DISSERTATION ON
EFFICACY OF TOPICAL 1% FLUCONAZOLE GEL IN DERMATOPHYTOSIS

Dissertation Submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
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CERTIFICATE

This is to certify that this dissertation entitled "**EFFICACY OF TOPICAL 1% FLUCONAZOLE GEL IN DERMATOPHYTOSIS**" is a bonafide work done by **Dr.B.SHARMILA** doing post graduation in M.D. (Pharmacology), Stanley Medical College, Chennai - 1 who is appearing for final M.D. Examination in March 2008 in partial fulfillment of the regulation by THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI.

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DECLARATION

I solemnly declare that this dissertation "**EFFICACY OF TOPICAL 1% FLUCONAZOLE GEL IN DERMATOPHYTOSIS**" was written by me in the Department of Pharmacology, Govt. Stanley Medical College and Hospital, Chennai, under the guidance and supervision of **Prof. Dr. S. MADHAVAN, M.D.,** Professor and Head of the Department of Pharmacology, Govt. Stanley Medical College, Chennai - 600 001.

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Place : Chennai.
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CONTENTS

INTRODUCTION

The accelerating pace of change in medicine stems from an explosion of scientific information and there is a need to blend this information into the art and practice of medicine.

The challenge of managing skin diseases lies not only in proper diagnosis, but also in the use of correct drug without causing any discomfort to the patient. It is also of cosmetic importance and infact this is the cause for anxiety, both among the young and the older people.

Superficial fungal infections are caused by Dermatophytes and are termed Dermatophytosis. The Dermatophytes are a group of taxonomically related fungi, which have the ability to form attachment to keratin, that is Stratum corneum of the epidermis, hair, nails and the horny tissues of animals.[1]

Fungal infection of the skin is very common in India. In the Department of Dermatology, Stanley Medical College and hospital where the study was conducted, incidence of fungal infection for the year 2006 was 12%. The Dermatophyte infection was 8% and the remaining fungal infections were 4%.

The patients who are included in this study are from low socio economic status and engaged in labour work. Their personal hygiene is very poor. Most of them wear the same dress for many days. Spores and vegetative forms in the unwashed cloth causes reinfection. This leads to increased incidence of superficial fungal infection in lower socio economic group.

Drugs which are available for the treatment of fungal infections are enumerable. In addition to this, drugs are also available in ayurvedic, siddha and unani.

Topical 1% Fluconazole gel has been recently introduced. Fluconazole was available only as tablets or capsules and as an IV formulation. The oral and parenteral dosage forms are indicated only for systemic candidiasis like oropharyngeal candidiasis, oesophageal candidiasis, vaginal candidiasis, Cryptococcal meningitis, Coccidiodal meningitis and other fungal meningitis. It is also available as 0.3% eye drops for treating fungal keratitis [2]. It is also used orally for prophylaxis against candida infection in immunocompromised patients. Dermatophytosis and cutaneous candidiasis are treated with oral Fluconazole, 150 mg once a week for 4 weeks.

Topical Fluconazole had been introduced only recently for the treatment of Dermatophytosis.

In this study an attempt has been made to assess the efficacy of topical 1% Fluconazole gel in Dermatophytosis in comparison with oxiconazole cream, topical once daily and tablet Fluconazole 150 mg given once weekly for 4 weeks and the details are presented in the ensuing chapters.

AIM OF THE STUDY

To determine the efficacy of topical 1% Fluconazole gel in Dermatophyte infections.

OBJECTIVES

1. To evaluate Topical 1% Fluconazole gel in Dermatophyte infections.

2. To compare the efficacy of Topical 1% Fluconazole gel with orally administered Fluconazole tablet and Topical 1% oxiconazole cream.

SCOPE OF THE STUDY

Dermatophytes are a group of closely related filamentous fungi that infect only superficial keratinised tissue namely the skin, hair and nails. The clinical condition caused, is collectively known as Dermatophytosis. It is also known as Tinea or ring worm infection.

Dermatophytosis should be differentiated from Dermatomycosis; some times they are used as synonyms. Dermatomycosis also includes skin lesions produced by other fungi like candida albicans.[3]

Numerous drugs are available for the treatment of Dermatophytosis. Drugs can be given both orally and Topically. The orally given drugs are Griseofulvin and azole derivatives like Fluconazole, Ketoconazole and Itraconazole. Topically administered drugs are Benzoic acid and salicylic acid, miconazole, clotrimazole, tolnaftate, undecylinic acid, Ciclopirox olamine etc.

Fluconazole is given for Dermatophytosis in the dose of 150-200 mg once weekly for 4 weeks. Topical Fluconazole 1% gel is a recent introduction. Dermatophyte infection occurs recurrently

even after adequate treatment with topical agents especially in hot region like South India.

This could be due to poor hygiene, over crowding, washing clothes under insanitary conditions both in the laundry and at home. So, repeated treatment is necessary. The oral antifungal agents and intravenous Amphotericin B can be used only in special circumstances. The orally administered azoles can produce serious drug interactions and adverse effects, if given repeatedly.

Moreover, they have greater use in immuno compromised patients. Therefore, to treat chronic simple Dermatophytosis, simple and safe drug is required. Though ayurveda and siddha claim that many preparations are highly effective on topical administration in superficial fungal infection, the claims are yet to be scientifically documented.

Fluconazole is a known antifungal drug. This study has been undertaken to find out its usefulness as a topical agent, in the outpatient population attending the Department of Dermatology at Stanley Medical College hospital.

Topical Fluconazole gel can be an effective substitute for other topical agents, for which the fungi have become resistant.

Generally, Topical antifungal therapy is better than systemic antifungal therapy, since serious side effects do not occur. With Topical therapy there is no need to monitor the therapy with costly laboratory procedures. The treatment is restricted to affected site. Hence, even though there are many topical antifungal drugs, addition of one more topically effective agent to the list will only be a boon to mankind.

REVIEW OF LITERATURE

1.

1.1 MYCOLOGY

Mycology is the study of fungi. The fungi had been recognized as causative agents of human disease earlier than bacteria. There are thousands of species of fungi. Majority are beneficial and help mankind in the production of food and spirits, breaking down organic matter or by providing useful antibiotics and immunosuppressive drugs like cyclosporine.[4]

Fungi are eukaryotic protista and they differ from bacteria in many ways. They possess rigid cell wall; the cytoplasmic membrane contains sterols. They divide either sexually or asexually.

Depending upon the cell morphology, the fungi are divided into 4 classes [5].

1 - Yeast

2 - Yeast like fungi

3 - Moulds

4 - Dimorphic fungi.

Yeast :

They are unicellular fungi. The only pathogenic yeast is *Cryptococcus neoformans*.

Yeast like fungi :

They grow partly as yeast and partly as elongated cells resembling hyphae. The latter form a pseudomycelium. Eg. *Candida albicans.*

Moulds :

They are filamentous fungi. They reproduce by the formation of different types of spores. Eg. Dermatophytes, which are pathogenic moulds.

Dimorphic fungi :

They occur as filaments or as yeasts depending upon the growth condition. Most fungi causing systemic infections are dimorphic fungi.

1.2 MYCOSIS

Human fungal infections are broadly of two types.

1. Superficial
2. Systemic

Superficial fungal infections are more common and comprise various types of tinea affecting the skin, hair and nails. They run a chronic course.

Systemic mycoses occur in varying degrees of severity, ranging from asymptomatic infection to fatal disease.

A third type of fungal infection is opportunistic infection, occurring in immunocompromised patients. They are caused mainly by fungi that are normally avirulent such as Mucor, Pencillium and Aspergillus.

1.3 SUPERFICIAL MYCOSIS

Superficial mycosis are of two types – Surface infections and cutaneous infections.

1. Surface infections:

Here the fungi live exclusively on the dead layers of skin and its appendages. No inflammatory reactions are produced as they are not in contact with the living tissue.

Eg. Tinea Versicolor, Tinea Nigra and Tinea Piedra.

2. Cutaneous infections :

Here the infection is confined to the cornified layer of the skin and its appendages. Allergic and inflammatory reaction occurs in the host due to the fungi and their metabolic products.

Eg. Dermatophytes and candida albicans. Candida albicans can also cause systemic disease.

1.4 Pityriasis versicolor:

It is a chronic asymptomatic condition involving the stratum corneum. The causative agent is a yeast like fungus called Pityrosporum orbiculare (*Malassezia furfur*).

The sites involved are mainly the chest, abdomen, upperlimbs and back.

1.5 Tinea Nigra:

It is caused by *Cladosporium wernickii*. It is localised to stratum corneum especially of the palms, producing dark macular lesions.

1.6 Tinea Piedra:

Two varieties of piedra are recognised

1. Black piedra caused by *Piedraia hortai*
2. White piedra caused by *Trichosporon beigellii*.

This is a fungus infection of hair and they occur as nodules along the hair shaft.

1.7 Dermatophytosis

Dermatophytes have been classified into three genera namely

Trichophyton

Microsporum and

Epidermophyton

General characters[6a,6b]

They infect only superficial keratinised tissues- the skin, hair and nails. The Dermatophyte infections of hair most commonly present as Tinea Capitis but may also present as Tinea Barbae (Majocchi's granuloma).

The Dermatophyte infection of the trunk and extremities are known as Tinea Corporis. The Dermatophyte infection of the groin is known as Tinea Cruris. The Dermatophyte infection of the hand is known as Tinea Manum and the Dermatophyte infection of the feet is Tinea Pedis.

The Dermatophytes are restricted to the non viable skin because they are unable to grow at 37°c or in the presence of serum. The three genera of Dermatophytes consists of about 40 related fungi. In culture, many species are closely related and often difficult to identify.

Depending upon whether their usual habitat is soil, animals or humans, Dermatophytes can also be classified as

Geophilic

Zoophilic

Anthropophilic species.

Anthropophilic species, which cause the greatest number of human infections, cause relatively mild and chronic infections and may be difficult to eradicate. Whereas geophilic and zoophilic dermatophytes, produce acute infections that tend to resolve rapidly.

1.8 CLINICAL FEATURES OF DERMATOPHYTE INFECTION

This is presented as a Tabular column as shown[8]

TABLE – 1

Skin Disease	Location of Lesions	Clinical Features	Fungi Most Frequently Responsible
Tinea corporis (ringworm)	Nonhairy, smooth skin.	Circular patches with advancing red, vesiculated border and central scaling. Pruritic.	T.rubrum, E.floccosum.
Tinea pedis (athlete's foot)	Interdigital spaces on feet of persons wearing shoes.	Acute: itching, red vesicular. Chronic: itching, scaling, fissures.	T.rubrum, T.mentagrophytes, E.floccosum.
Tinea cruris (jock itch)	Groin	Erythematous scaling lesion in intertriginous area . Pruritic.	T.rubrum, T.mentagrophytes, E.floccosum.
Tinea capitis	Scalp hair. Endothrix: fungus inside hair shaft. Ectothrix: fungus on surface of hair.	Circular bald patches with short hair stubs or broken hair within hair follicles. Kerion rare. Microsporum-infected hairs, fluoresce.	T.mentagrophytes, M canis.
Tinea barbae	Beard hair	Edematous, erythematous lesion	T.mentagrophytes.
Tinea unguium (onychomy-cosis)	Nail	Nails thickened or crumbling distally, discolored; lusterless. Usually associated with tinea pedis.	T.rubrum, T.mentagrophytes, E floccosum.
Dermatophytids ('id' reaction)	Usually sides and flexor aspects of fingers. Palm. Any site on body.	Pruritic, vesicular to bullous lesions. Most commonly associated with tinea pedis.	No fungi present in lesion. May become secondarily infected with bacteria.

1.9 Common Dermatophytes Are:

T. Rubrum	T. Schoenleinii
T. Mentagrophytes	T. Violaceum
T. Tonsurans	M. Canis
E. Floccosum	M. Gypseum
	M. Audouinii [9]

1.10 Deep Mycoses:

They may be classified as

- Those that affect exclusively the subcutaneous tissues (subcutaneous or intermediate mycoses)

  Eg. Mycotic mycetoma
  Chromo blastomycosis
  Rhino sporidiosis etc.

- Those that involve the internal organs (deep seated or systemic mycoses)

  Eg. Cryptococcosis
  Blastomycosis
  Histoplasmosis etc.

Since this study is about the effect of Fluconazole and other drugs on Dermatophytes, detailed discussion about candida albicans and deep fungi have not been presented.

2. LABORATORY DIAGNOSIS:

It is essential to know the meaning of certain words used in the description of fungi, for the proper identification of fungus causing the infection obtained from skin scrapings and isolated by culture.

Each fungus has characteristic appearance and they can be differentiated by the appearance of hyphae, conidia, etc.

2.1 Growth characteristics:

They are useful for identification of the fungus. The growth characteristics studied are the rapidity of the growth, colour and morphology of the colony and pigmentation.

The morphology of the hyphae, spores and other structures are studied in teased mounts or slide cultures.[10 a, 10 b]

EXPLANATION OF CERTAIN TERMS :

HYPHAE :

These are tubular, branching filaments 2-10 micro meter in width. The interwined mass of hyphae which accumulate during active growth is known as mycelium. Some hyphae are divided into cells by cross wall or septa.

SPORES :

These are specialised structures and are capable of surviving under adverse conditions.

Spores may result from asexual or sexual reproduction.

The asexual spores are Sporangiospores and Conidia. Conidia can be microconidia (small) or macroconidia (large) and arthro conidia (multicellular)

Sexual spores are Ascospores, Basidio spores and Zygospores. Asexual spores are formed by mitosis; sexual spores are produced by meiosis.[11]

2.2 LABORATORY METHODS:

Three methods are followed for the lab diagnosis of fungal infections. They are:

1. Microscopic examination of skin scrapings in KOH slide mount
2. Culture methods and slide examination
3. Histopathological studies.

1. KOH STAIN:

This is a simple diagnostic method with excellent positive predictive value. By this method it is possible to visualise the hyphae, which is characteristic of Dermatophytes. The 'scrapings' obtained from the affected site is placed on the microscope slide. The scrapings are obtained from the edge of the lesion, since it is the active border of lesion.[12]

Then the slide is covered with a coverslip and few drops of 10% KOH solution is added to the side of the coverslip. The capillary action draws the KOH to the scaly sample. The slide is gently heated. Then the slide is allowed to cool and 'ripen' a few minutes before examination.

The KOH clears the specimen by digesting protein rich debris and other pigments and loosening the sclerotic material without damaging the fungus.[13] In a well cleared mount it is possible to visualize the nuclei, organelles and fat droplets with in the mycelium, since the hyphae become highly refractile.

2. CULTURE METHODS:

The standard medium for primary isolation of Dermatophytes is 'SABOURAUD'S AGAR'. It consists of a source of energy (Dextrose), a source of protein (peptone), and a firm surface (agar). Apart from this there are two additives in the medium.

One is cyclohexamide and other one is an antibiotic; cyclohexamide is used in the concentration of 0.1 - 0.4 mg/ml. This supresses the growth of saprophytic fungi, without affecting the growth of Dermatophytes.

The Antibacterial antibiotics which are commonly used are Chloramphenicol (.05 mg/ml) or Aureomycin (0.1 mg/ml) or Penicillin or Streptomycin.[14 a, 14 b]

Some times a diagnostic indicator is also added to the medium. This act as a PH indicator. This is based upon the fact, that Dermatophytes produce a change in PH during their growth, resulting in a alkaline medium. This medium is known as 'DERMATOPHYTE TEST MEDIUM'.

Cultures are examined for colour, shape, speed of growth, pattern of growth and surface characteristics. Haley (1982) has devised a system for grouping these fungi on the basis of gross colony morphology.[15]

The three sets of observations useful for the identification of most fungi are as follows:

1. **Colony obverse**

Here the following are identified:

(a) Colour (e.g., white, pearl, ivory, black).

(b) Consistency (e.g., cottony, fluffy, suedelike, wiry)

(c) Topography (e.g., flat, folded, plicate, rugose)

2. Colony reverse

Here the presence of pigment is noted.

3. **Microscopic morphology** :

Here the type of conidia present, their size, shape and arrangement are noted.

3. HISTOPATHOLOGIC STUDIES

It is not routinely done. Only when there is no response to treatment, biopsy specimens are taken for histopathological evaluation.

STRUCTURE OF THE SKIN

The skin of an average adult covers an area of about $2m.^2$ It is the largest organ of the body.[16]

Structurally the skin consists of two principle layers-epidermis and dermis.[17]

1. Epidermis

Epidermis is the outer layer. The thickness varies from site to site. It is thickest on palms and soles and thinnest on eyelids.

The epidermis contains 5 layers and they are stratum basale, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum. These are named from bottom to top.

The bottom layer is stratum basale, and the top most layer is stratum corneum. Stratum corneum is made up of dead, flat, skin cells which shed every week.

In the stratum basale, the cells divide and push the already formed cells into higher layers.

As they move higher, they flatten and eventually die. Thus the epidermis is mainly made up of keratinocytes and the proliferative compartment of epidermis resides in the basal layer and in the layer immediately adjacent to the basal layer. Apart from this, three more cell types are seen in the epidermis and these three cell types make up the 10% of epidermal cells

These are,

1. Melanocytes found predominantly in the basal layer and they synthesise the pigment melanin

2. The Langerhans cells whose prime function is presentation of foreign antigen to lymphocytes.

3. Merkel cells present in the basal layer, play a role in signal transduction of fine touch.

2. Dermis :

The Dermis is vascular and supports the epidermis structurally and nutritionally. The thickness of dermis varies at different locations, thinnest on the eyelids and thickest on the Palms & Soles.

Dermis contains 3 types of tissues. These are collagen, elastic tissue and reticular fibres.

