Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13143
DOI URL: http://dx.doi.org/10.21474/IJAR01/13143

*RESEARCH ARTICLE*

# COMPARATIVE STUDY OF EFFICACY OF ORAL TERBINAFINE ALONE AND ORAL TERBINAFINE WITH TOPICAL 8% CICLOPIROX OLAMINE IN ONYCHOMYCOSIS

**Dr. Vinnakoti Anitha MD[1] and Dr. Boina Kinnera MD[2]**

1. Assistant professor, Department of DVL, Rangaraya Medical College, Kakinada.
2. Senior resident, Department of DVL, Andhra Medical College, Visakhapatnam.

## *Manuscript Info*

***Manuscript History***
Received: 10 May 2021
Final Accepted: 14 June 2021
Published: July 2021

## *Abstract*

Onychomycosis is a common fungal infection of nail plate caused by dermatophytes, non dermatophyte molds & yeasts. Tinea unguium on the other hand refers specifically to infection caused by dermatophytes. Onychomycosis represents 50% of all nail disorders and 30% of all mycotic infections of skin.1 It is distributed worldwide with prevalence of 3% to 9%. It is generally considered as a disease of middle aged and elderly affecting a large and significant number of people. There has been a recent increase in the incidence as well as a spectrum of causative pathogens associated with onychomycosis. 50 patients of onychomycosis who attended our outpatient department were randomly selected. These 50 patients were equally divided into two groups A and B. Patients in group A (25) were given only oral terbinafine 250mg/once daily for 12 weeks. Patients in group B (25) were given oral terbinafine 250mg/once daily for 12 weeks along with 8% Ciclopirox Olamine nail lacquer which is applied topically once daily at night. In our present study combination therapy give high mycological cure rates than oral terbinafine monotherapy. Combination therapy (oral terbinafine 250mg daily dose with 8% ciclopirox olamine nail lacquer) showed 70 % clinical cure rate and 60 % mycological cure.



## Introduction:-

Onychomycosis is a common fungal infection of nail plate caused by dermatophytes,non dermatophytemolds &yeasts.Tineaunguium on the other hand refers specifically to infection caused by dermatophytes.Onychomycosis represents 50% of all nail disordersand 30% of all mycotic infections of skin.[1] It is distributed worldwide with prevalence of 3% to9%.It is generally considered as adisease of middle aged and elderly affecting a large and significant number of people.There has been a recent increase in the incidence as well as a spectrum of causative pathogens associated with onychomycosis.This increase in the incidence can be attributed to various factors like an aging population, use of immunosuppresive drugs, spread of HIV infection and changing life styles.Onychomycosis associated HIV is clinically more aggressive with a higher frequency of unusual presentation and therapeutically more difficult to treat.[2]

Although usually asymptomatic, onychomycosis can be a source of significant pain as well as great embarrassment and discomfort. It is a disease which generates many physical, psychosocial and occupational problems, there by

**Corresponding Author:- Dr. Boina Kinnera MD**
Address:- Senior resident, Department of DVL, Andhra Medical College, Visakhapatnam.

impairing patient's quality of life.Almost all dermatophytes have been reported to infect nails[3]. Anthropophilic species Trichophytonrubrum and Trichophytonmentagrophytes are the most common offenders worldwide; both invade the nail plate with relative ease[3]. Microsporum nail infections are relatively rare[4]. If a dermatophyte is endemic to a certain geographical area, it is often the cause of nail infection in that area.

Majority of the toe nail infections are due to dermatophytes, while infection by yeasts such as Candida albicans is almost exclusively observed in fingernails[5]. Non- dermatophyte moulds predominantly affect toenails, accounting for 1.5-6% of infections[6]. Trauma is the prerequisite to infection of nails with non-dermatophytes in healthy individuals, with the exception of Scytalidium and Scopulariopsisbrevicaulis.

In 1972, Zaias[7] proposed four clinical types of onychomycosis, each of which has its own host parasite relationship.
1. Distal subungualonychomycosis.
2. White superficial onychomycosis.
3. Proximal subungualonychomycosis.
4.Candidalonychomycosis.

Each type is differentiated on the basis of the fungal invasion into the nail plate and by the causative pathogen. With the exception of superficial white onychomycosis, all others begin in the horny layer of the epidermis following adherence of the infections fungal elements to the stratum corneum in a suitable environment. Majority of the infections are caused by T.rubrum and these infections are chronic because of following immunological causes:

1. Many patients cannot elicit specific cellular immunity against T.rubrum despite persistent infection which may be due to activation of specific suppressor T cells.
2. The mannan cell wall component of Trichophytonrubrum, is thought to suppress cellular immune responses better, than mannans of other dermatophytes.
3. T.rubrum being less aggressive remains in the stratum corneum and does not stimulate an intense inflammatory reaction, there by evading immune surveillance.

The treatment of onychomycosis is far from satisfactory due to several factors. Older and traditional Griseofulvin give unsatisfactory results. After 1991 Terbinafine has revolutionized the therapy of onychomycosis. The recent introduction of the newer topical preparations like 8% ciclopiroxolamine and 5%amorolfine with better drug delivery methods, low cost and low adverse effect profile has allowed it to combine with the oral antifungal agents and this may cut short the treatment duration, achieve better results and reduce post treatment relapse. Thus an attempt has been made to study efficacy of oral Terbinafine alone versus oral Terbinafine with topical 8% cyclopiroxolamine nail lacquer.

## Aims And Objectives:-

To compare the efficacy of oral terbinafine alone and oral terbinafine along with topical 8% cyclopiroxolamine nail lacquer in onychomycosis patients.

