be used with less adverse effects in mild to moderate psoriasis as compared to monotherapy with steroid group of drugs.

BIBLIOGRAPHY

1) Frank O , Nestle , Daniel H, Kaplan, Jonathan Baker. Mechanisms of Disease –Psoriasis. N Engl J Med 2009; 361: 496-509.

2) Gottlieb AB. Psoriasis. Dis Manage Clin Outcomes 1998; 1: 195-202.

3) Richards HL, Fortune DG. Psychological distress and adherence in patients with psoriasis. J Eur Acad Dermatol Veneral 2006; 20: 33-41.

4) Bury Y, Rulf D, Hansen CM . Molecular evaluation of vitamin D_3 receptor agonists designed for topical treatment of skin disease. J Invest Dermatol 2001; 116: 785-92.

5)Muller K , Diamant M , Bendtzen K . Inhibition of production and function of Interleukin – 6 by 1,25-dihydroxy vitamin D_3. Immunol Lett 1991; 28: 115-20.

6) Muller K, Svenson M, Bendtzen K. 1alpha,25-dihydroxy vitamin D_3 and a novel vitamin D analogue MC903 are potent inhibitors of human interleukin 1 in vivo. Immunol Lett 1988 ; 17: 361-65.

7) Vissers WH, Berends M, Muys L. The effect of the combination of calcipotriol and betamethasone dipropionate versus both monotherapies on epidermal proliferation, keratinization and T-cell subset in chronic plaque psoriasis. Exp Dermatol 2004; 13: 106-12.

8) Christophers E, Mrowietz U. Psoriasis. In: Freeberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw Hill; 2007. p.407-27.

9) Farber EM, Peterson JB. Variations in the natural history of psoriasis. Calif Med 1961; 95: 6-11

10) Fry L. Psoriasis. Br J Dermatol 1988; 119: 445-61.

11) Bernhard JD. Auspitz sign is not sensitive or specific for psoriasis. J Am Acad Dermatol 1990 ; 22 :1079-81.

12) Camp RDR. Psoriasis. In: Champion RH, Burton JL, Burns DA, Breathnach SM, editors. Textbook of dermatology. 6th ed. London: Blackwell Science;1998.p.1589-649.

13) Ronald M, Roxberg AC.Psoriasis.In: Roxberghs common skin disease. 17 ed. London: Arnold; 2003.p.128-42.

14) Chalmers. RJG. Psoriasis. In: Williams H, Bigby M, Diepgen T, Hercheimer A, Naldi L, Rjany B. editors. Evidence – based dermatology. London: BMJ Publishing house group ; 2003 .p. 226-52.

15) Gibson LE, Perry HO. Papulosquamous eruption and exfoliative dermatitis. In: Moschella SL, Hurley HJ, editors Dermatology. 3rd ed. Philadelphia: W.B. Saunders; 1992 .p. 607-51.

16) Farber EM, Nall L. Epidemiology: Natural history and genetics. In: Roenigk HH, Maibach HL, editors. Psoriasis. 3rd ed. New York: Marcel Dekker Inc; 1998 .p.107-57.

17) Ambady BM, Gopinath T, Nair BKH. Psoriasis. Indian J Dermatol Venereol 1961; 27: 23-30.

18) Sharma TP, Sepaha GU. Psoriasis – A clinical study. Indian J Dermatol Venereol 1964; 30: 191-203.

19) Buntin DM: Onset of psoriasis at age 108. J Am Acad Dermatol 1983; 9: 276-7.

20) Honseler T, Christophers E. Psoriasis of early and late onset: Characterization of two types of psoriasis vulgaris. J Am Acad Dermatol 1985; 13: L450-52.

21) Gunawardena DA, Gunavardena LA, Vasanthanathan. Psoriasis in Sri Lanka. Br J Dermatol 1978; 98: 85-86.

22) Kavil G, Faerde OH, Arnesen E. Psoriasis: familial predisposition and environmental factor. Br Med J 1985; 291: 999-1000.

23) Bedi TR. Clinical profile of psoriasis in North India. Indian J Dermatol Venereol Leprol 1995; 61: 202-5.