The 2 layers of Dermis are

1. Papillary layer
2. The reticular layer

The **upper papillary layer** contains a thin arrangement of collagen fibres.

The **lower reticular layer** consists of dense, irregular connective tissue and this layer comprises the bulk of the dermis. The dermis also contains many specialised cells and structures. These are the hair follicles, along with the erector pili muscle, sebaceous glands, sweat glands, blood vessels and nerves. The nerves transmit various sensation. Specialised nerve cells called meissner's and pacinian corpuscles, transmitting sensation of touch and pressure are also present.

4. Drugs used in fungal infections

4.1 ANTI FUNGAL DRUGS.

CLASSIFICATION [18]

1. Antibiotics
    a. Polyenes-Amphotericin B, Nystatin, Hamycin, Natamycin.
    b. Heterocyclic Benzofuran - Griseofulvin.
2. Anti metabolite

    Flucytosine (5-FC).
3. Azoles
    a. Imidazoles

        (Topical): Clotrimazole, Econazole, Miconazole.

        (Systemic): Ketoconazole
    b. Triazoles

        (Systemic): Fluconazole and Itraconazole.
4. Allylamine

    Terbinafine.

5. Other Topical Agents

    Tolnaftate, Undecylenic acid, Benzoic Acid, Quiniodochlor, Ciclopirox olamine, Sodium thiosulfate

Another classification depending upon the mechanism of action is as follows[19]

* Inhibition of fungal cell wall synthesis

  Caspofungin

* Bind to fungal cell membrane ergosterol

  Amphotericin B, Nystatin

* Inhibition of ergosterol and lanosterol synthesis

  Terbinafine, Naftifine, Butenafine.

* Inhibition of ergosterol synthesis

  Miconazole, clotrimazole, ketoconazole, Fluconazole, Itraconazole, and Voriconazole.

* Inhibition of nucleic acid synthesis

  5 - Flucytosine.

* Disruption of mitotic spindle and inhibition of fungal mitosis

  Griseofulvin

* Miscellaneous agents

  Ciclopirox, Tolnaftate, Haloprogin, Undecylenic acid, Topical azoles.

4.2 DRUGS IN DERMATOPHYTOSIS

Drugs which are used for treating Dermatophytosis are

Griseofluvin (oral)

Ketoconazole (oral and topical)

Oral administration of Ketoconazole is restricted due to potential adverse effects.

Fluconazole (oral)

Itraconazole (oral)

Terbinafine (oral and topical)

Voriconazole (oral)

Ciclopirox olamine (Topical)

Clioquinol (Topical)

Undecylenic acid (Topical)

Benzoic acid and salicylic acid (Topical)

Haloprogin (Topical)

4.3 DRUGS USED IN THE STUDY

Two drugs are used in the study

- **Fluconazole and Oxiconazole.**

The two drugs belong to azole group of Antifungal drugs.

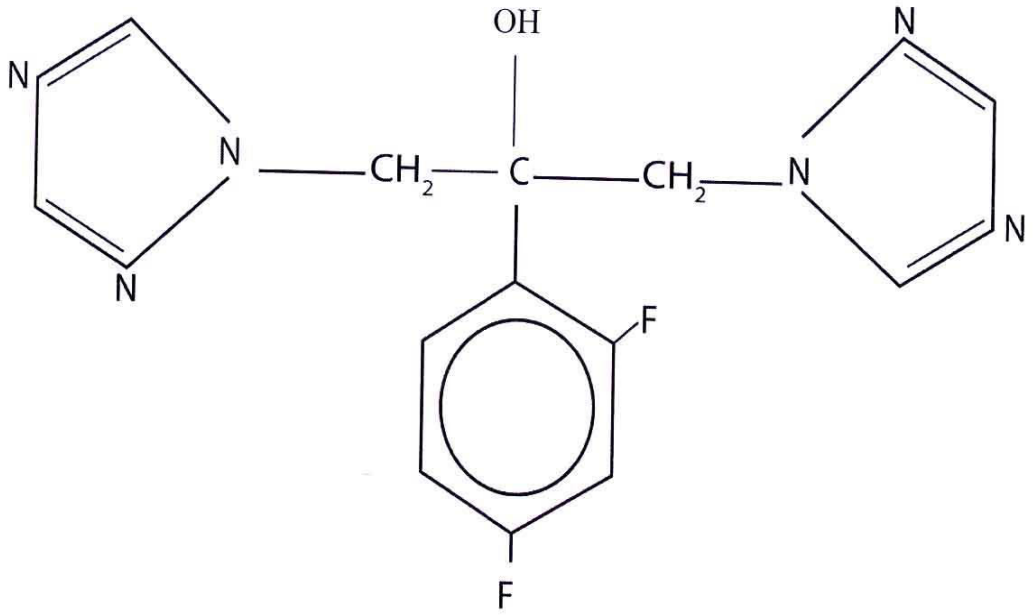
Mechanism of Action of Azoles:

Both imidazoles and triazoles have the same mechanism of action. These drugs bind to the fungal cytochrome P450 dependent enzyme, 14 alpha demethylase and this results in impairment of ergosterol synthesis, which in turn causes membrane abnormalities in the fungus.

Other antifungal mechanism like inhibition of purine transport and interference with mitochondrial respiration also seem to be responsible.

A. FLUCONAZOLE

Its structure is as follows:



It is a water soluble fluorinated Bistriazole.[20] It has broad spectrum antifungal activity and is effective against Dermatophytes, Candida and other fungi involved in deep mycosis. It is also effective against Nocardia, Staphylococcus aureus, some gram positive anaerobic bacteria (Streptococcus faecalis, Bacteroides fragilis) and also against leishmania.

Pharmacokinetics:

1. **Absorption:**

When given orally, it is 94% absorbed from GIT.

2. **Plasma protein binding:**

It is weakly bound (10-12%) to plasma proteins.

3. **Distribution:**

It is distributed through out the body, including CSF. Fungicidal concentrations are achieved in nails, vagina and saliva.

4. **Plasma half life:**

The half life is 27- 37 hrs[21] and this permits once daily dosing. About 80% of the drug is excreted unchanged in the urine, while 10% is excreted unchanged in the faeces. Dosage reductions are necessary in the presence of renal insufficiency. Of all the azoles, Fluconazole has the least effect on hepatic microsomal enzymes.

Availability:

Fluconazole is available as capsules for oral administration, containing 50, 100, 150 and 200 mg per capsule and also for intravenous infusion in the strength of 2mg/ml and as eye drops in the strength of 0.3 %.

Therapeutic uses

The drug is administered orally for the following conditions and in severe conditions, can be given as Intravenous infusion.

1. Vaginal candidiasis - Single dose of 150 mg

2. Oropharyngeal candidiasis - 200 mg on the first day followed by 100 mg daily for 2 weeks[22].

3. Disseminated candidiasis, cryptococcal meningitis, coccidiodal meningitis - 200 - 400 mg / day for 4-12 weeks.

4. Tinea infections and cutaneous candidiasis-150 mg oral dose once a week for 4 weeks.

5. T.Unguim-150 mg every week for 12 months.

6. Fungal keratitis-Fluconazole 0.3% Eye drops.

Adverse effects

Fluconazole is well tolerated. Nausea, vomiting, diarrhea, headache and rashes have been reported in 2 to 3 % of patients.

Selectivity for fungal cytochrome P 450 is higher. It has very little effect on mammalian cytochrome P 450 enzyme.

Unlike ketoconazole, it does not inhibit steriod synthesis; no anti androgenic effect or endocrine side effects.

Prolonged therapy can cause elevated serum transaminase and alopecia. Drug should be avoided during pregnancy as it can be teratogenic. Only 3 cases of teratogenicity have been reported.[23]

Drug interactions

Usually drug interactions are mild and they are not clinically significant.

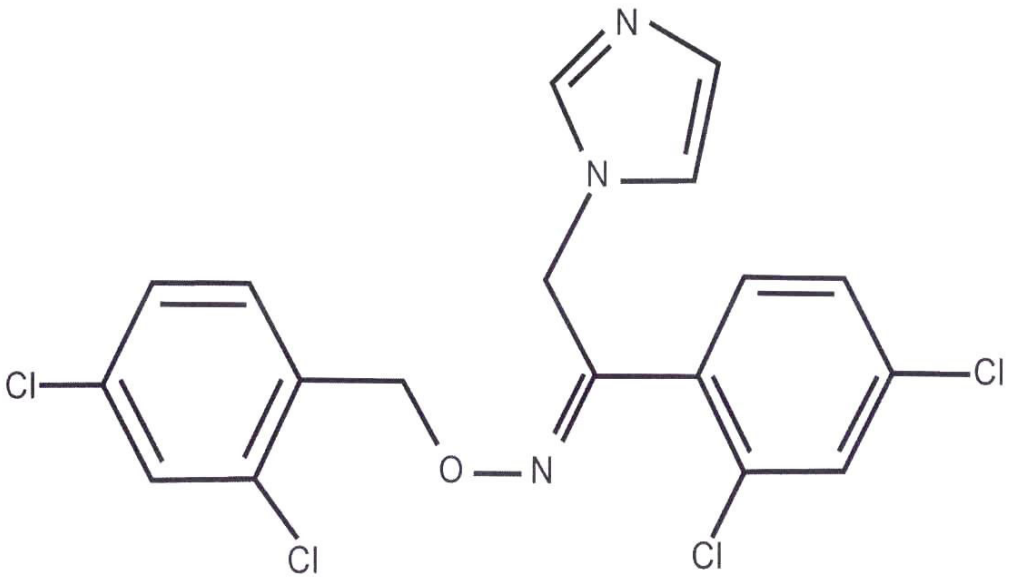
1. A few cases of ventricular tachycardia have been reported when Fluconazole was given with cisapride.

2. Increased plasma levels of phenytoin, astemizole, cyclosporine, warfarin, zidovudine and sulfonylureas can occur.

3. Hepatic microsomal enzyme inducer like rifampicin decrease the efficacy of Fluconazole.

4. Unlike in the case of Ketoconazole, H2 receptor blockers and proton pump inhibitors do not affect the absorption of Fluconazole. Like any other azole, Fluconazole should not be administered with Amphotericin B.

B. OXICONAZOLE: Its structure is as follows



Oxiconazole is an imidazole derivative. It is used topically in the treatment of Dermatophytosis. It is available as 1% cream and lotion. The drug is not available for systemic therapy. Therefore adverse effects are not encountered.

Oxiconazole topical cream has also been introduced recently and various multicentric studies have shown, topical oxiconazole cream to be highly effective in Dermatophytosis and the drug is well tolerated.

MATERIALS AND METHODS

Study centre:

Out patient section,

Department of Dermatology,

Government Stanley medical college and Hospital.

Study Period:

June 2006 to July 2007

Study Duration:

Total - 8 weeks.

Drug administration and follow up - 6 weeks.

Post drug administration and follow up - 2 weeks.

Study design:

Prospective, Randomised, controlled, clinical trial.

Drugs used:

- 1% Fluconazole gel
- Tablet Fluconazole 150 mg
- 1% Oxiconazole cream

Sources of drugs:

Topical Fluconazole gel supplied by Cosme pharmaceuticals

Tablet Fluconazole supplied by Cosme pharmaceuticals

Oxiconazole cream supplied by glaxo smith Kline

Dosage forms of drugs used:

Fluconazole is used as Topical gel. Gels are semisolid preparations in which a liquid phase is constrained within a three dimensional polymeric matrix in which a high degree of physical cross linking has been introduced.

The polymers used for preparing the gels include the natural gums Tragacanth, Pectin, Agar, semisynthetic substances like methyl cellulose, carboxy methyl cellulose.[24]

In simple terms, the drug is dissolved in liquid and then dispersed in some jelling agents. Gels provide a faster release of drug substance, independent of the water solubility of the drug.[25]

Creams are semisolid emulsions with opaque appearances and thus they differ from ointment which are translucent.

Fluconazole tablet is used in solid dosage forms and administered orally.

INCLUSION CRITERIA

1. Patient suffering from T.Cruris and T. Corporis only.
2. Patient in the age group of 18-60 yrs.
3. Both male and female patients
4. Duration of suffering from T. Cruris and T. Corporis more than 10 days but less than 20 days.
5. Willing to give written informed consent.

6. Not already under drug therapy for Dermatophytosis.

7. Not suffering from any other systemic illness

8. No H/o Arrhythmias or any other heart disease.

EXCLUSION CRITERIA

1. Patients having associated T. Barbae, T. Capitis and fungal infections of nails of fingers and toes.

2. Fungal infections other than T. Cruris and T. Corporis.

3. Age below 15 yrs and above 60 yrs.

4. Known cases of Diabetes mellitus, Dyslipidemia, Hypertension, Cardiac and Renal disease.

5. Those who are not willing to give informed written consent.

6. Pregnant and lactating women.

7. Those who are suffering from T. Versicolor alone or in association with T. Corporis and T. Cruris.

JUSTIFICATION FOR INCLUSION AND EXCLUSION CRITERIA

In this study, the idea is to evaluate the effect of the drugs in T. Cruris and T.Corporis. Though the same Dermatophytes are causative agents for fungal infection of scalp, beard and finger and toe nails, these cases are not included in the study.

The duration of study period is only 8 weeks. So, fungal infections other than T. Cruris and T. Corporis require a longer study period and therefore these cases cannot be taken for this study, as they interfere with assessment of results.

Only those patients having fungal infections of more than 10 days duration but less than 20 days duration are included in this study.

Duration of more than 20 days is sufficient enough for a person to seek some treatment. Hence, inclusion of such patients may interfere with assessment of the effectiveness of the drug under study, even though the patient may claim that he or she has not taken any treatment. Patients having fungal infections of less than 10 days of

duration are also not taken because the skin lesions are not well developed though itching is persistent.

People suffering from Diabetes mellitus and other immuno compromised states who present with Dermatophytosis are not included since the severity of fungal infection waxes and wanes depending upon the original disorder. For example in Diabetic mellitus patient's fungal infections do not cause any problem, if the blood sugar is under control. So, if there is no itching the patient may not use the antifungal drug and if symptomless may not report for subsequent evaluation.

METHODOLOGY

Informed written consent is obtained from the patient in their own language, after explaining in detail about the study.

The patients who are included in the study are randomised in 3 groups. 60 patients are alloted to each group. Before starting the therapy, basic investigations for blood urea, sugar, serum creatinine and haemogram were done, in appropriate cases.

Group 1:

This group consists of 60 patients. All the patients in this group were treated by topical application of 1% Fluconazole gel.

The patients were asked to apply the gel over the lesion every day just before going to bed. The drug was applied everyday, continuously for 6 weeks. Before starting the therapy, the fungal infections were confirmed with KOH staining and scrapings from the site of lesion were taken for mycological culture.

Patients were asked to report on the first day of every week for a period of 6 weeks and also on the first day of 7th week and 8th week.

During every visit, the patient was assessed clinically in terms of itching, erythema or discolouration, scaling and burning sensation. These parameters were graded according to the severity and the procedure followed for assessing the severity is explained in the later part of the same chapter.

The patients were also assessed by lab investigations. KOH staining was done on 0,2,4,6,8 visits (weeks). Mycological culture was done on 0,3rd and 4th visits (weeks).

The patients received the actual drug for 6 weeks only. But, the patients were followed up for a further period of 2 weeks ie, 7th and 8th weeks, which is the drug free period.

Group 2:

60 patients were allotted to group 2. These patients were given oral Fluconazole tablet 150 mg weekly once, for a period of 6 weeks.

Oral Fluconazole tablet was given on the first day of every week for 6 weeks. Improvement was assessed clinically and also by lab investigations in the same manner as it was done in group 1. In this group also, the patients were followed up for 8 weeks, in which first 6 weeks was drug administration period and the last 2 weeks were drug free post treatment follow up.

Group 3:

Here also 60 patients were allotted. All the patients in this group were treated by topical application of 1% oxiconazole cream daily for 6 weeks. The drug was applied just before going to bed. The patient was reviewed at the beginning of every week for 6 weeks, and also at the beginning of 7th and 8th week which were drug free periods.

Clinical assessment, lab investigations were done as in the previous 2 groups.

Assessment Criteria

The efficacy of drug therapy is clinically assessed by improvement of itching, erythema / discolouration, scaling and burning sensation.

Itching / Pruritis

The exact method of assessing and grading pruritis/itching is very difficult and there are no documented standards. So, the investigator has to rely upon the patient's expression of subjective feeling, to grade the itching. Visual analogue scales are also not satisfactory [26].

Hence, for this study, the severity of itching has been graded as follows:

0 - No itching

1 + - Mild, present occasionally; does not disturb the normal activity

2 + - Moderate, patient is aware of itching. Scratches frequently. But, itching is intermittent.

3 + - Severe, disturbs patient's normal activity like sleeping. Itching is present almost throughout the day.

Scaling:

It is also difficult to grade the severity of scaling. We can only say if scaling is present or absent. So, Scoring is done as

+ for present

- for absent.

Erythema/Discolouration:

In this also (+) indicates presence of erythema/discolouration and (-) indicates absence of erythema / discolouration.

Burning sensation:

Here also (+) indicates presence of burning sensation and (-) indicates absence of burning sensation.

The Table designed to record the observations is shown in the next page.

RESULTS

Analysis of Demographic details

The results of the study is analysed and Oneway ANOVA and Chi Square tests were used to compare the results.

60 patients were enrolled in each group. The mean age of patients in group1, who were treated by application of topical Fluconazole gel is 33.73 and the mean age of patients in group2, who received oral Fluconazole tablet, on weekly basis, has been found to be 35.28. The mean age of patients in group3, who were treated by applying oxiconazole cream is 34.83.

The age distribution is shown in table number2. There is no significant difference in the age of the patients enrolled in all the three groups.