24) Russell TJ, Schultes LM, Kaban DJ. Histocompatibility (HL-A) antigens associated with psoriasis. N Engl J Med 1972; 287: 738-40.

25) Watson W, Howard M, Farber EM, Nall ML. The genetic of psoriasis. Arch Dermatol 1972; 105: 197-207.

26) Dobson RL. The inheritance of psoriasis. Arch Dermatol 1980; 116: 657.

27) Tiwari JL, Lowe NJ, Abromovits W, Hawkins BR, Park MS. Association of psoriasis with HLA-DR7. Br J Dermatol 1982; 106: 227.

28) Nanney LB, Stoscheck CM, Magid M. and King Jr. LE. Altered (I125) epidermal growth factor binding and receptor distribution in psoriasis. J Invest Dermatol 1986; 86: 260-5.

29) Krueger JG, Pathogenic interaction of keratinocytes and T- lymphocytes in psoriasis. In: Roenigk HH, Maiback HI, editors. Psoriasis. 3rd ed. New York: Mercell Dekker Inc; 1998. p.315-27.

30) Griffiths TW, Griffiths CEM, Voorhees JJ. Immunopathogenesis and immunotherapy of psoriasis. Dermatol Clinics 1995; 13: 739-49.

31) Beta-Csorgo Z, Hammerberg C, Voorhees JJ, Copper KD. Flow cytometric identification of proliferative sub population within normal human epidermis and

localization of the primary hyperproliferative population in psoriasis. J Exp Med 1998; 178: 1271-81.

32) Brain S, Camp R, Derm FF, Dwon P, Black AK, Graves M. The release of leukotriene B4- like material in biologically active amounts from the lesional skin of patients with psoriasis. J Invest Dermatol 1984; 83: 70-3.

33) Voorhees JJ, Chambe DA, Duell EA, Marcelock, Kruger GG. Molecular mechanism in proliferative skin disorders. J Invest Dermatol 1976; 67: 442-50.

34) Muto M, Fujikura Y, Hamamoto Y, Ichmiya M, Ohmura A, Sasajuki T. et al. Immune response to streptococcus pyogens and the susceptibility to psoriasis. Australias J Dermtol 1996; 37: 54-5.

35) Bartenjev I, Rogl Butina M, Potocï Nik M. Subclinical microbial infection in patients with chronic plaque psoriasis. Acta Derm Venereol 2000; 211: 17- 8.

36) Shelly WB, Aurthur RB. Biochemical and physiological clues to the nature of psoriasis. Arch Dermatol 1958; 78: 14-29.

37) Peters BP, Weissman FG, Gill MA. Pathophysiology and treatment of psoriasis. Am J Health-Syst Pharm 2000;57:645-59.

38) Dunna SF, Finlay AY. Psoriasis: improvement during and worsening after pregnancy. Br J Dermatol 1989; 120: 584.

39) Murase JE, Chan KK, Garite TJ, Cooper DM, Weinstein GD . Hormonal Effect on Psoriasis in Pregnancy and Post Partum. Arch Dermatol 2005;141:601-6.

40) Peserico A. Development of psoriasis during dialysis. Arch Dermatol 1979; 115:1169.

41) Pavithran K. Disorders of kertinization. In: Valia RG, Ameet RV. Editors. IADVL textbook and atlas of dermatology. 2nd Edn, Vol.II, Mumbai: Bhalani Publishing House; 2001. p.799-846.

42) Chapman BP, Moynihan J. The Brain-Skin Connection: Role of Psychosocial Factors and Neuropeptides in Psoriasis. Expert Rev Clin Immunol. 2009 ; 5: 623–7.

43) Anderson TF, Voohees JJ. Psoriasis: In Theirs BH, Dobson RL, editors. Pathogenesis of skin disease: New York: Churchill Livingstone, 1986. p.67-84.

44) Naldi L, Peli L, Parazini F. Association of early – stage psoriasis with smoking and male alcohol consumption. Arch Dermatol 1999; 135: 1479-84.

45) Duvic M. Immunology of AIDS related to psoriasis. J Invest Dermatol 1990; 95:538.

46) Heng MCY, Heng MK. Beta-adrenoceptor antagonist induced psoriasiform eruption. Int J of Dermatol 1988; 27: 619-27.

47) Kim GK, Del Rosso JQ. Drug-Provoked Psoriasis: Is It Drug Induced or Drug Aggravated? Understanding Pathophysiology and Clinical Relevance. J Clin Aesthetic Dermatol 2010;3:32–8.

48) Abel EA, DiCicco LM, Orenberg EK, Fraki JE, Farber EM. Drugs in exacerbation of psoriasis. J Am Acad Dermatol 1986; 15: 1007-22.

49) Penneys NS, Ziboh V, Simon P, Lord J. Pathogenesis of Woronoff ring in psoriasis. Arch Dermatol 1976; 112 : 955-7.

50) Luba KM, Stulberg DL. Chronic Plaque Psoriasis. American Family Physician 2006 ;73 : 636-44.

51) Stankler L, Ewen SWB. Follicular psoriasis. Br J of Dermatol 1981; 104: 153-56.

52) Wagner G, Luckasen JR, Robert WG. Mucous membrane involvement in generalized pustular psoriasis. Arch Dermatol 1976; 112: 1010-14.

53) Babu M, Ramachandran P, Nair BKH. Psoriasis of the mucous membrane. Ind J Dermatol Venereol 1967; 33: 83-85.

54) Robbins TO, Kouskaukis CE, Ackerman AB. Onycholysis in psoriatic nails. Am J Dermtopathol 1983; 5: 39-41.

55) Kouskoukis CE, Scher RK, Ackerman AB. The “oil drop” sign of psoriatic nails : A clinical finding specific for psoriasis. Am J Dermatopathol 1983; 5: 259-62.

56) Malaviya AN. Psoriatic arthropathy. Indian J Dermatol Venereol 1984; 50: 127-30.

57) Marples RR, Heaton C, Kligman AM. Staphylococcus aureus in psoriasis. Arch Dermatol 1973; 107: 568-70.

58) Lafi SA, Hasan AS, Al-Alowssi MM. Secondary Bacterial Infections Complicating Psoriasis.Egypt Acad J biolog Sci 2010;2: 37- 42.

59) Sehgal VN, Srivastava G, Sardana K. Erythroderma/exfoliative dermatitis: a synopsis. International Journal of Dermatology 2004; 43: 39–47.

60) Charles Camisa. Variantes of psoriasis. In: Charles Camisa Edt. Psoriasis. Boston: Blackwell Scientific Publication; 1994. p.5-83.

61) Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. Journal Of Hepatology 2009;51:758-64.

62) Santra G, Sinha PK, Dibyendu De. Nephropathy in Association with Annular Psoriasis. JAPI 2011; 59:595-7.

63) Warton DJ, Winney RS, Beveridge G, Oligaemia, renal failure and jaundice associated with acute pustular psoriasis. Br Med J 1974; 11: 406-08.

64) Warton DJ, Winney RS, Beveridge G, Oligaemia, renal failure and jaundice associated with acute pustular psoriasis. Br Med J 1974; 11: 406-8.

65) Berger PA. Amyloidosis-a Complication of Pustular Psoriasis. British Medical Journal 1969; 2: 351-3.

66) Lowe NJ, Tars, Keratolytics and Emollients. In: Lowe NJ, editor. Practical psoriasis therapy. 2nd ed. California: Mosby Year Book; 1993. p.45-57.

67) Federman DG, Froelich CW, Kirsner RS. Topical Psoriasis Therapy. Am Fam Physician 1999;59: 957-62.

68) Lowe NJ, Breeding J, Wortman MS. The pharmacological variability of crude coal tar. Br J Dermatol 1982 ;107: 475-80.

69) Ippen H. Basic questions on toxicology and pharmacology of anthralin. Br J Dermatol 1981; 105: 72-6.

70) Anderson R, Lukey PT, Dippenaar U, Eftychis HA, Findlay GH, Wooten MW, et al. Dithranol mediated pro-oxidative inhibition of polymorphonuclear leukocyte migration and lymphocyte proliferation. Br J Dermatol 1987; 117: 405-18.

71) Peus D, Beyerle A, Rittner HL,Pott M, Meves A,Weyand C,et al. Anti- psoriatic drug anthralin activates JNK via lipid peroxidation : Mononuclear cells are more sensitive than keratinocytes. J Invest Dermatol 2000;114:688-92.