The number of patients in the various age groups enrolled in the 3 trial groups has also been analysed and is presented in table number 3.This also shows no significant difference among the 3 groups .

Sex Distribution

Number of female and male patients in each group and the percentage in each group was also analysed and is presented in table number 4.This also shows no significant difference among the 3 groups .

The lesion type

The percentage of patients with Tinea corporis and Tinea cruris in each group has been analysed and is presented in table number5.

The percentage of patients having Tinea corporis is 50% in the Group1 , 56.7% in Group2 and 56.7% in Group3.

The Percentage of patients with Tinea cruris enrolled in each group is 50% in the Group1, 43.3% in Group2 and 43.3% in Group3.

The lesion duration

The mean duration of lesion in all the three groups before starting therapy has been analysed .It is 12.67 days in group 1, 12.72 days in group 2 and 12.28 days in group 3.

The mean duration of lesions for all the 180 patients enrolled in 3groups is 12.56 days and there is no significant difference among the 3 groups as is shown in the table Number 6.

Box plots to compare the age distribution, percentage bar diagram for sex distribution & the type of lession, simple bar diagram has also been presented.

For the above mentioned analysis one way ANOVA TEST & Chi-Square test were employed.

Analysis of Drug Effects in the Trial Groups

Comparison of Itching between Group 1 and Group 2

Since Pruritis is the main symptom in fungal infection this has been compared in Table number 7.

The criteria followed for grading the severity of itching has already been discussed under materials and methods.

The severity of itching between Group1 (Fluconazole gel) and Group2 (Fluconazole tablet) has been compared. Before starting therapy, that is on the 1st visit, the baseline values of the severity of itching are as follows:

Mild 1+ – 8 in Group 1and 17 in Group 2

Moderate 2+ – 29 in Group 1and 26 in Group 2

Severe 3+ – 23 in Group 1and 17 in Group 2

This was analysed by Chi-square test and no significant difference was observed.

On comparing the severity of itching on the first day of the first week, that is one week after therapy, the severity of itching has been found to be as follows:

Mild 1+ – 14 in Group 1and 47 in Group 2

Moderate 2+ – 0 in Group 1and 13 in Group 2

Nil 0 – 46 in Group 1and No one in Group2

To explain this, no itching was present in 46 patients at the beginning of first week in group 1(Fluconazole gel treated) and mild itching (+1) was present in 14 patients. Where as in group 2, 47 patients were still having mild itching (+1) at the beginning of first week. The P value is .001 which is highly significant.

The severity of itching between group1 and 2 has also been compared 2 weeks after therapy.

This shows that in group 1, all the 60 patients showed no itching (nil or 0), Where as in group2 (Fluconazole tablet) only 43 patients out of 60 enrolled had no pruritis.

Similarly, the number of patients having mild itching in group 1 is nil(no pruritis), where as in group 2, 17 patients still had mild itching(+1).

The P value has been found to be .001 and this is highly significant.

Comparison of burning sensation between group 1 and group 2.

The baseline value on the 1st visit, before starting therapy, shows that all the 60 patients in both the groups had burning sensation.

One week after therapy, burning sensation was absent in 50 patients in group 1, whereas it was absent in 36 patients in group 2. The P value is also highly significant.

Two weeks after therapy, burning sensation was absent in 60 patients in group 1, where as it was present in 18 patients out of 60 patients enrolled in group 2.This is also statistically significant.

Three weeks after therapy, no burning sensation was present in the patients in group 1, where as only 54 patients did not have burning sensation in group 2.The P value for this has been found to be 0.04 which is significant. This data has been presented in table number 8.

Comparison of scaling between Group 1 and Group 2

Scaling between group1 and group 2 has been compared and for the statistical analysis, chi-square test has been employed.

The baseline value shows that all the 60 patients in both the groups had Scaling. One week after therapy, scaling was absent in 50 patients in group 1, but it was absent only in 3 patients in group 2.

The statistical analysis also shows P value as 0.001, which is highly significant.

Two weeks after therapy, scaling was absent in 59 patients in group 1, and 42 patients in group 2. That is scaling was still present in 18 patients in group 2. This has also been found to be statistically highly significant.

Three weeks after therapy, scaling was absent in all the patients in group 1, where as in group 2, it was absent in 55 patients and still present in 5 patients .The P value in this group is not significant. This data has been presented in table number 9.

Comparison of Erythema between group 1 and group 2

The baseline value shows (that is on the first visit,before starting therapy) that erythema /discolouration was present in all the patients in both the groups.

One week after therapy, it was absent in 50 patients in group 1, but it was absent only in 5 patients in group 2.In otherwords, Erythema/discolouration was present in 55 patients in group 2(tablet).This is also statistically highly significant.

Analysis shows that it is also statistically highly significant 2 weeks after therapy, where all the 60 patients in group 1 had no Erythema / discolouration, whereas it was still present in 25 patients in group 2.

Three weeks after therapy, 56 patients showed absence of Erythema/discolouration in group 2 and it was still present in 4 patients in the same group. These data are presented in table number 10.

Comparison of lab investigations of group1 with group 2

Number 1- KOH STAINING

KOH Staining of the scrapings obtained from the skin lesions was done and examined for the presence of fungal filaments under microscope. On the first visit, Fungal filaments are positive in all the 60 patients in both the groups and this is shown as baseline value in table number 11.

One week after therapy, fungal filaments were absent in 50 patients in group 1 (Fluconazole gel), where as it was still present in 26 patients and absent only in 34 patients in group 2(Fluconazole tablet). This is statistically highly significant.

Two weeks after therapy, no fungal filaments were detected in all the 60 patients in group 1(Fluconazole gel), where as in group 2, it was absent in 58 patients and present in only 2 patients. This is not statistically significant.

To explain this, Fluconazole gel was able to produce negative KOH staining in greater number of patients at the end of 1st week of therapy, when compared to the patients in group 2 which is on oral Fluconazole tablet. This has been presented in table number 11.

Number 2 Mycological culture

Mycological culture was done on the first visit (that is before starting therapy) and then again on the first day of the 3rd week and on the first day of the 4th week.

In both group 1 and group 2 patients, Mycological culture was positive in all the patients before starting therapy.

In cultures done from the scrapings taken at the begining of the 3rd week, there was no Mycological growth in both group 1 and group 2.

No growth was observed in both the groups in cultures done at the begining of the 4th week. This has also been depicted in multiple bar diagram.

From the Mycological culture, it has been observed that Trichophyton is the major dermatophyte in all the three groups under study. This is followed by Microsporum and then by epidermophyton. This is also shown in table number 12. This table shows the percentage of each species of fungus grown in culture, in all the three groups.

Growth of certain other fungi was also observed. This is discussed in the later chapters.

Analysis and comparison of drug effects in group 1 and group 3.

Comparison of Pruritis/itching between Group 1 (Gel) and Group 3 (Cream)

The severity of itching on the 1st visit that is before starting the therapy are as follows

Mild	1+ – 8 in Group 1and 10 in Group 3
Moderate	2+ – 29 in Group 1and 30 in Group 3
Severe	3+ – 23 in Group 1and 20 in Group 3

The severity of itching was compared one week after therapy. No itching was present among 46 patients in Group 1 and 43 patients in Group 3.

And comparing the same parameters 2 weeks after therapy, itching was absent in all the 60 patients in Group 1 (Gel treated group) and absent in 57 patients in Group 3. This is presented in Table No.13.

The results obtained show that both Fluconazole Gel and Oxiconazole cream have produced similar effects in controlling pruritis.

Comparison of burning sensation between Group 1 and Group 3

This is presented in Table No.14, where the burning sensation between group 1 and group 3 is compared.

All the 60 patients in both the groups complained of burning sensation before starting the therapy and this is shown as 'Baseline' in the table.

One week after therapy, burning sensation was absent among 50 patients in group 1, where as it was absent in 30 patients in group 3. The difference is statistically significant and the P value is .001.

Two weeks after starting therapy, burning sensation was absent in all the 60 patients in group 1 and 59 patients in Group 3.

Comparison of scaling between Group 1 and Group 3

Scaling was present in all the 60 patients in both the groups before starting the therapy (baseline). One week, after starting therapy, scaling was absent in 50 patients in group 1 (Gel Group) and 31 patients in Group 3 (Cream). The difference is found to be statistically significant.

Two weeks after starting therapy, scaling was absent in 59 patients in group 1 and 54 patients in group 3. There is not much difference between the 2 groups.

Three weeks after starting therapy, scaling was not present in either of the groups. This data is shown in Table No.15.

Comparison of Erythema between group 1 and group 3

Erythema /discolouration was present in all the patients in both the groups before starting therapy. This is shown as baseline value in Table No.16.

One week after starting therapy, erythema was absent in 50 patients in group 1, but it was absent only in 25 patients in group 3. This is statistically significant.

Two weeks after starting therapy, erythema/discolouration was absent in all the 60 patients in Group 1 and 53 patients in Group 3. This is also statistically significant.

Three weeks after starting therapy, erythema has disappeared in all the patients, except one in group 3.

Comparision of lab investigations of group1 with group 3

Number 1- KOH STAINING

Fungal filaments were present in all the patients in both the groups before starting therapy which is shown as baseline value in Table Number 17.

One week after starting therapy, fungal filaments were absent in 50 patients in group 1 and 32 patients in Group 3. The difference is statistically significant, since the P value is .001.

Two weeks after starting therapy, fungal filaments were absent in all the 60 patients in both the groups. This is presented in table number 17.

Number 2 Mycological culture

The results of Mycological culture of Group 1 has been discussed already.

The cultures done from the scrapings obtained from Group 3 patients (oxiconazole cream) showed Mycological growth in all the 60 patients before starting therapy.

In cultures done from the material from the same patients, that is in the beginning of 3rd and 4th weeks, showed no fungal growth in culture.

DISCUSSION

From the results, following are inferred:

1. Age wise and sex wise, there is no significant difference among the patients enrolled in all the 3 groups. So this does not interfere with the outcome of the study.

2. Fluconazole topical gel has been found to be more effective than once a week oral Fluconazole tablet in relieving pruritis/itching.

3. Fluconazole gel also reduces the severity of pruritis / itching and the duration of pruritis more effectively than once a week Fluconazole oral tablet.

As far as pruritis/itching is concerned, Fluconazole gel and oxiconazole cream have been found to produce similar effects in controlling pruritis with regard to severity & duration.

4. Fluconazole gel and Fluconazole tablet have almost similar effects in controlling burning sensation.

5. Fluconazole gel and oxiconazole cream also have almost similar effects in controlling burning sensation.

6. On comparing Fluconazole gel and oral Fluconazole tablet, as far as scaling is concerned, Fluconazole gel has faster onset of action than Fluconazole tablet, and the tablet takes a longer time to produce disappearance of scaling.

Fluconazole gel and oxiconazole cream are almost equally effective in controlling the scaling.

7. As far as Erythema is concerned, Fluconazole gel is more effective than Fluconazole tablet, where as Oxiconazole cream produces an effect which is slower than that of the gel.

From the above discussion, it is evident that Fluconazole gel when applied topically everyday produces rapid control of the duration and severity of symptoms in T.Corporis and T.Cruris.

Oxiconazole cream used as control also produces similar effects like topical Fluconazole gel. Both the topical formulation produced almost identical effects. So the topical formulations used,

significantly do not alter the therapeutic outcome. There is no much difference between Gel and Cream.

Differences are observed only with Fluconazole tablet. The differences being continuation of pruritis in the 2nd week and presence of scaling and erythema in the 3rd week.

Though the KOH stainings taken at the beginning of 2nd week, show absence of filaments in the group treated with oral Fluconazole tablet and no mycological growth in the culture in the beginning of the 3rd week and in the beginning of the 4th week, symptoms persisted in group 2 (oral Fluconazole tablet) upto the end of 2nd week.

Clinical symptoms are of more value for comparison purposes, in this situation; Therefore absence of filaments in KOH staining and fungal growth in culture are not of much relevance after the 3rd week of therapy, since the symptoms disappeared in all the 3 groups within the maximum period of 3 weeks of continuous therapy.

The decreased effectiveness of Fluconazole tablet could be due to its once a week administration. Fluconazole has a plasma elimination half life of 27-37 hrs.

Therefore persistent concentration may not be maintained. Since the prescribed dose of Fluconazole is 150mg once a week / orally.

Since the person is exposed to the spores, as a result of poor hygienic measures, non maintenance of the effective plasma concentration for the whole week after a single dose of Fluconazole tablet could not have been adequate enough.

This dosing schedule along with the poor hygienic conditions, would have led to slow disappearance of the symptoms.

Fluconazole tablet, in the dose of 150mg once a week would be highly effective in patients in whom the chances of getting reinfected is less. This is possible in Geographical regions where sweating is less or absent and in high socio economic groups following good hygienic measures in clothing and personal hygiene.

In this part of the country, where this study has been undertaken, sweating is excessive. Most of the patients are from poor socio economic group.

Adequate information could not be obtained from them about the personal hygiene.

In such circumstances, the effect of Fluconazole tablet administered orally in a smaller dose of 50mg daily for a period of 6 weeks could have been more effective.

This is supported by the fact, that increased doses of Fluconazole when used on daily basis for Oesophageal Candidiasis, Cryptococcal meningitis etc., are highly effective, where a constant plasma concentration is maintained.

The psychological factor of the patient may also contribute to the effectiveness of the therapy followed.

Fluconazole gel and Oxiconazole cream are applied everyday, but the tablet is given orally once a week. Most of the patients in the study group, who received oral Fluconazole tablet once a week felt that drug administration only once a week is not sufficient to treat their skin condition.This could have led to persistence of pruritis in this group.

Patient's compliance would have been greater if the drug had been given daily or along with a topical dosage form combined with once a week oral drug administration.

The greater effectiveness of Fluconazole gel and Oxiconazole cream are definitely due to persistent concentrations at the site of application.

Since this is a study, observations are recorded for 8 weeks but in actual clinical practice the topical dosage forms are applied daily for 3 to 4 weeks and the oral Fluconazole tablet of 150 mg is administered once a week for 4 weeks. These therapies are sufficient to treat Tinea infections.

So the patients in all the 3 groups are not hesitant about the daily topical administration or combined topical therapy along with a once a week oral therapy. So, the cost factor is not a bar.

Out of the total 180 cases taken up for the study, in 3% of the cases, the causative organism is found to be Candida albicans. It is not possible to isolate those ones which are due to candida, from the rest, where the causative organisms are Dermatophytes, based on the

clinical symptoms. Growth of the candida was observed only on Mycological culture.

Great care has been taken not to include patients with Diabetes Mellitus and other chronic illness where candida could be the causative organism, for the dermal lesion.

All the three formulations used in the study have been found to be effective against candida.

Griseofulvin is the drug which is commonly given for Tinea infections. From this study, it is inferred that mycological culture is essential in all cases of fungal skin lesions, since organisms other than Dermatophytes can also be the causative agent. It can also be an infection by more than one type of fungus.

Griseofulvin is not effective against candida. Hence, for such cases administration of Griseofulvin can lead to treatment failure.

Fluconazole oral administration is also well tolerated, because it has least effect, of all the azoles, on hepatic microsomal enzymes.

So, drug interactions are mild or of no significance.[27] The incidence of drug interactions with Cisapride, Terfenadine, Astemizole etc are less,when compared to Ketoconazole; It does not inhibit steroid synthesis in man. Hence, no antiandrogenic and other endocrine side effects.

Mycological culture shows growth of Aspergillus in 1 case and Penicillium species in 1 case. Fluconazole has no effect on Aspergillus and other filamentous fungi. In these patients also the drugs were effective in controlling the clinical symptoms.

Therefore the growth of these fungi are due to contamination, masking the growth of the actual pathogen.

Such an occurrence is common in Mycological culture. Under such a situation, the effectiveness of Fluconazole whether topical or oral and the effectiveness of topical Oxiconazole cream, in suppressing the clinical symptoms should be taken as more relevant and not the Mycological culture.

CONCLUSION

This study was taken up in the Department of Dermatology, Stanley Medical College, Royapuram, Chennai.

The study was taken up to assess the efficacy of Topical Fluconazole gel in Dermatophytosis. The efficacy of topical Fluconazole gel was compared with topical Oxiconazole cream and once a week orally administered Fluconazole tablet.

Fluconazole was available only for oral therapy and topical Fluconazole is a recent introduction. Hence, this study was taken up to determine its antifungal efficacy, in unique situations prevailing in this part of the country.

Topical Fluconazole has been proved to be very effective in Tinea infections.

Though, oral Fluconazole tablet, given once a week was expected to produce equally effective response, the results actually showed the reduced effectiveness, when compared with topical formulation. This is a serendipitious observation. More studies at different centres are required to confirm this finding.

Studies to find out the efficacy of oral Fluconazole tablet administered in a smaller dose, on daily basis is also essential to find out the effectiveness of such therapy.