72) Lawlor EF, Hindson JC. Allergy to dithranol. Contact Dermatitis 1982; 8: 137-38.

73) Afi fi T, Gannes G, Huang C, Zhou Y.Topical therapies for psoriasis. Can Fam Physician 2005;51:519-25.

74) Ellis CN, Berberian B, Sulica VI, Dodd WA, Jarratt MT, Katz HI. Et al. A double blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol 1993; 29: 438-42.

75) Lebwohl M, Alis. Treatment of psoriasis. Part 1. Topical therapy and phototherapy. J Am Acad Dermatol 2001; 45: 487-98.

76) Scimmer BP,Funder JW. ACTH ,Adrenal steroids and pharmacology of the adrenal cortex.In:Brunton LL, Chabner BA, Kollmann BC. editors. Goodman and

Gilman's The pharmacological basis of therapeutics.12th ed. New York; McGraw Hill: 2011.p.1209-36.

77) Chrousos GP. Adrenocorticosteroids and adrenocortical antagonists.In : Katzung BG, Masters SB, Trevor AJ, editors.Basic and clinical pharmacology 11th ed.Tata McGraw Hill;New Delhi:2009.p.681-98.

78) Pershing LK, Lambert L,Wright ED, Shah VP,Williams RL: Topical 0.050% betamethasone dipropionate. Pharmacokinetic and pharmacodynamic dose-response studies in humans. Arch Dermatol 1994 ;130: 740-7.

79) Cornell RC, Stoughton RB. Correlation of the vasoconstriction assay and clinical activity in psoriasis. Arch Dermatol 1985;121:63–7.

80) Ference JD, Last AR. Choosing Topical Corticosteroids. Am Fam Physician 2009;79:135-40.

81) Lebwohl M,Ting PT, Koo JYM. Psoriasis treatment: traditional therapy. Ann Rheum Dis 2005;64:83-6.

82) Lidbrink P, Johanesson A, hammer H. Psoriasis treatment faster clearance when UVB – dithranol is combined with topical clobetaso l propionate. Dermatologica 1986; 172: 164-68.

83) Del Rosso JQD, Kim GK, DO. The Rationale Behind Topical Vitamin D Analogs in the Treatment of Psoriasis Where Does Topical Calcitriol Fit In?.The Journal of Clinical and Aesthetic Dermatology 2010;3:46-53.

84) Shaaban D, El-Samad ZA. Vitamin D and its Analogs: Dermatologic uses. The Gulf Journal of Dermatology and Venereology 2011;18:1-13.

85) Charakida A, Dadzie O, Teixeira F, Charakida M, Evangelou G, Chu AC. Calcipotriol / betamethasone dipropionate for the treatment of psoriasis. Expert Opin Pharmacother 2006;**7**:597-606.

86) Delaney C, Liao W, Cohen M .Percutaneous absorption of calcipotriene (calcipotriol) in normal volunteers and psoriatic patients after a single dose of ^{3}H-calcipotriene and in psoriatic patients after a single dose of 3H-calcipotriene following multiple dose treatment with nonradiolabeled calcipotriene 0.005% ointment. J Investig Dermatol Symp 1996;1:112.

87) Masuda S, Strugnell S, Calverley MJ, Makin HL, Kremer R, Jones G: In vitro metabolism of the anti-psoriatic vitamin D analog, calcipotriol, in two cultured human keratinocyte models. J Biol Chem 1994;269:4794 - 803.

88) Shahzad A, Shahzad M, Khurshid K. Topical calcipotriol in dermatology. Journal of Pakistan Association of Dermatologists 2006; 16: 104 - 7.

89) Roenigk HH, Auerbach R, Maibach H, Weinstein G, Lebwohl M. Methotrexate in psoriasis: consensus conference. J Am Acad Dermatol 1998; 38: 478-85.

90) C.C. Geilen, C.E. Orfanos. Standard and innovative therapy of psoriasis. Clin Exp Rheumatol 2002; 20:81-7.

91) Roenigh HH, Aurebach R, Maibach H. Methotrexate guidelines revised. J Am Acad Dermatol 1982; 6: 145-55.

92) Gollnick HPM.Oral retinoids-efficacy and toxicity in psoriasis. Br J Dermatol 1996;135:6 -17.

93) Hrehorów E, Salomon J, Matusia LK, Reich A, Szepietows ki JC. Patients with Psoriasis Feel Stigmatized. Acta Derm Venereol 2012; 92: 67–72.

94) Ortonne J, Noerrelund KL, Papp K, Van Herpe L,Sebastian M, Herrera E, Bodalia B. Comparison of two different dose combinations of calcipotriol/hydrocortisone ointment used once daily for the treatment of psoriasis vulgaris on the face and body. Eur J Dermatol 2010; 20: 585-9.

95) Dogra S,Yadav S.Psoriasis In India :Prevalence and pattern.Indian J Dermatol Venerol Leprol 2010;76:595-601.

96) Okhandiar RP, Banerjee BN. Psoriasis in the tropics : An epidemiological survey. J Indian Med Assoc 1963;41:550-6.

97) Naldi L, Mercuri S M. Smoking and Psoriasis: From Epidemiology to Pathomechanisms. Journal of Investigative Dermatology 2009; 129: 2741–3.

98) Bedi TR. Psoriasis in north India. Geographical variations. Dermatologics 1977;155:310-4.

99) Neimann A L, Porter S B, Gelfand J M. The epidemiology of Psoriasis. Expert Rev Dermatol 2006;1: 63-75.

100) Dediol I, Buljan M, Buljan D, Bulat V, Zivkovic M V, Situm M .Association of psoriasis and alcoholism: Psychodermatological Issue .Psychiatria Danubina 2009; 21: 9–13.

101) Naldi L, Gambini D. The clinical spectrum of psoriasis. Clinics in Dermatology 2007; 25: 510–8.

102) Parslew R, Traulsen J . Efficacy and local safety of a calcipotriol / betamethasone dipropionate ointment in elderly patients with psoriasis vulgaris. Therapeutics and Clinical Risk Management 2008; 4 :141–8.

103) Kragballe K, Noerrelund KL, Lui H, Ortonne JP, Wozel G, Uurasmaa T et al. Efficacy of once-daily treatment regimens with calcipotriol/betamethasone dipropionate ointment and calcipotriol ointment in psoriasis vulgaris. Br J Dermatol 2004;150:1167-73.

Proforma

Op/Ip no : **Date:**

Serial no :

1. Name :
2. Age :
3. Sex :
4. Occupation :
5. Education status :
6. Address with phone number :
7. Complaints :

   Duration
   Age of onset
   Symptoms
   Seasonal variation
   Aggravating factors
8. Family history :
9. Personal history : smoking/alcohol/drugs/others.
10. Past history : h/o same complaints in the past: yes/no.

    if yes : a) treatment taken or not

    b) duration of treatment taken- in months.
    c) was treatment taken in the past 3 months.

    h/o diabetes : yes/no… if yes : is on tretment –yes/no.

    hypertension: yes/no… if yes : is on tretment –yes/no.

    others…
11. Clinical features :

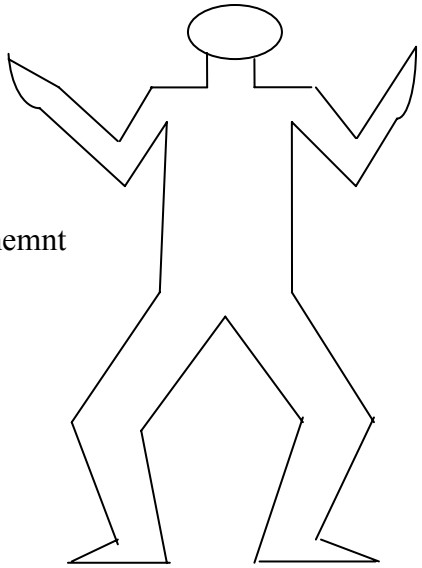
    A. General physical examination:
       Built:
       Pulse:
       B P :
       Temperature:
       Respiratory rate:

Pallor:
Icterus:
Cyanosis :
Lymphadenopathy:
Edema :

b.Area of skin involvement : Head
Face and neck
Trunk –A / P
Upper limbs.. Left-A / P
Right-A / P
Lower limbs..Left-A / P
Right-A / P

c.Type of skin lesions : Papules
Macules and papules
Plaques

d.Skin lesions :



i .Percentage of involvement

ii. Mucous membrane involvememnt

iii. Nail / joint involment

iv. Skin lesion score

e.Other system examination :
CVS :
RS :
PA :

12. Investigations : Complete haemogram-
HB%- , TC- , DC-
Urine -
Sugar :
Protein:

13 . Diagnosis :

14 . Treatment and dosage :

	Follow up visit -1	Follow up visit- 2	Follow up visit -3
1. Patient response & compliance: a) Does he feel better: yes/no b) Was medication taken regularly yes/no			
2. Examination a) General b) Specific			
3. Adverse reaction if any:			
	Follow up visit- 4	Follow up visit -5	Follow up visit -6
1.Patient response & compliance: a) Does he feel better: yes/no b) Was medication taken regularly yes/no			
2. Examination a) General b) Specific			
3. Adverse reaction if any:			

KEY TO MASTER CHART

Sl no	-	Serial number
Itc	-	itchy
Scal	-	scaly
Seas varia	-	Seasonal variation
Aggr fact	-	Aggrevating factor
Trav	-	Travel
Stres	-	stress
h/o smok	-	History of smoking
h/o alco	-	History of alcoholism
typ of les	-	Type of lesion
are of inv	-	Area of invasion
T	-	Trunk
U	-	Upper limb
L	-	Lower limb
P	-	Plaque
M	-	Macules
Adv effect	-	Adverse effect
↑	-	increase