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Table-2

AGE DISTRIBUTION

Group	N	Mean Age	Std. Deviation	One-way ANOVA F-Test
Group1-Gel	60	33.73	12.059	
Group2- Tablet	60	35.28	13.196	P=0.79 Not significant
Group3-Cream	60	34.83	12.550	
	180	34.62	12.557	

N= Number of patients

P= Probability

Table-3

AGE DISTRIBUTION

Age Group	GROUP					
	1 Gel		2 Tablet		3 Cream	
	n	%	n	%	n	%
18-30	28	46.7%	27	45.0%	27	45.0%
31-40	17	28.3%	16	26.7%	14	23.3%
41-50	9	15.0%	8	13.3%	11	18.3%
51-60	6	10.0%	9	15.0%	8	13.3%

n= Number of patients

P=0.96 Not significant

Table-4

SEX DISTRIBUTION

SEX	Group					
	1 Gel		2 Tablet		3 Cream	
	n	%	n	%	n	%
Male	26	43.3%	35	58.3%	28	46.7%
Female	34	56.7%	25	41.7%	32	53.3%

n= Number of patients

P=0.23 Not significant

Table-5

LESION - TYPE

LESION - TYPE	Group					
	1 Gel		2 Tablet		3 Cream	
	n	%	n	%	n	%
T.Corporis	30	50.0%	34	56.7%	34	56.7%
T.Cruris	30	50.0%	26	43.3%	26	43.3%

n= Number of patients

P= Probability

P=0.70 Not significant

Table-6

LESION-DURATION

GROUPS	n	Mean	Std. Deviation	Oneway ANOVA F-test
Gel-1	60	12.67	1.902	
Tablet-2	60	12.72	2.018	P=0.46
Cream-3	60	12.28	2.322	Not significant
	180	12.56	2.085	

n= Number of patients

P= Probability

Table-7

COMPARISON OF ITCHING BETWEEN GEL & TABLET

	Grading of Itching	Group 1 Gel	Group 2 Tablet	Chi-square test
Base line	3+	23	17	p=0.11 Not significant
	2+	29	26	
	1+	8	17	
	NIL	0	0	
1st Week	2+	0	13	p=0.001 significant
	1+	14	47	
	NIL	46	0	
2nd Week	2+	0	0	p=0.001 significant
	1+	0	17	
	NIL	60	43	

ITCHING (VISUAL ANALOGUE SCALE)

0-No Itching

1+ - Mild, present occasionally. Does not disturb normal Activity.

2+ - Moderate, patient is aware of the itching. Scratches frequently. But Itching is intermittent.

3+ - Severe, disturb patient's normal activity, like sleeping . Itching is constant.

Table-8

COMPARISON OF BURNING SENSATION BETWEEN GEL & TABLET

	BURNING SENSATION	Group 1 GEL	Group 2 TABLET	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	24	p=0.001 SIGNIFICANT
	Absent	50	36	
2nd Week	Present	0	18	p=0.001 SIGNIFICANT
	Absent	60	42	
3rd Week	Present	0	6	p=0.04 SIGNIFICANT
	Absent	60	54	

Table-9

COMPARISON OF SCALING BETWEEN GEL & TABLET

	SCALING	Group 1 GEL	Group 2 TABLET	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	57	p=0.001 SIGNIFICANT
	Absent	50	3	
2nd Week	Present	1	18	p=0.001 SIGNIFICANT
	Absent	59	42	
3rd Week	Present	0	5	p=0.02 NOT SIGNIFICANT
	Absent	60	55	

Table-10

COMPARISON OF ERYTHEMA BETWEEN GEL & TABLET

	ERYTHEMA	Group 1 GEL	Group 2 TABLET	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	55	p=0.001 SIGNIFICANT
	Absent	50	5	
2nd Week	Present	0	25	p=0.001 SIGNIFICANT
	Absent	60	35	
3rd Week	Present	0	4	p=0.02 NOT SIGNIFICANT
	Absent	60	56	

Table-11

COMPARISON OF KOH STAIN BETWEEN GEL & TABLET

	FUNGAL FILAMENTS IN KOH STAIN	Group 1 GEL	Group 2 TABLET	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	26	p=0.001 SIGNIFICANT
	Absent	50	34	
2nd Week	Present	0	2	p=0.47 NOT SIGNIFICANT
	Absent	60	58	
3rd Week	Present	0	0	p=1.00 NOT SIGNIFICANT
	Absent	60	60	

Table-12

MYCOLOGICAL STUDY

group		No growth		Tricho phyton		Micro sporum		Epidermo phyton		Candida		Pencillium		Aspergillus	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Cream	Base line			**39**	**65.0%**	**12**	**20.0%**	**6**	**10.0%**	**2**	**3.3%**	**1**	**1.7%**		
	3rd Week	**60**	**100.0%**												
	4th Week	**60**	**100.0%**												
Gel	Base line			**37**	**61.7%**	**12**	**20.0%**	**7**	**11.7%**	**2**	**3.3%**	**1**	**1.7%**	**1**	**1.7%**
	3rd Week	**60**	**100.0%**												
	4th Week	**60**	**100.0%**												
Tablet	Base line			**31**	**51.7%**	**15**	**25.0%**	**9**	**15.0%**	**3**	**5.0%**	**1**	**1.7%**	**1**	**1.7%**
	3rd Week	**60**	**100.0%**												
	4th Week	**60**	**100.0%**												

Table-13

COMPARISON OF ITCHING BETWEEN GEL & CREAM

	Grading of Itching	Group 1 Gel	Group 3 Cream	**CHI-SQUARE TEST**
Base line	3+	23	20	p=0.80 Not significant
	2+	29	30	
	1+	8	10	
	NIL	0	0	
1st Week	2+	0	4	p=0.12 Not significant
	1+	14	13	
	NIL	46	43	
2nd Week	2+	0	0	p=0.12 not significant
	1+	0	3	
	NIL	60	57	

ITCHING (VISUAL ANALOGUE SCALE)

0-No Itching

1+ - Mild, present occasionally. Does not disturb normal Activity.

2+ - Moderate, patient is aware of the itching. Scratches frequently. But Itching is intermittent.

3+ - Severe, disturb patient's normal activity, like sleeping. Itching is constant.

Table-14

COMPARISON OF BURNING SENSATION BETWEEN GEL & CREAM

	BURNING SENSATION	Group 1 GEL	Group 3 CREAM	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	30	p=0.001 SIGNIFICANT
	Absent	50	30	
2nd Week	Present	0	4	p=0.12 NOT SIGNIFICANT
	Absent	60	56	
3rd Week	Present	0	1	p=1.00 NOT SIGNIFICANT
	Absent	60	59	

Table-15

COMPARISON OF SCALING BETWEEN GEL & CREAM

	SCALING	Group 1 GEL	Group 3 CREAM	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00
	Absent	0	0	NOT SIGNIFICANT
1st Week	Present	10	29	p=0.001
	Absent	50	31	SIGNIFICANT
2nd Week	Present	1	6	p=0.86
	Absent	59	54	NOT SIGNIFICANT
3rd Week	Present	0	0	p=1.00
	Absent	60	60	NOT SIGNIFICANT

Table-16

COMPARISON OF ERYTHEMA BETWEEN GEL & CREAM

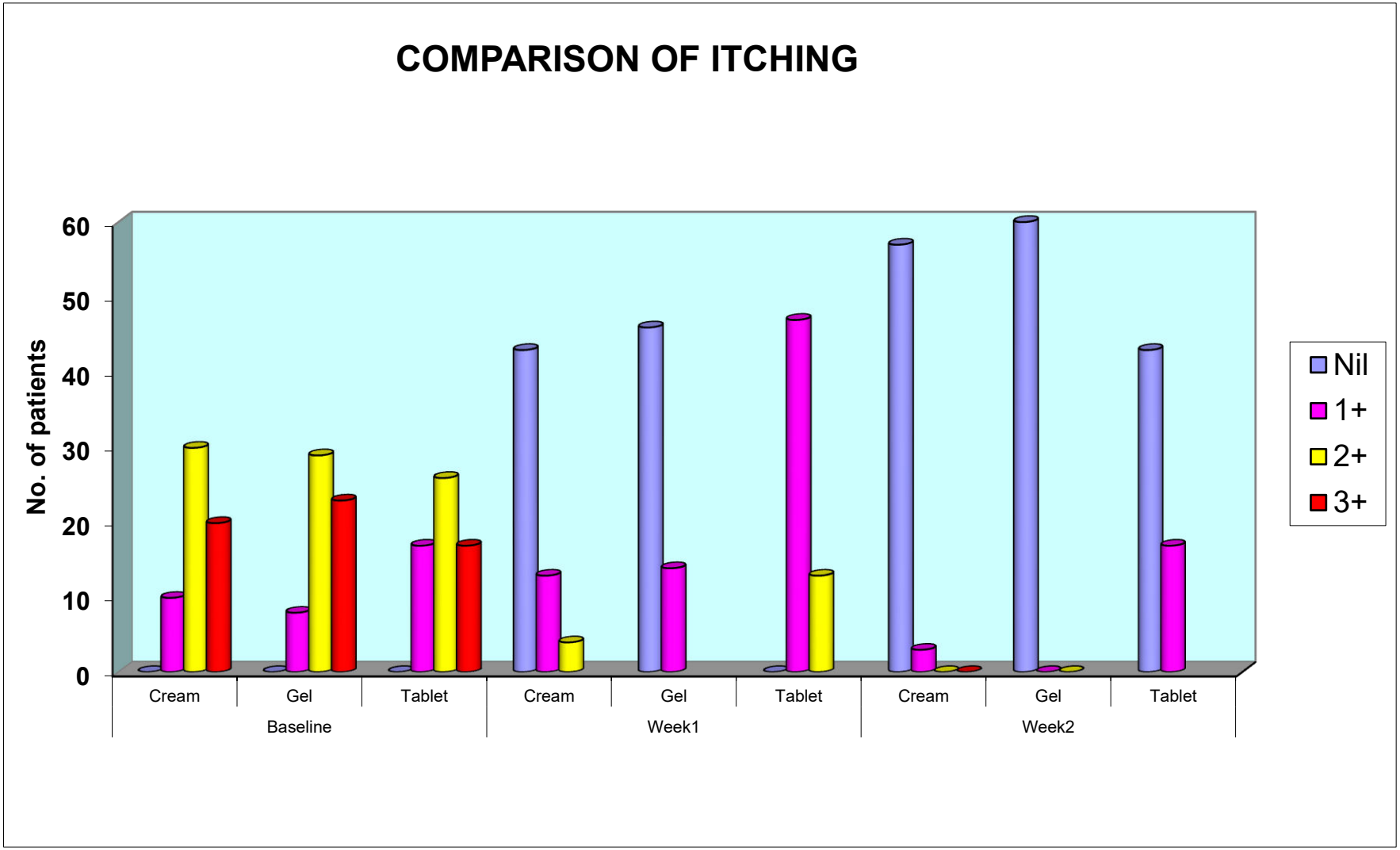
	ERYTHEMA	Group 1 GEL	Group 3 CREAM	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	35	p=0.001 SIGNIFICANT
	Absent	50	25	
2nd Week	Present	0	7	p=0.02 SIGNIFICANT
	Absent	60	53	
3rd Week	Present	0	1	p=1.00 NOT SIGNIFICANT
	Absent	60	59	

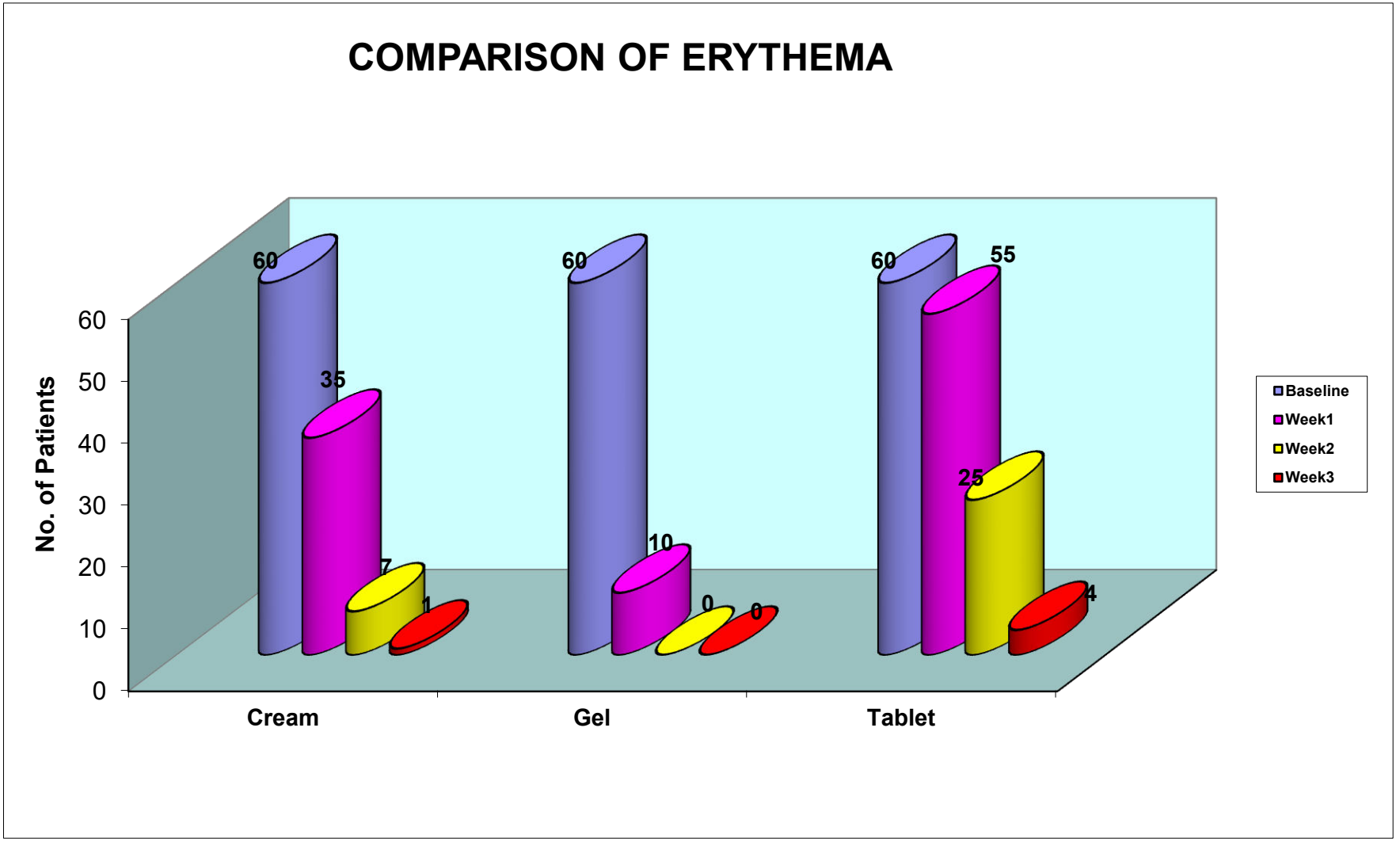
Table-17

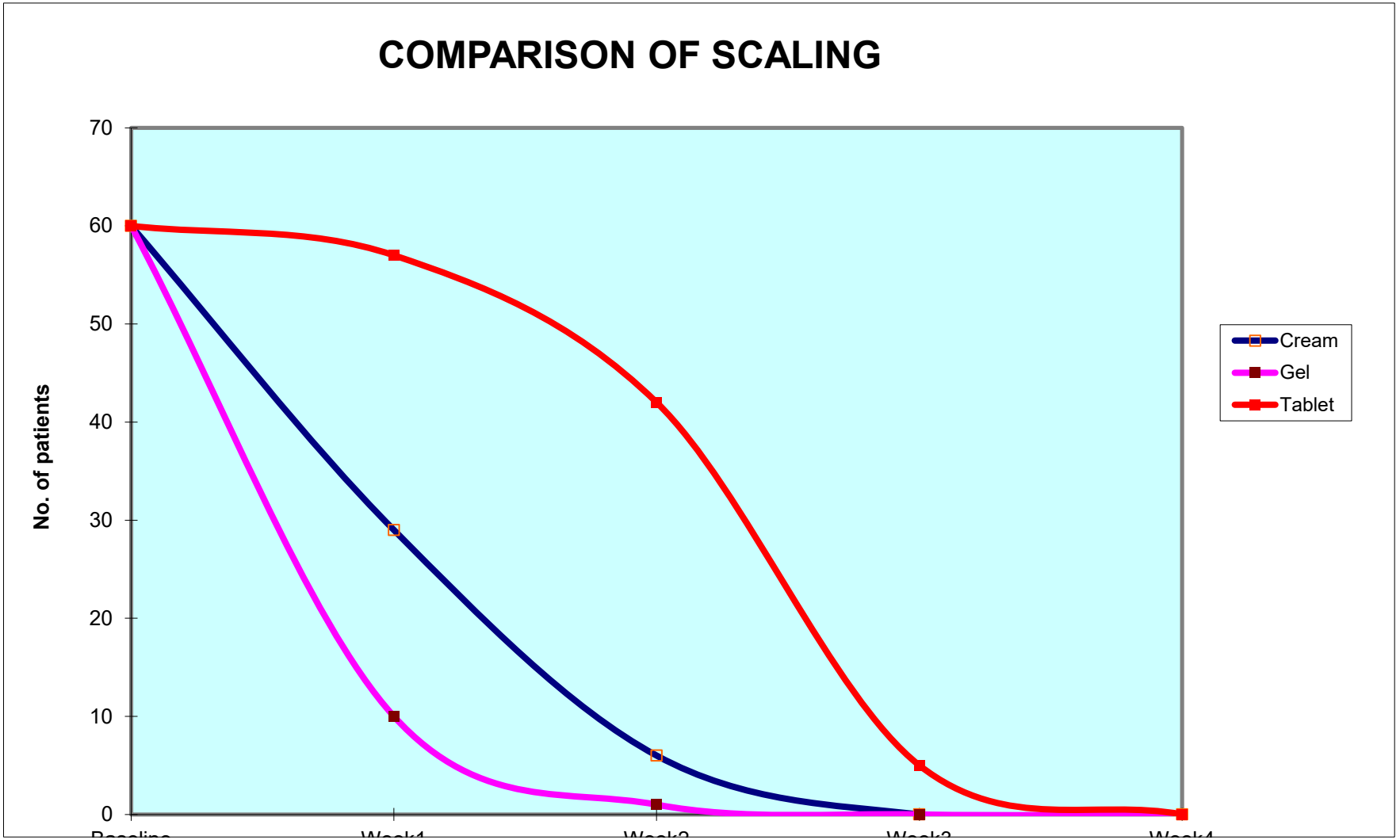
COMPARISON OF KOH STAIN BETWEEN GEL & CREAM