GROUP A- CALCIPOTRIOL AND BETAMETHASONE

sl no	Gender	Age	Education	Duration of disease	Age-onset	Symptoms	seas varia	aggr fact	h/o smok	h/o alco	h/o diab	h/o hype	typ of les	are of inv	PASI-score	O	2	4	6	8	10	12	Adv effec
1	M	34	nil	1 1/2	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	UL		2.2	1.2	0.4	0	0	0	0	NIL
2	M	55	< 10 th	1	>50	itchy scaly	NIL	NIL	no	no	no		plaque	UL		2.2	1	0.2	0	0	0	0	NIL
3	M	23	nil	1	<30	itchy scaly	NIL	NIL	no	no	no		plaque	TUL		8.1	4.3	2	0.4	0	0	0	NIL
4	F	38	nil	0.3	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	UL		4.2	1.8	0.6	0	0	0	0	NIL
5	M	40	nil	0.2	<30	itchy scaly	NIL	NIL	no	no	no		plaque	TUL		8	6	2.9	0.9	0	0	0	NIL
6	M	34	< 10 th	0.08	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	TL		4.5	2.4	0.7	0	0	0	0	NIL
7	M	24	nil	0.5	<30	itchy scaly	NIL	NIL	no	no	no		plaque	L		3.4	1.5	0.5	0	0	0	0	NIL
8	M	20	nil	0.08	<30	scaly	NIL	NIL	no	no	no		plaque	U		2.2	1	0.4	0	0	0	0	NIL
9	F	38	< 10 th	4	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	L		3.6	1.6	0.4	0	0	0	0	NIL
10	M	41	< 10 th	2	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	TL		4	2	0.5	0	0	0	0	NIL
11	M	39	< 10 th	1	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	U		2.2	0.6	0.2	0	0	0	0	NIL
12	M	60	degree	2	>50	itchy scaly	NIL	NIL	yes	yes	yes		plaque	TUL		7.9	4	1.8	0.3	0	0	0	NIL
13	M	55	nil	2	>50	itchy scaly	NIL	NIL	no	no	no		plaque	UL		4.2	2.8	1	0	0	0	0	NIL
14	M	42	nil	0.5	30-50	itchy scaly	NIL	NIL	yes	no	no		plaque	L		3.2	1.2	0.4	0	0	0	0	NIL
15	M	29	12 th	2	<30	itchy scaly	NIL	NIL	yes	no	no		plaque	TU		3.9	1.7	0.5	0	0	0	0	NIL
16	M	56	degree	3.5	>50	itchy scaly	↑ winter	NIL	yes	no	no		plaque	TUL		6.5	3.6	1.3	0.4	0	0	0	NIL
17	M	55	nil	6	30-50	itchy scaly	↑ winter	stres,trav	yes	no	no		plaque	TUL		3.9	2.1	0.9	0	0	0	0	NIL
18	M	18	12 th	3	<30	itchy scaly	NIL	NIL	no	no	no		plaque	TU		4.8	3	1.5	0	0	0	0	NIL
19	M	22	degree	6	<30	itchy scaly	↑ winter	NIL	no	no	no		plaque	L		5.4	3.4	1.6	0	0	0	0	NIL
20	F	48	nil	8	30-50	itchy scaly	↑ winter	NIL	no	no	no		plaque	UL		4.2	2.4	0.9	0.2	0	0	0	NIL
21	M	52	< 10 th	2	30-50	itchy scaly	NIL	stres,trav	yes	no	no		mac ,pap	TU		4.9	2.7	1.2	0.2	0	0	0	NIL
22	F	38	nil	1	30-50	scaly	↑ sumr	NIL	no	no	no		plaque	UL		6.4	3.6	1.4	0.2	0	0	0	NIL
23	F	54	nil	3	>50	itchy scaly	NIL	NIL	no	no	no		plaque	TU		5.4	2.6	0.9	0	0	0	0	NIL
24	F	44	nil	3	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	TU		5.3	3	1	0.2	0	0	0	NIL
25	M	45	nil	2	30-50	itchy scaly	NIL	NIL	yes	yes	no		mac ,pap	U		2	0.8	0.2	0	0	0	0	NIL
26	M	52	nil	4	30-50	scaly	NIL	NIL	yes	no	no		mac ,pap	TL		7.3	3.9	1.4	0.4	0	0	0	NIL
27	F	40	< 10 th	3	30-50	scaly	NIL	NIL	no	no	no		plaque	TU		6	3.2	1.4	0.4	0	0	0	NIL
28	M	48	< 10 th	3	30-50	itchy scaly	NIL	NIL	yes	no	no		plaque	TL		4.8	2.5	0.7	0.2	0	0	0	NIL
29	M	34	degree	3.5	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	L		4.4	2	0.8	0	0	0	0	NIL
30	F	22	degree	2	<30	itchy scaly	NIL	NIL	no	no	no		plaque	L		4	2	0.8	0	0	0	0	NIL
31	F	32	nil	2	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	U		4.2	2.6	-	-	-	-	-	NIL
32	M	35	degree	0.5	30-50	itchy scaly	NIL	NIL	no	no	no		plaque	TU		5.4	2.8	1.2	0.6	-	-	-	NIL

GROUP B- BETAMETHASONE

sl no	Gender	Age	Education	Dur of tre	Age-onset	Symptoms	seas varia	aggr fact	h/o smok	h/o alco	h/o diab	h/o hype	typ of les	are of inv	PASI-score	O	2	4	6	8	10	12	Adv effec
1	M	42	11-12 th	3 Y	31-50	itc , scal	↑winter	trav,stres	yes	yes	no	no	P	UL		3.8	3.2	2.6	1.8	1	0.4	0.2	
2	F	28	11-12 th	4 Y	<30	itc , scal	↑summer	NIL	no	no	no	no	P	L		3.2	2.1	1.8	1.2	0.6	0.3	0	ITCHING
3	M	45	NIL	2.5 Y	31-50	scaly	↑winter	NIL	yes	no	no	no	P	TL		5.2	4.5	3.1	2.1	1.4	0.7	0.4	
4	M	42	NIL	2 Y	31-50	scaly	NIL	NIL	no	no	no	no	P	L		4.5	3.8	2.8	1.7	1.4	0.7	0.3	
5	F	34	NIL	3 Y	31-50	itc , scal	↑summer	NIL	no	no	no	no	P	TU		3.2	2.6	1.8	1	0.6	0.4	0	
6	M	45	NIL	1 Y	31-50	scaly	NIL	NIL	no	no	no	no	P	UL		4.2	3.6	2.6	1.2	0.8	0.2	0	ITCHING
7	M	30	< 10 th	0.25 Y	<30	itc , scal	NIL	NIL	yes	no	no	no	P	UL		4.2	3.4	2.2	1.2	0.6	0.2	0	
8	M	20	11-12 th	0.5 Y	<30	itc , scal	NIL	NIL	no	no	no	no	P	L		2.4	2	1.6	0.4	0	0	0	
9	M	58	< 10 th	1 Y	>50	itc , scal	NIL	NIL	yes	no	no	no	P	U		1.4	1	0.4	0.2	0	0	0	
10	M	35	degree	1 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	M+P	L		2.8	2	1.2	0.8	0.4	0	0	
11	M	44	degree	2 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	L		2.4	1.6	1.2	0.8	0.4	0	0	
12	F	45	11-12 th	2 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	L		2	1.6	1.2	0.8	0.4	0	0	
13	F	50	NIL	1 Y	31-50	itc , scal	NIL	NIL	yes	no	no	no	P	L		3.2	2.8	2.4	2	1.6	0.4	0.2	
14	M	46	< 10 th	0.5 Y	31-50	itc , scal	NIL	NIL	yes	yes	no	no	P	L		3.2	2.4	1.6	0.8	0.4	0	0	
15	M	48	NIL	1 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	U		1.6	1.4	0.8	0.6	0.4	0.2	0	
16	M	27	degree	0.5 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	L		2.8	2.4	1.6	0.8	0.4	0	0	
17	F	20	degree	1 Y	<30	itc , scal	NIL	NIL	no	no	no	no	P	L		2.8	2.4	1.6	1.2	0.8	0.4	0.2	
18	M	51	NIL	0.3 Y	>50	itc , scal	NIL	NIL	yes	yes	no	no	P	U		1.2	1	0.6	0.4	0.2	0	0	
19	M	55	NIL	2 Y	>50	itc , scal	NIL	NIL	yes	no	no	no	M+P	UL		3.2	2.6	1.8	1	0.4	0	0	
20	F	45	NIL	4 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	TU		3.2	2.7	2.2	1.5	0.7	0.2	0	
21	F	36	NIL	2 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	L		4.4	3.6	2.8	2	0.8	0.4	0.2	
22	M	28	< 10 th	4 Y	<30	itc , scal	NIL	NIL	yes	yes	no	no	P	TL		7.7	5.6	4.6	3.5	1.8	0.4	0.2	
23	M	40	< 10 th	3 Y	31-50	itc , scal	NIL	NIL	yes	no	no	no	P	TU		5	4	2.7	1.7	0.8	0.3	0	
24	F	34	NIL	3 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	TU		4.7	3.7	2.7	1.2	0.5	0	0	
25	F	30	NIL	3 Y	<30	itc , scal	NIL	NIL	no	no	no	no	P	TL		6.7	5.3	4.2	2.8	1.4	0.7	0.3	
26	F	32	< 10 th	4 Y	<30	itc , scal	NIL	NIL	no	no	no	no	P	L		4.4	3.2	2.4	1.2	0.4	0	0	
27	M	38	degree	3.5 Y	31-50	itc , scal	NIL	NIL	yes	no	no	no	P	L		4	3.2	2.4	1.6	0.4	0	0	
28	M	48	11-12 th	3 Y	31-50	itc , scal	NIL	NIL	yes	yes	no	no	P	TL		7.1	5.7	4.6	2.8	1.4	0.7	0.3	
29	M	48	< 10 th	3 Y	31-50	itc , scal	NIL	NIL	yes	yes	no	no	P	TU		5.2	4.2	2.9	1.4	0.5	0.2	0	
30	M	25	degree	2 Y	<30	itc , scal	NIL	NIL	no	no	no	no	P	UL		6	4.8	3	1.6	0.6	0.4	0.2	
31	M	28	degree	2 Y	<30	itc , scal	NIL	NIL	no	no	no	no	P	U		4.2	3.4	3	-	-	-	-	
32	F	32	11- 12 th	4 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	UL		5.4	4.8	-	-		-	-	
33	M	42	nil	0.5 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	TUL		3.8	3.1	-	-	-	-	-	
34	M	35	nil	3 Y	31-50	itc , scal	NIL	NIL	no	no	no	no	P	TU		4.8	3.8	3		-	-	-	