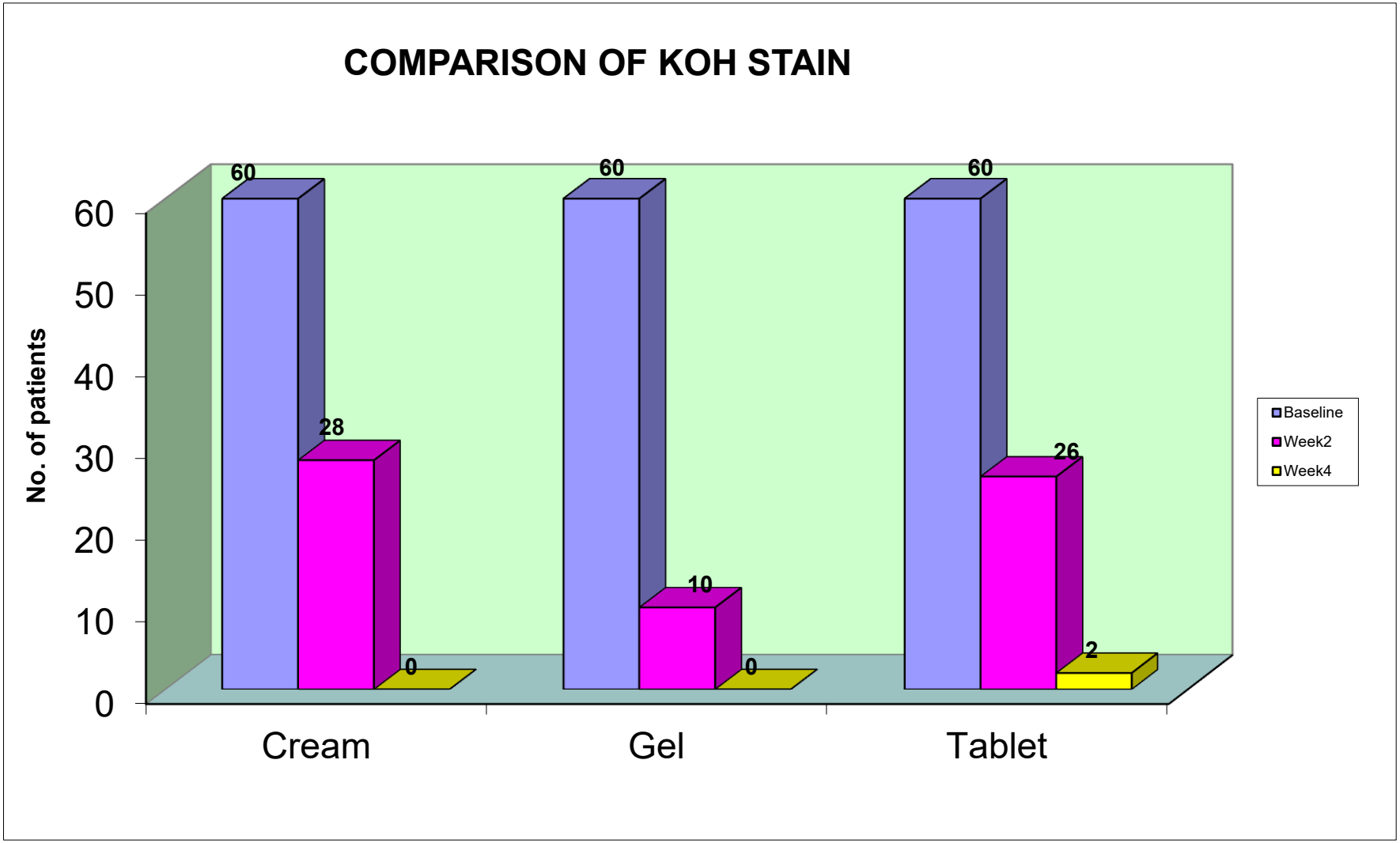
	FUNGAL FILAMENTS IN KOH STAIN	Group 1 GEL	Group 3 CREAM	CHI-SQUARE TEST
Base line	Present	60	60	p=1.00 NOT SIGNIFICANT
	Absent	0	0	
1st Week	Present	10	28	p=0.001 SIGNIFICANT
	Absent	50	32	
2nd Week	Present	0	0	p=1.00 NOT SIGNIFICANT
	Absent	60	60	
3rd Week	Present	0	0	p=1.00 NOT SIGNIFICANT
	Absent	60	60	

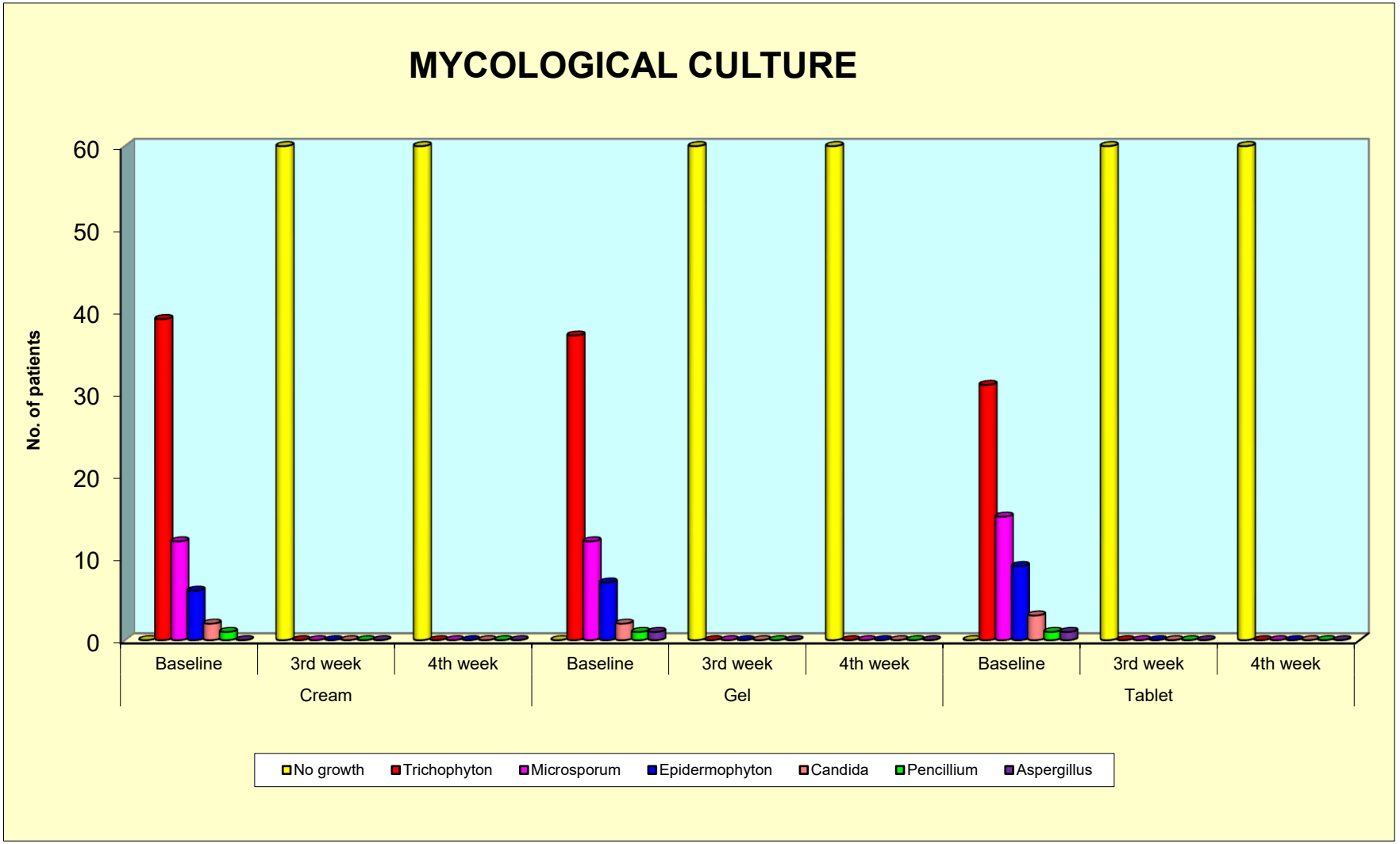
COMPARISON OF ITCHING

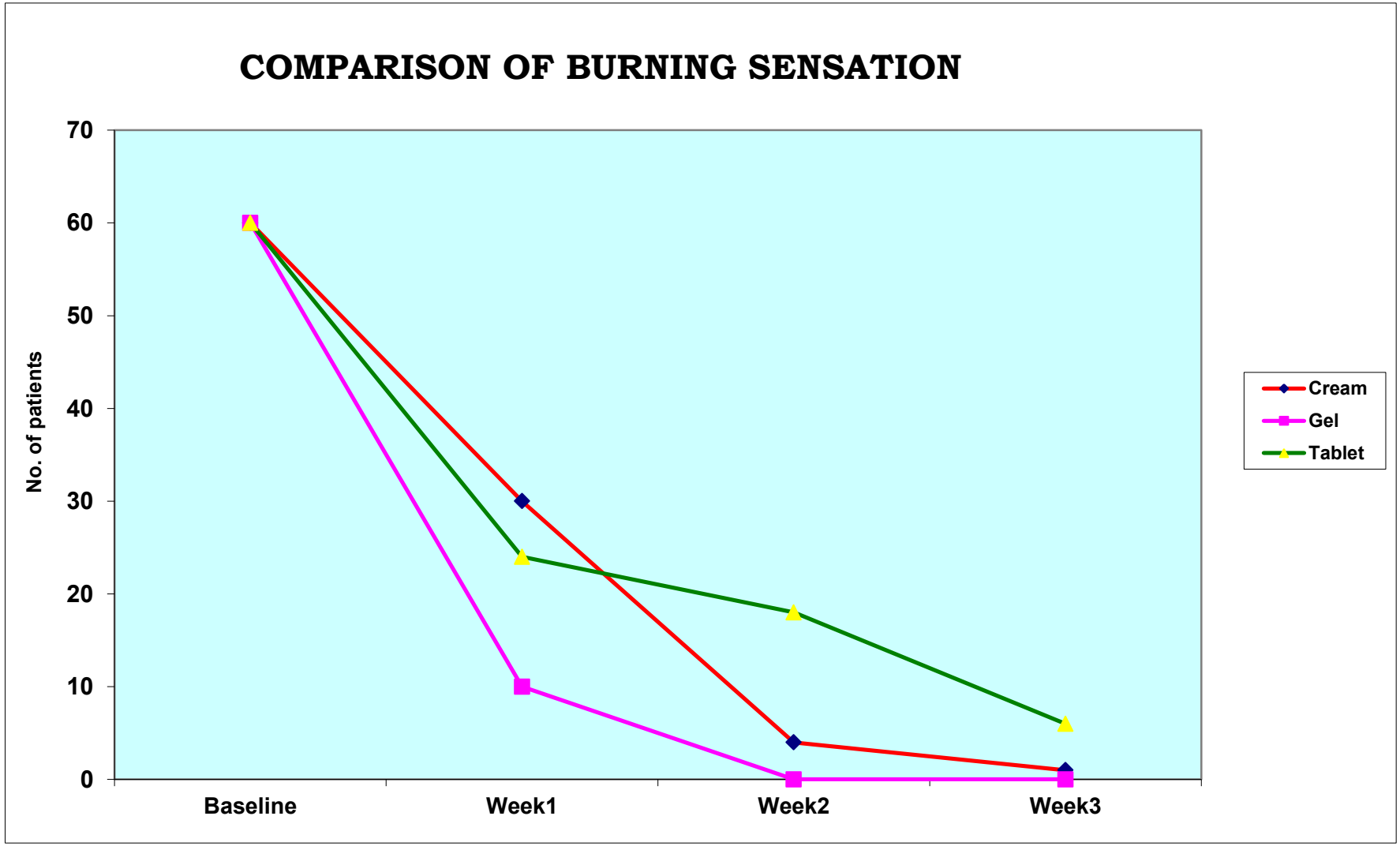


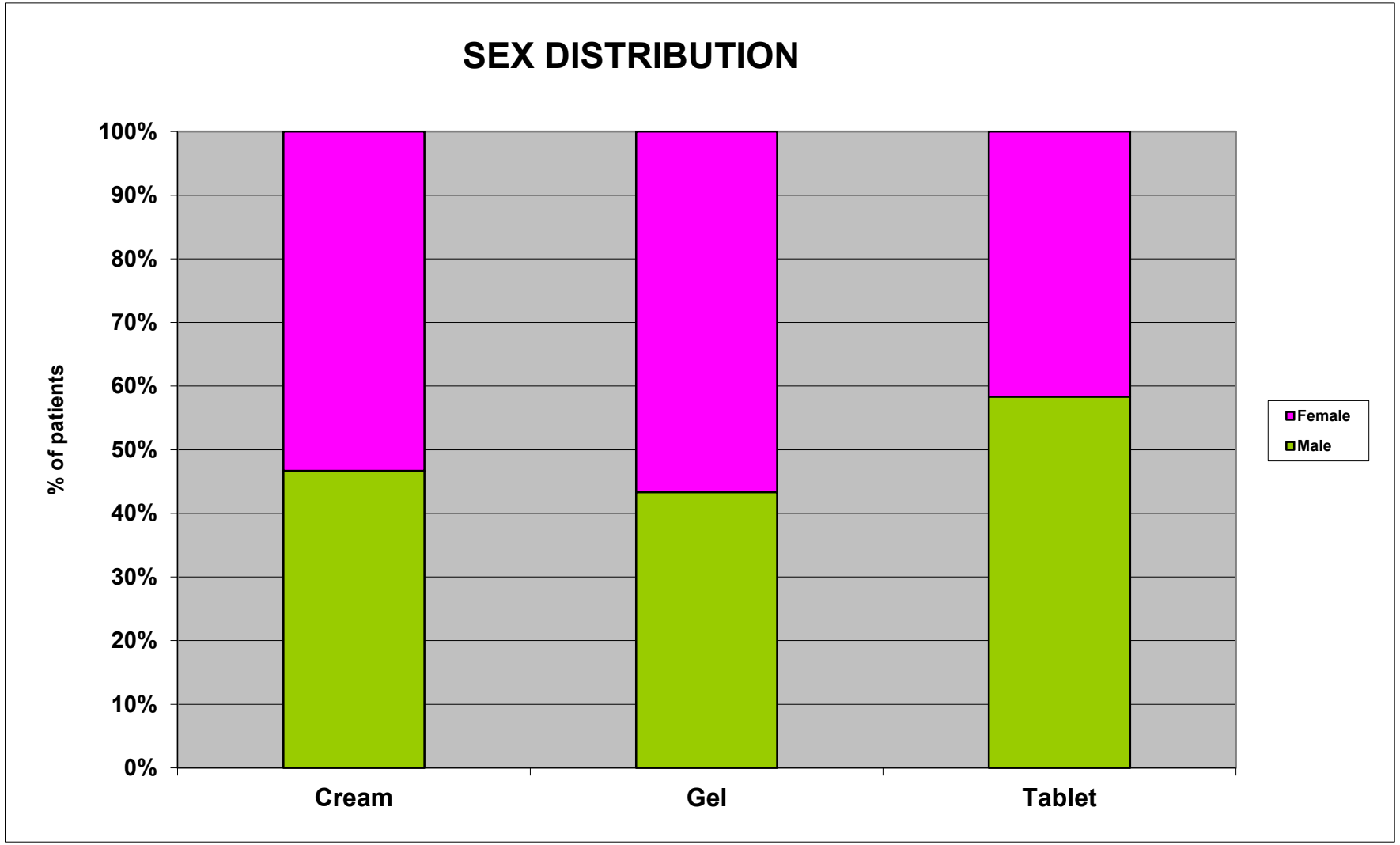

COMPARISON OF ERYTHEMA
No. of Patients
0
10
20
30
40
50
60
Cream
Gel
Tablet
60
35
7
1
60
10
0
0
60
55
25
4
Baseline
Week1
Week2
Week3

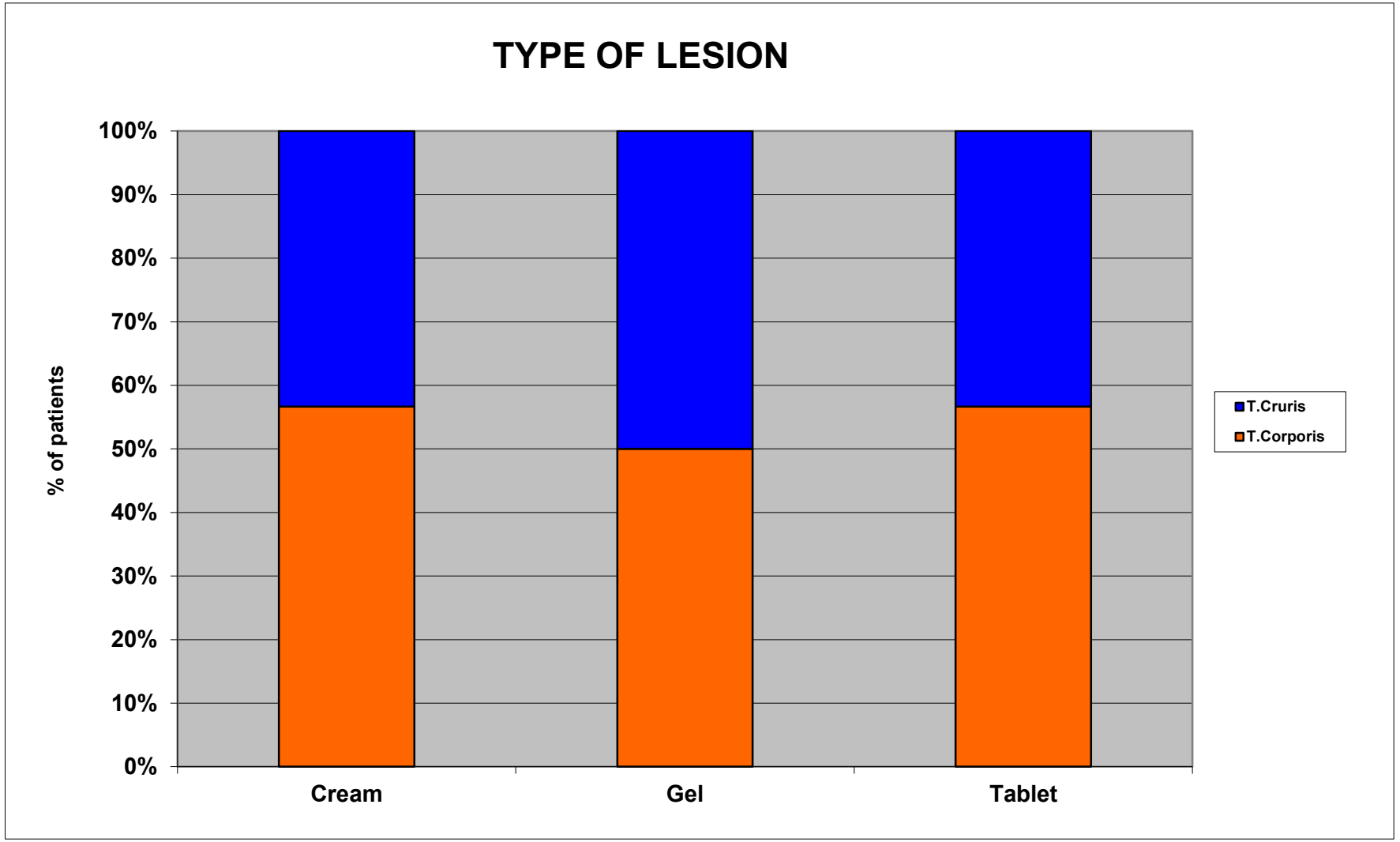

COMPARISON OF SCALING
No. of patients
70
60
50
40
30
20
10
0
Cream
Gel
Tablet


COMPARISON OF KOH STAIN
No. of patients
0
10
20
30
40
50
60
Cream
Gel
Tablet
60
28
0
60
10
0
60
26
2
Baseline
Week2
Week4

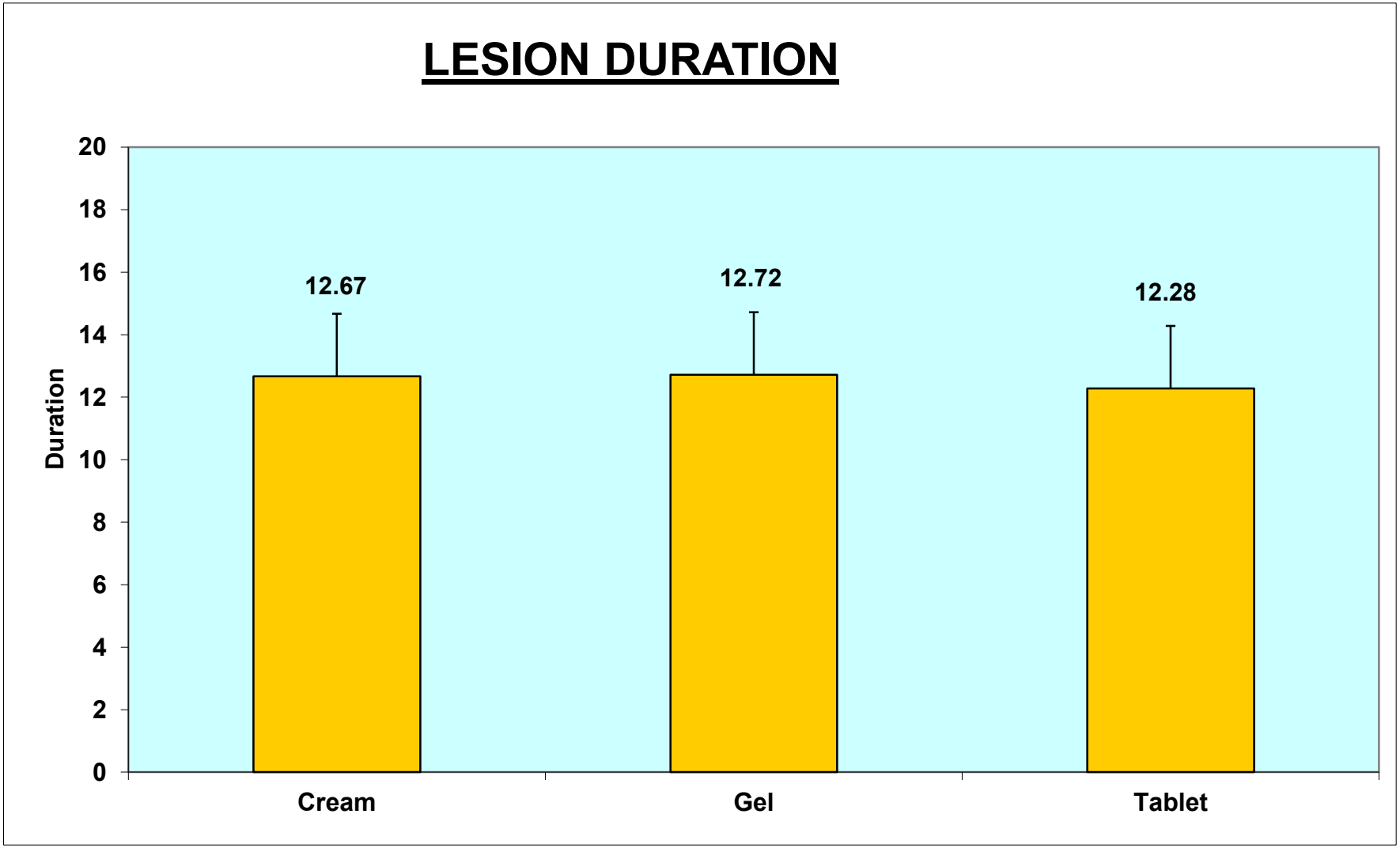

MYCOLOGICAL CULTURE
No. of patients
60
50
40
30
20
10
0
Baseline
3rd week
4th week
Baseline
3rd week
4th week
Baseline
3rd week
4th week
Cream
Gel
Tablet
No growth
Trichophyton
Microsporum
Epidermophyton
Candida
Pencillium
Aspergillus


COMPARISON OF BURNING SENSATION
No. of patients
70
60
50
40
30
20
10
0
Baseline
Week1
Week2
Week3
Cream
Gel
Tablet


SEX DISTRIBUTION
% of patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cream
Gel
Tablet
Female
Male


TYPE OF LESION
% of patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cream
Gel
Tablet
T.Cruris
T.Corporis

LESION DURATION



		Nil	1+	2+	3+
Baseline	Cream	0	10	30	20
	Gel	0	8	29	23
	Tablet	0	17	26	17
Week1	Cream	43	13	4	
	Gel	46	14		
	Tablet	0	47	13	
Week2	Cream	57	3	0	0
	Gel	60	0	0	
	Tablet	43	17		

	Cream	Gel	Tablet
Baseline	60	60	60
Week1	35	10	55
Week2	7	0	25
Week3	1	0	4

Multiple bar diagram

	Cream	Gel	Tablet	scaling	
Baseline	60	60	60		line diagram
Week1	29	10	57		
Week2	6	1	42		
Week3	0	0	5		
Week4	0	0	0		

	Cream	Gel	Tablet
Baseline	60	60	60
Week2	28	10	26
Week4	0	0	2

		No growth	Trichophyton	Microsporum	Epidermophyton	Candida	Pencillium	Aspergillus
Cream	Baseline		39	12	6	2	1	
	3rd week	60						
	4th week	60						
Gel	Baseline		37	12	7	2	1	1
	3rd week	60						
	4th week	60						
Tablet	Baseline		31	15	9	3	1	1
	3rd week	60						
	4th week	60						

	Cream	Gel	Tablet
Baseline	60	60	60
Week1	30	10	24
Week2	4	0	18
Week3	1	0	6

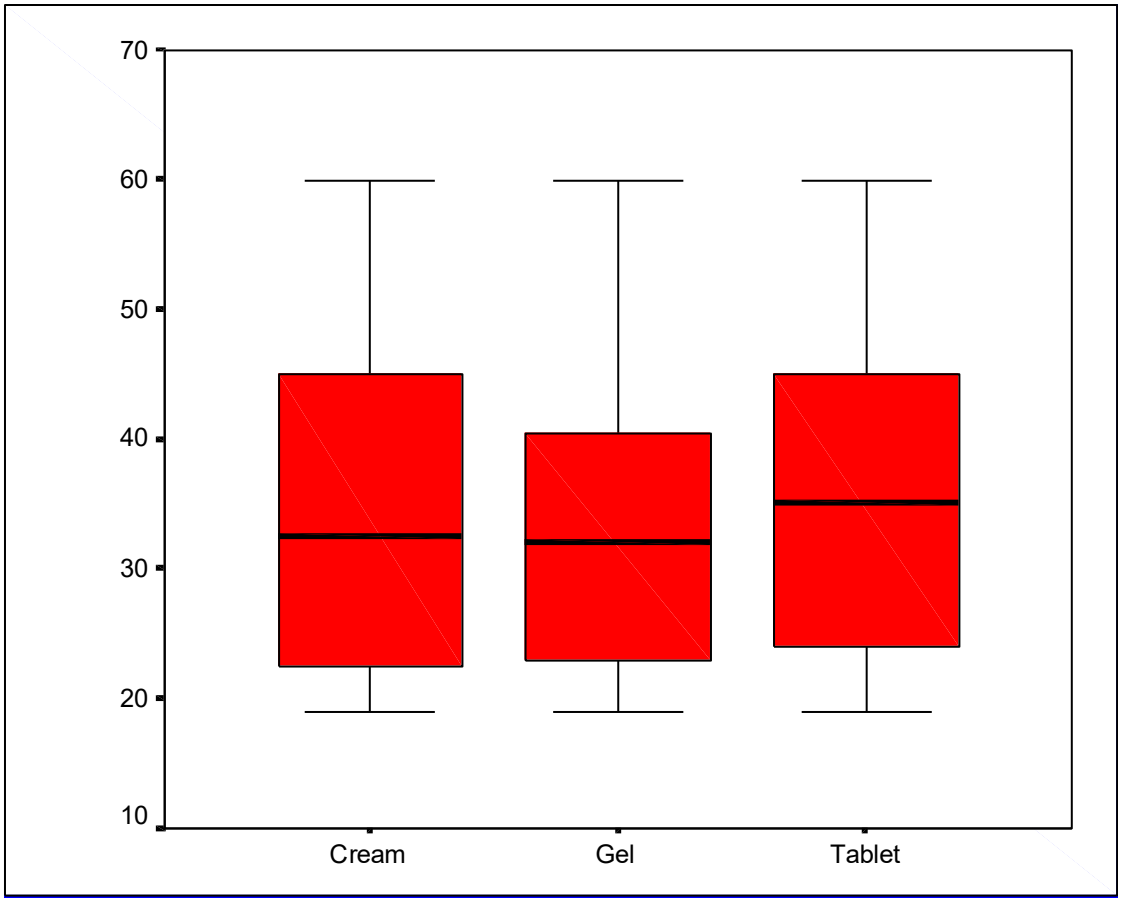
	Cream	Gel	Tablet	
Male	28	26		35
Female	32	34		25

	Cream	Gel	Tablet
T.Corporis	34	30	34
T.Cruris	26	30	26

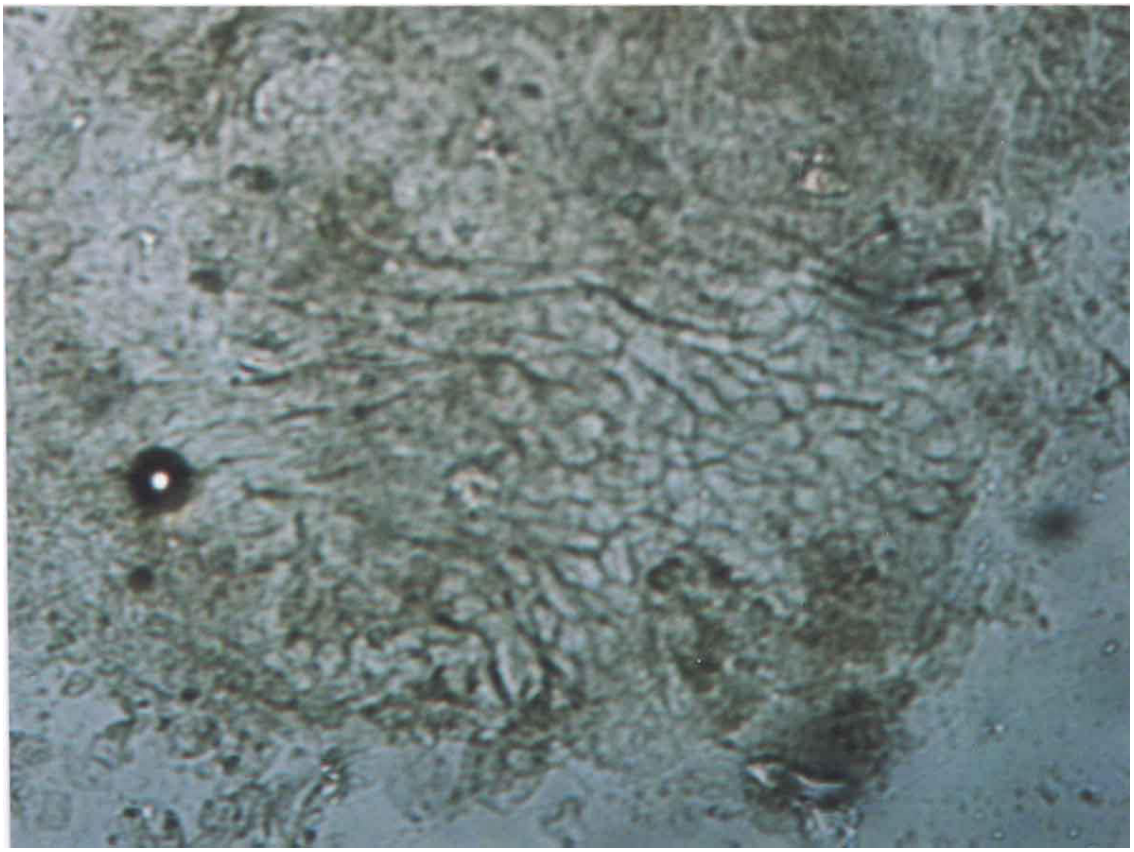
	Cream	Gel	Tablet
1X1			1
1X2		2	1
1X3			1
2X1	2	1	2
2X2	8	4	6
2X3	8	5	6
2X4	3	1	6
2X5	3	2	4
2X6		1	
3X1		2	1
3X2	3	7	4
3X3	1	6	2
3X4	4	3	3
3X5	2	8	6
3X6	1	3	1
4X2	2		1
4X3	2	1	1
4X4	1		
4X5		1	3
4X6		3	
5X2	3	1	
5X3	4	2	3
5X4	6	3	4
5X5	1	2	2
5X6		1	1
6X3	1		1
6X4	2		
6X5	1		
7X6		1	
7X8	1		
8X4	1		

Cream	Gel	Tablet
12.67	12.72	12.28

BOX-PLOT COMPARES THE AGE DISTRIBUTION BETWEEN THREE GROUPS



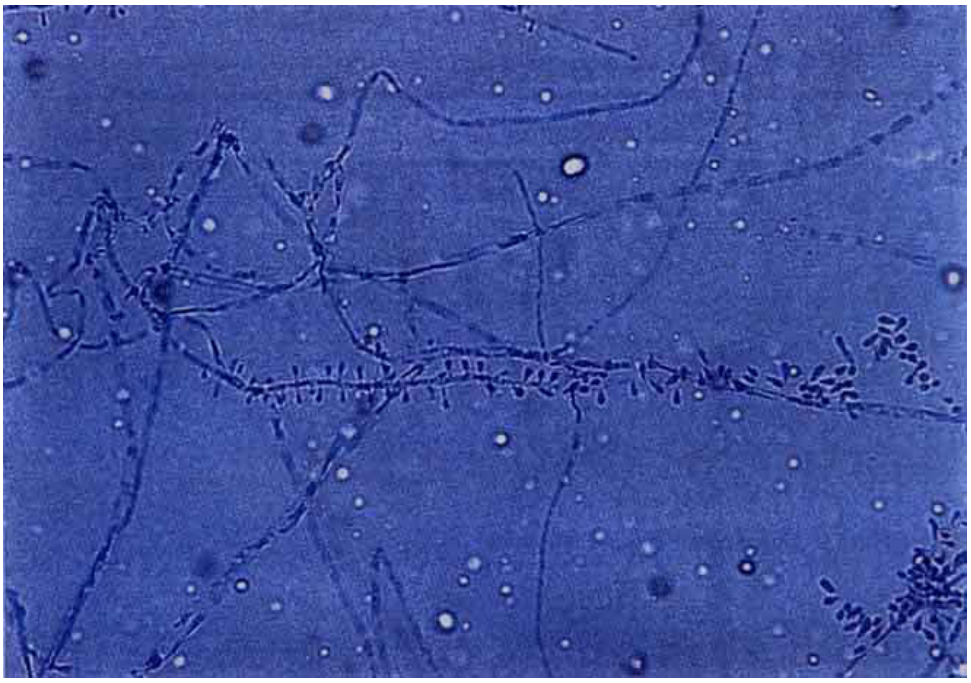
FUNGAL FILAMENTS IN KOH STAIN



TRICHOPHYTON RUBRUM

SABOURAUD'S AGAR MEDIUM

LACTOPHENOL COTTON BLUE



MICROSPORUM GYPSEUM

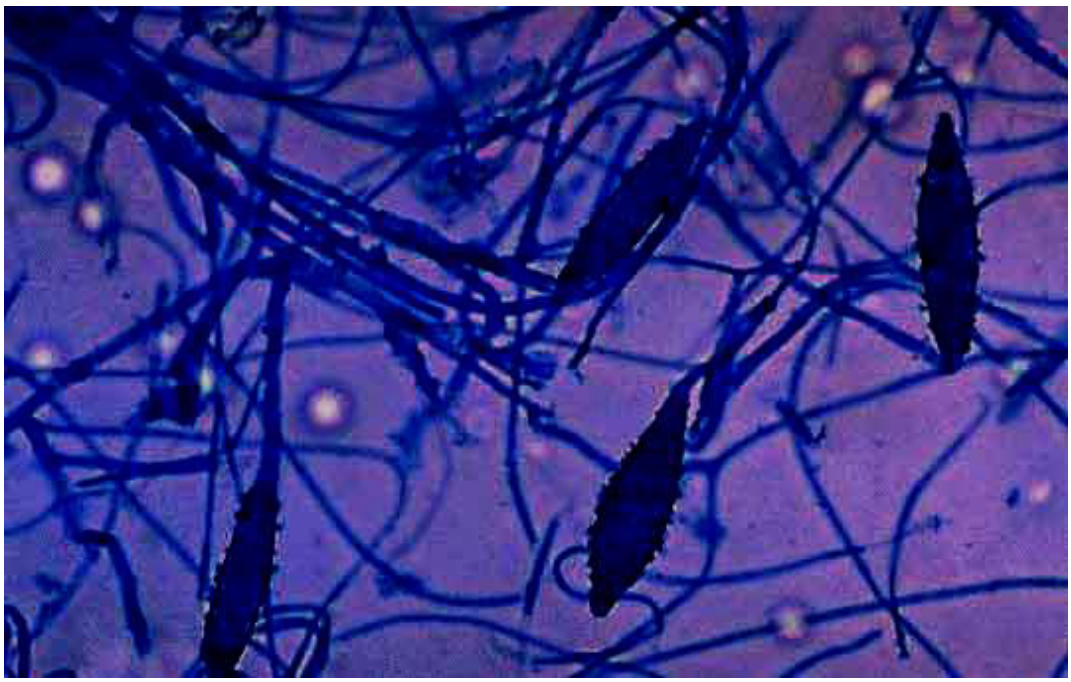
SABOURAUD'S AGAR MEDIUM

LACTOPHENOL COTTON BLUE

MICROSPORUM CANIS

SABOURAUD'S AGAR MEDIUM

LACTOPHENOL COTTON BLUE



EPIDERMOPHYTON FLOCCOSUM

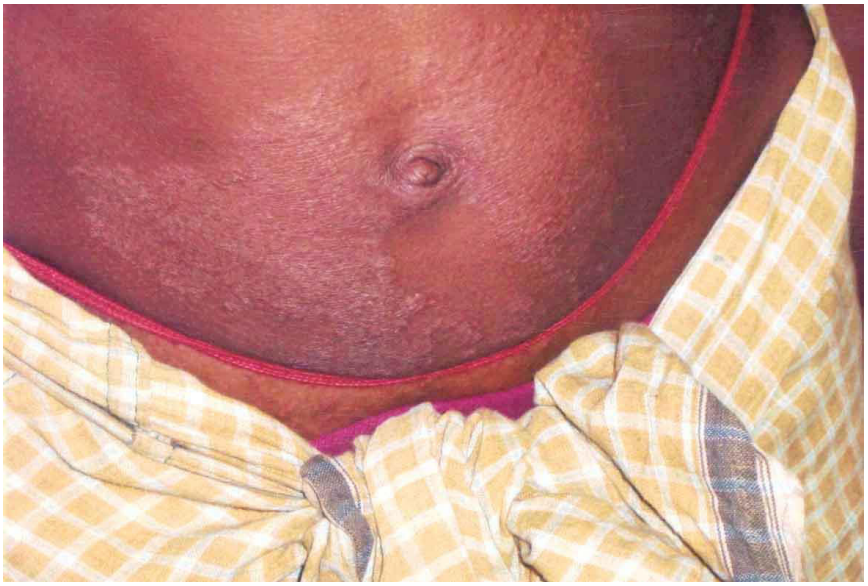
SABOURAUD'S AGAR MEDIUM

LACTOPHENOL COTTON BLUE

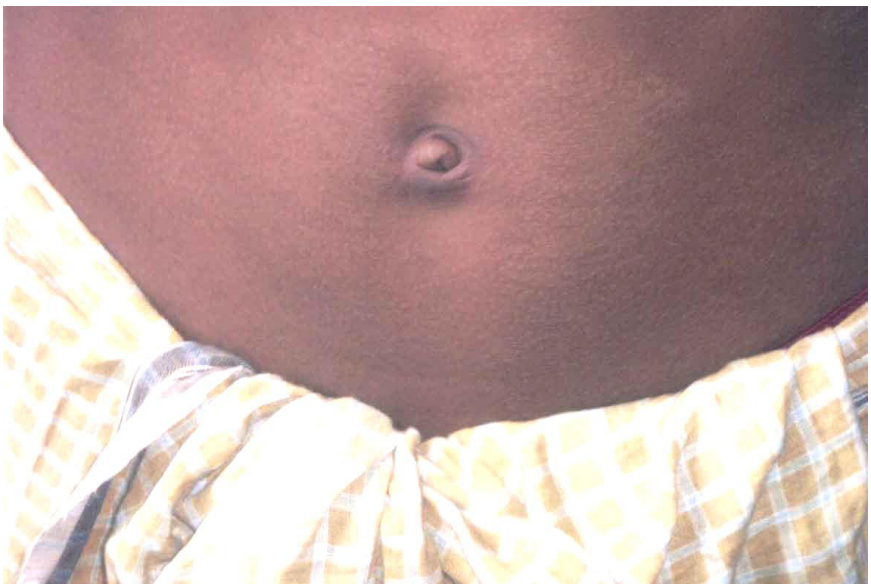
GROUP 1 - PATIENT TREATED WITH FLUCONAZOLE GEL

TINEA CORPORIS

BEFORE TREATMENT



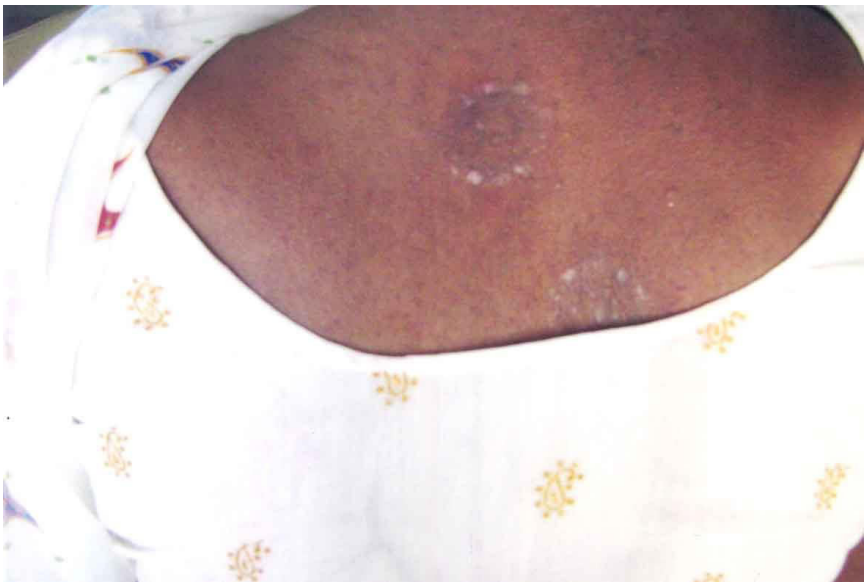
2 Weeks - AFTER TREATMENT



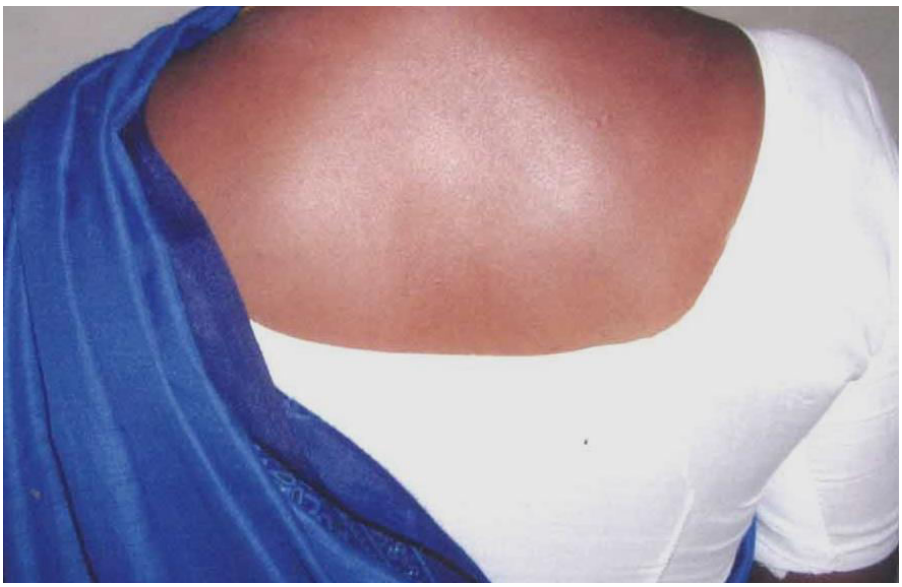
GROUP 2 - PATIENT TREATED WITH FLUCONAZOLE TABLET

TINEA CORPORIS

BEFORE TREATMENT



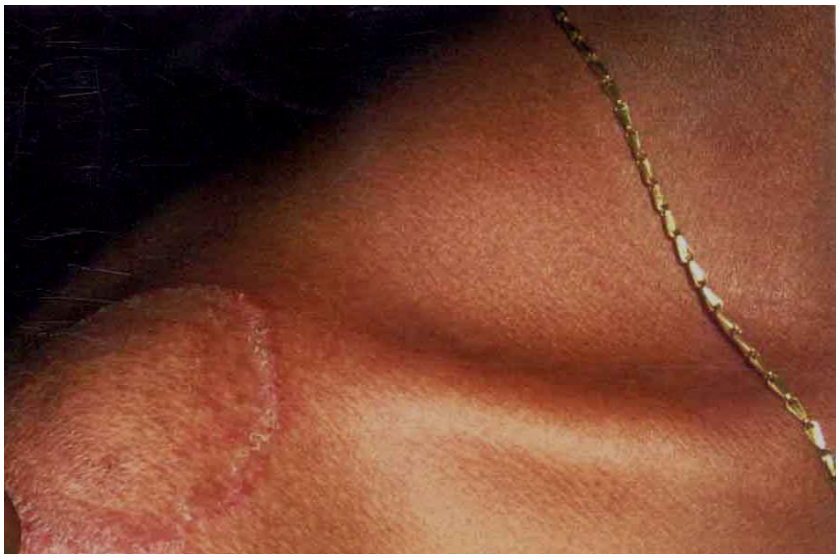
3 Weeks - AFTER TREATMENT



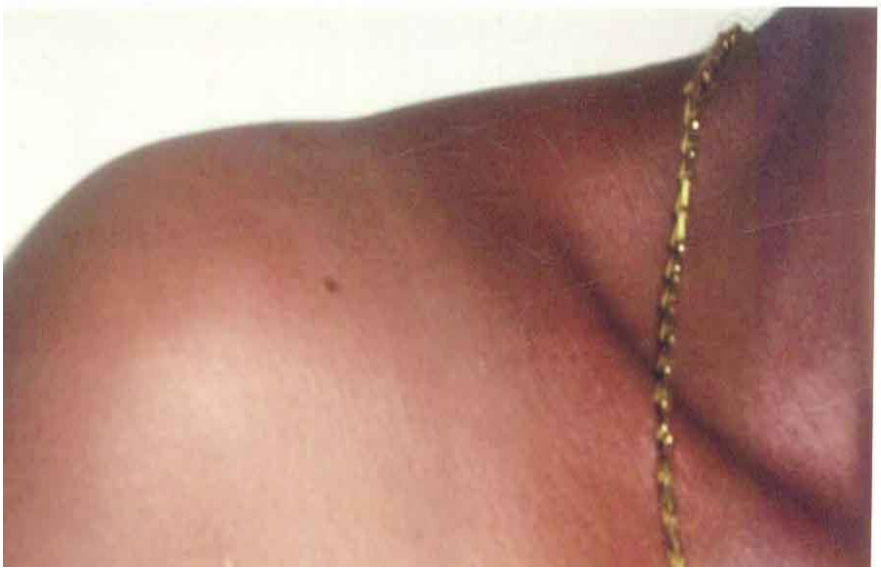
GROUP 3 - PATIENT TREATED WITH OXICONAZOLE CREAM

TINEA CORPORIS

BEFORE TREATMENT



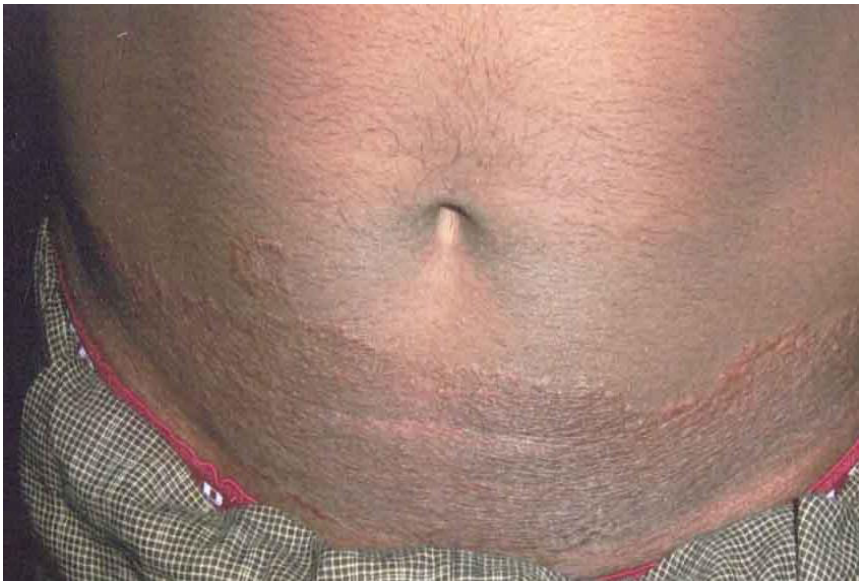
2 Weeks - AFTER TREATMENT



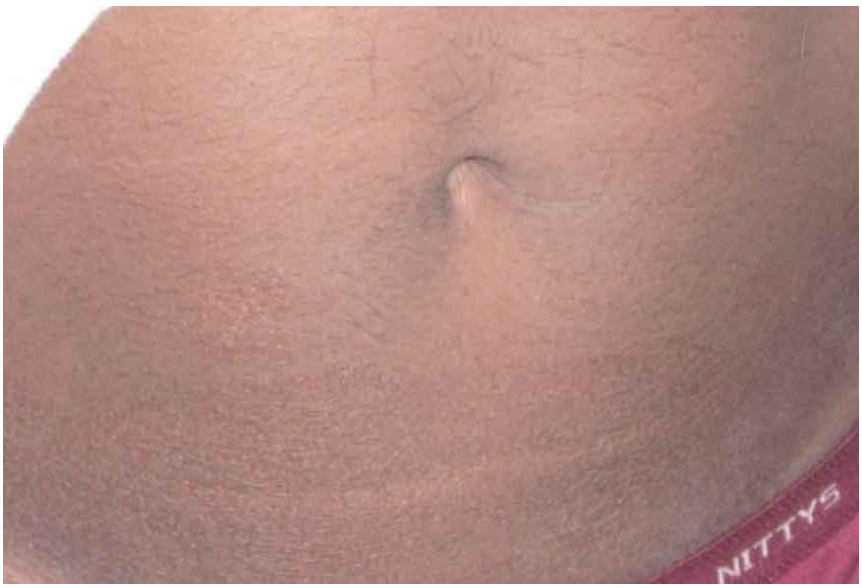
GROUP 1 - PATIENT TREATED WITH FLUCONAZOLE GEL

TINEA CRURIS

BEFORE TREATMENT



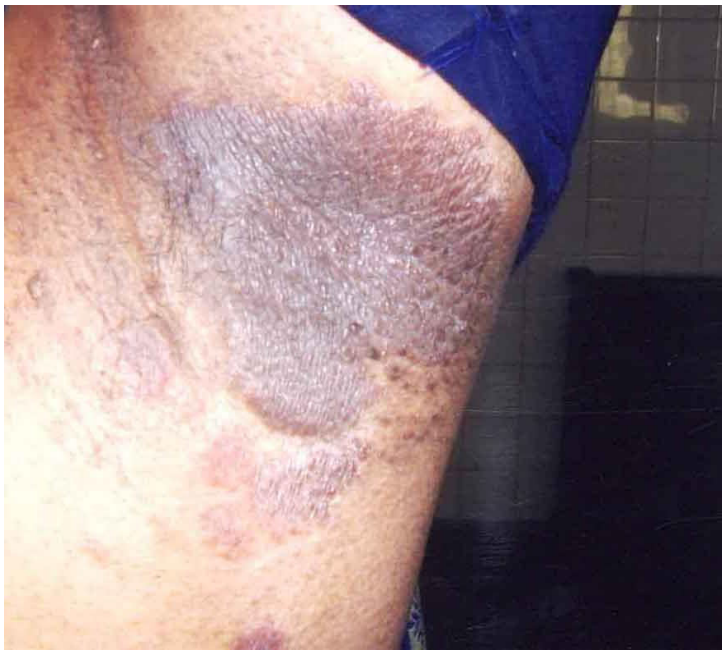
2 Weeks - AFTER TREATMENT



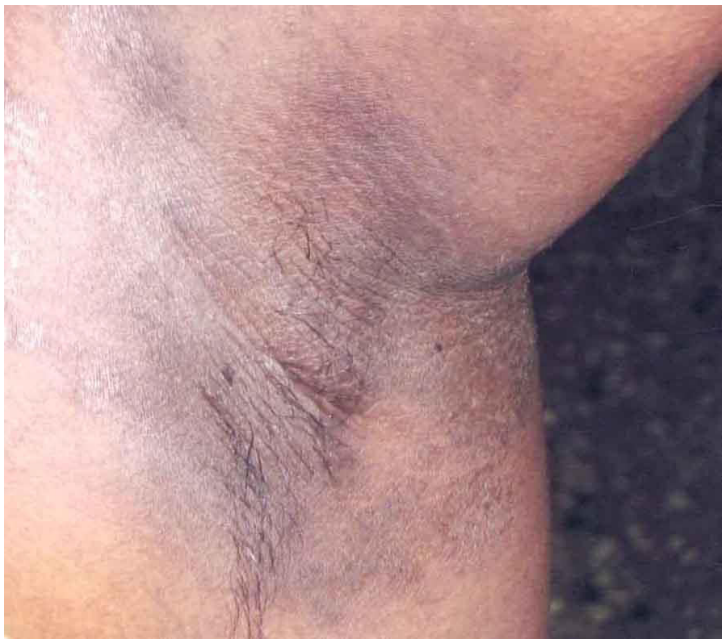
GROUP 2 - PATIENT TREATED WITH FLUCONAZOLE TABLET

TINEA CRURIS

BEFORE TREATMENT



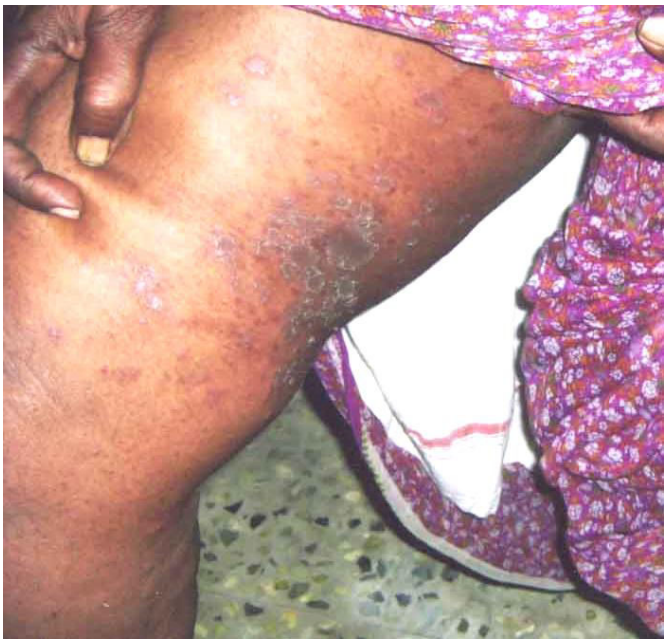
3 Weeks - AFTER TREATMENT



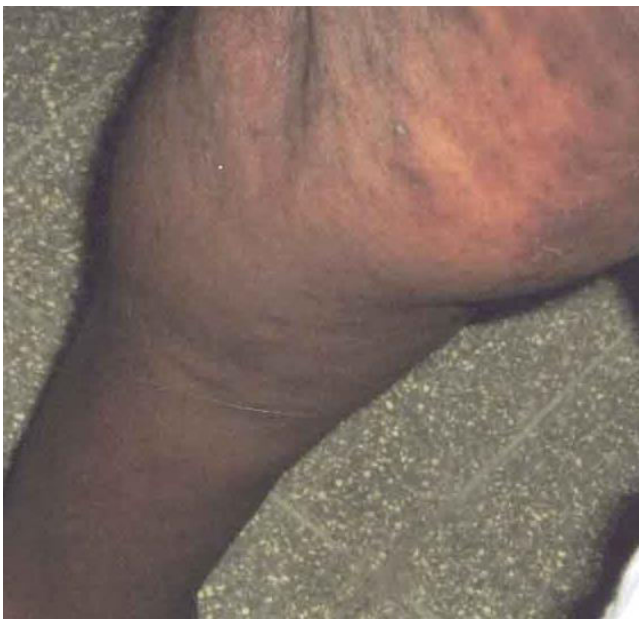
GROUP 3 - PATIENT TREATED WITH OXICONAZOLE CREAM

TINEA CRURIS

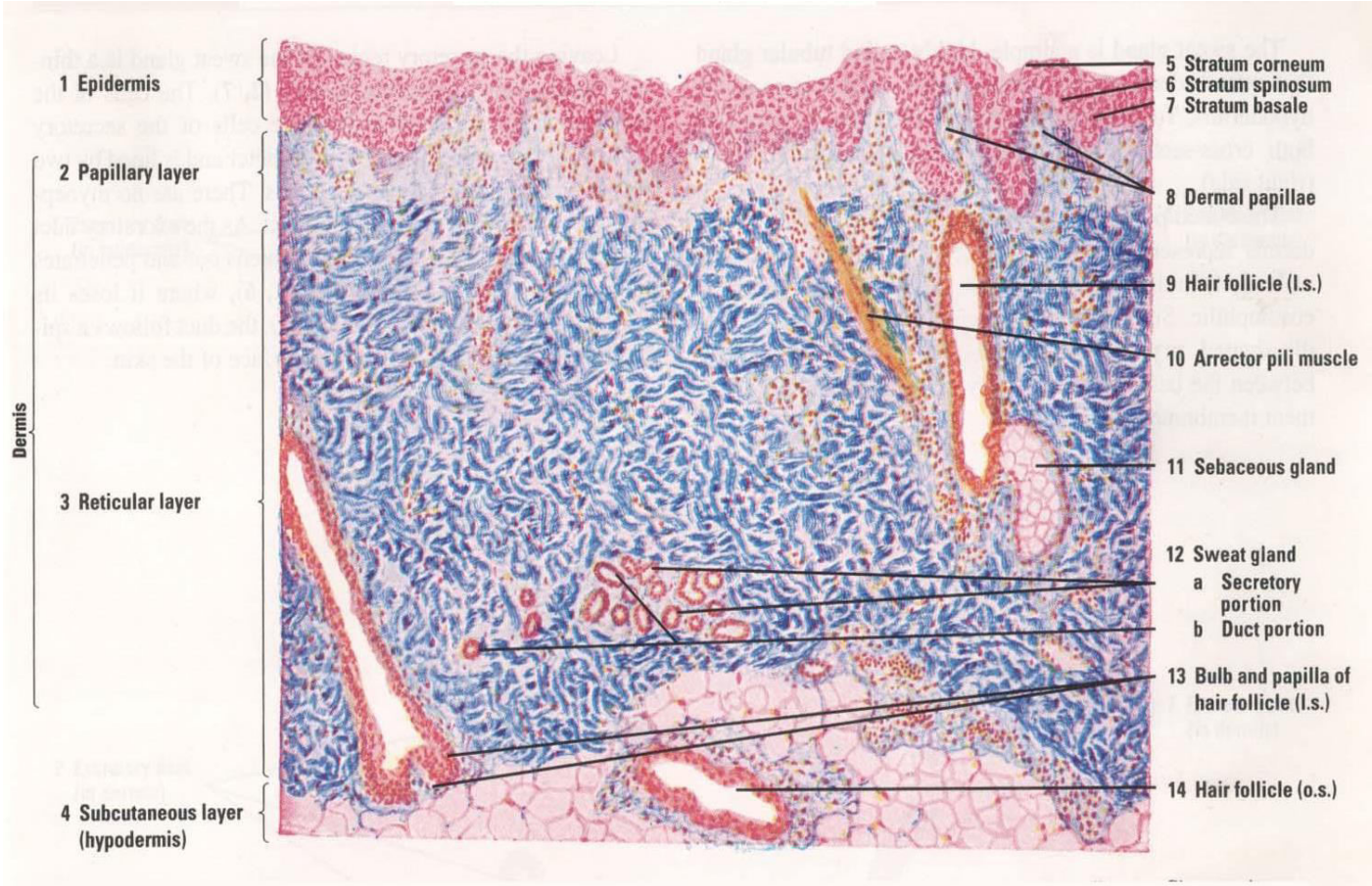
BEFORE TREATMENT



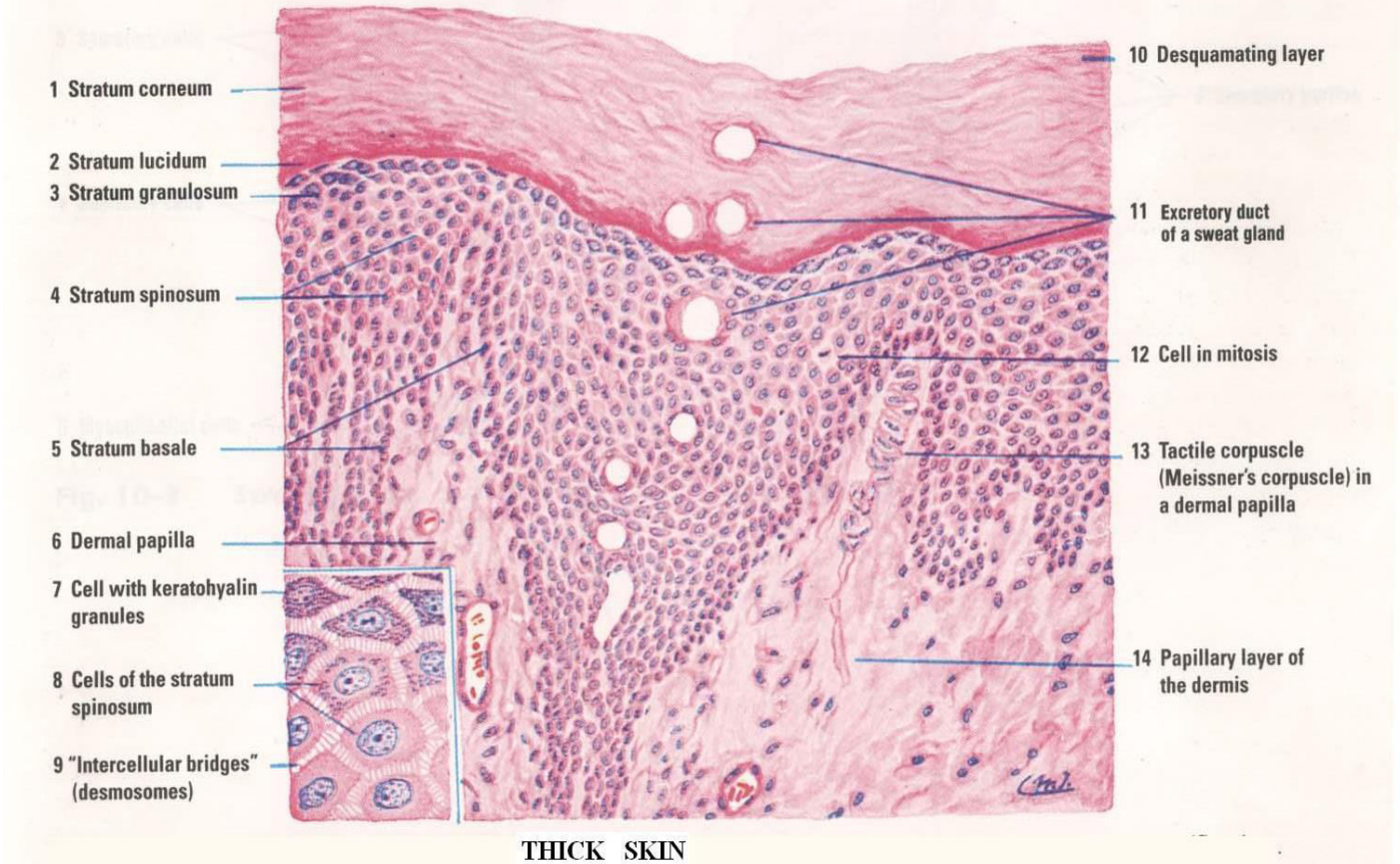
2 Weeks - AFTER TREATMENT



STRUCTURE OF THE SKIN



THIN SKIN



THICK SKIN

TABULATION OF THE DATA

The results are entered in the tabular column and the model of it is shown below:

Sl. No.	Name Age Sex O.p.no.	LESION	ITCHING							BURNING SENSATION							SCALING							ERYTHEMA							KOH STAIN					MYCOLOGICAL CULTURE		
		Type, No, Site, Size, Duration	Weeks							Weeks							Weeks							Weeks							Weeks					weeks		
			B	1	2	3	4	6	8	B	1	2	3	4	6	8	B	1	2	3	4	6	8	B	1	2	3	4	6	8	0	2	4	6	8	0	3	4

B - Baseline

CLINICAL TESTING

ITCHING Weeks							BURNING SENSATION Weeks							SCALING Weeks							ERYTHEMA Weeks						
B	1	2	3	4	6	8	B	1	2	3	4	6	8	B	1	2	3	4	6	8	B	1	2	3	4	6	8

B - Baseline

LAB INVESTIGATIONS

KOH STAIN weeks					MYCOLOGICAL CULTURE weeks		
B	2	4	6	8	B	3	4

B - Baseline

CASE REPORT FORM

EVALUATION OF TOPICAL 1% FLUCONAZOLE GEL IN DERMATOPHYTOSIS

NAME : AGE : SEX : O.P.No:

OCCUPATION : ADDRESS :

DOB :

CHIEF COMPLAINTS :

HISTORY OF PRESENT ILLNESS :

PAST HISTORY :

H/O

- DIABETES
- HYPERTENSION
- ISCHEMIC HEART DISEASE
- LIVER DISEASE
- CONTAGIOUS DISEASE
- SURGERY

FAMILY HISTORY :

HISTORY OF DRUG ALLERGY :

GENERAL EXAMINATION :

BUILD : PULSE :

NOURISHMENT : BP :

PALLOR : TEMPERATURE :

LYMPHADENOPATHY :

SYSTEMIC EXAMINATION :

1. CARDIOVASCULAR SYSTEM :
2. RESPIRATORY SYSTEM :
3. GASTRO INTESTINAL SYSTEM
4. CENTRAL NERVOUS SYSTEM :

LOCAL EXAMINATION :

INSPECTION :

AREAS OF INVOLVEMENT :

SITE : SIZE : COLOUR :

NUMBER : DISCHARGE :

PRESENCE OF VESICLES, ERYTHEMA, SCALING :

DIAGNOSIS :

ஒப்புதல்

திரு/திருமதி. ..... ஆகிய நான் இந்த மருத்துவ பரிசோதனை மேற்கொள்ள மனப்பூர்வமாக ஒப்புதல் தெரிவிக்கிறேன்.

இந்த மருத்துவ ஆய்வின் தலைப்பு ப்ளுகோனசோல் '(Fluconazole)' எனப்படும் மருந்தின் நோய் தீர்க்கும் தன்மையை மேல் பூச்சாக படை நோய்க்கு தடவி அதனால் ஏற்படும் நன்மை, தீமைகளை கண்டறிதல் ஆகும்.

இந்த மருந்து ஏற்கனவே வாய் வழியாக உட்கொள்ளப்படுகிறது என்றம், அதனால் எந்த வித பெரிய பக்க விளைவுகள் எதுவும் வரவில்லை என்பதையும் அறிந்தேன்.

இந்த சோதனையில் எற்கனவே உபயோகத்தில் உள்ள ஆக்ஸிகோனசோல் '(Oxiconazole)' மேல் பூச்சு, ப்ளுகோனசோல் '(Fluconazole)' வாய்மூலம் எடுத்துக் கொள்ளுதல் ஆகியவற்றுடன், ப்ளுகோனசோல் '(Fluconazole)' மேல்பூச்சு ஒப்பிடப்படுகிறது என்பதையும் தெரிந்து கொண்டேன்.

இந்த ஆய்வில் நான் .....என்ற மருந்தை வாய் மூலமாக / மேல் பூச்சாக எடுத்துக் கொள்ள சம்மதிக்கிறேன்.

மேலும் இந்த சோதனையில் சில கேள்விகளுக்கு பதில் அளிக்கம், எந்த வித பாதிப்பும் இல்லாத சில ஆய்வக பரிசோதனைக்கு உட்படுத்திக் கொள்ளவும் சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆய்வில் கண்டறியப்படும் விவரங்களை எந்த ஒரு அறிவியல் கூட்டத்திலும் தெரிவிக்கலாம் என்பதையும் தெரிந்து கொண்டேன்.

எப்பொழுது வேண்டுமானாலும் இந்த ஆய்வில் இருந்து விலகிக் கொள்ளலாம் என்பதையும், அதன் பின்னரும் எந்த வித இடையூறும் இன்றி மருத்துவ சிகிச்சையை இந்த மருத்துவமனையில் தொடர்ந்து மேற்கொள்ளலாம் என்பதையும் புரிந்து கொண்டேன்.

கையொப்பம்

முதன்மை ஆய்வாளர்

சாட்சி – 1

சாட்சி – 2