## Materials And Methods:-

**Inclusion criteria:**

50 patients of onychomycosis who attended our outpatient department were randomly selected. These 50 patients were equally divided into two groups A and B.

**Exclusion Criteria:**

1. Partiallytreated cases of onychomycosis.
2. Patients with liver dysfunction, diabetes mellitus, renal impairment, gross anemia, pregnancy and lactation
3. Patients on concomitant therapy with drugs having possible interactions with terbinafine.

Patients were examined clinically. Nail changes, associated systemic or skin diseases, especially the presence of mycotic infections elsewhere on the body were noted.

The following investigations were done for each patient - Hb%, TLC, DLC, ESR, random blood sugar, liver function tests, renal function tests,urine-albumin, sugar and microscopy.The patients were also tested for human immune deficiency virus (HIV) antibodies .

All the patients details like age, sex, occupation, personal history, family history, presenting complaints and duration, general condition and findings on clinical examination were recorded in proforma.

Affected nails were scrubbed thoroughly with 70% alcohol. Nail samples were collected aseptically using a sterile nail clipper. The nails were clipped as proximally as possible till the junction of healthy nail with the diseased nail was reached. The distal and outermost part of the nail clippings and subungual debris were discarded. The underlying nail bed and undersurface of nail plate were scraped using a sterile scalpel blade.When both finger nails and toe nails were affected, scrapings were collected from both the sites. The specimens were transported in whatman filter paper envelope, which allow the specimens to dry out, thereby reducing bacterial contamination and also providing conditions under which samples can be stored for a longer period without appreciable loss in the viability of the fungus. A small quantity of the material was placed on a microscopic slide. A drop of Parkers'stain made by mixing equal volumes of 20%potassium hydroxide and Parker's blue-black Qunik permanent fountain pen ink was added and a cover slip was then placed over the slide. The slide was gently warmed over a flame to hasten clearing, and the preparation was left inside a petridish for1-2hrs to a few days for it to dissolve completely for microscopic examination. Potassium hydroxide clears the specimen by digesting proteinaceous debris, bleaching pigments and loosening the sclerotic material without damaging the fungus. Parker's ink enhances the contrast by selectively colouring the hyphae, thereby making them more pronounced for easy detection. The preparations were observed under the low power with a reduced light source. The hyphae in case of dermatophyte fungi were seen as long, branched septate threads. Mature hyphae showed numerous septations with rounded or barrel shaped arthospores. In case of Candida species, spherical budding yeast cells, pseudohyphae or pseudomycelia were seen. Presence of nondermatophyte fungal filaments were correlated with culture findings. The remaining nail material was washed thoroughly with 70% alcohol and then powdered. This material was inoculated directly into 4bottles of Sabouraud's dextrose agar,(2 bottles containing cycloheximide 0.04%and 2 bottles without cyclohexamide)with a sterilized straight wire loop. 2 bottles, one from each group were incubated at $25^0$c and the remaining 2 bottles at $37^0$c . The addition of cycloheximide at 0.04%will inhibit the growth of non-dermatophyte moulds. Antibacterial antibiotic chloramphenicol 0.005%was added to reduce contamination of bacteria and the media was prepared.The Sabouraud's dextrose agar bottles were observed on the 3rd and 4th day, thereafter on alternate days for the presence of fungal growth for a total period of 4 weeks, after which they were discarded if there was no growth.

Patients in group A (25) were given only oral terbinafine250mg/once daily for 12 weeks. Patients in group B (25) were given oral terbinafine250mg/once daily for 12 weeks along with 8%CiclopiroxOlamine nail lacquer which is applied topically once daily at night.

The patients were evaluated at 4 weekly intervals till 16 weeks and then at 24 and 36 weeks.During these visits they were assessed for growth of a normal and healthy appearing nail plate and asked for any adverse effects of drugs.In addition microscopic examination in SDA was done at 16 and 36 weeks. The liver function test was done at the base line and 1-month from the start of therapy.

Clinical cure was defined as replacement of greater than of 90% of the mycotic nail bed and plate by normal and healthy appearing nail bed and plate. Mycological cure defined as negative microscopy under KOH examination and a negative culture in SDA at the end of the follow up period. At the end of the study, the results were compiled, tabulated and analysed using suitable statistical tools.

## Results:-

**Table 1:-** Distribution of age and nails involved in group A.

| Age in years | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| | Total no. of case | Finger nails | Toe nails | Finger nails+ Toe nails | Total no. of case | Finger nails | Toe nails | Finger nails+ Toe nails |
| 20-30 | 6 | 3 | 2 | 1 | 7 | 4 | 2 | 1 |
| 31-40 | 5 | 3 | 1 | 1 | 5 | 2 | 2 | 1 |
| 41-50 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| n=25 | 12 | 7 | 3 | 2 | 13 | 7 | 4 | 2 |

**Table 2:-** Distribution of age and nails involved in group B.

| Age in years | Male | Female |
|---|---|---|

| | Total no. of case | Finger nails | Toe nails | Finger nails+ Toe nails | Total no. of case | Finger nails | Toe nails | Finger nails+ Toe nails |
|---|---|---|---|---|---|---|---|---|
| 20-30 | 6 | 3 | 2 | 1 | 7 | 4 | 2 | 1 |
| 31-40 | 5 | 3 | 1 | 1 | 5 | 2 | 2 | 1 |
| 41-50 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| n=25 | 12 | 7 | 3 | 2 | 13 | 7 | 4 | 2 |

**Table 3:-** Distribution of dermatophytes, candida and non dermatophytemolds in group A and group B.

| Fungal class | Group A (Oral Terbinafin) | Group B (Oral Terbinafine + 8%Ciclopirox Olamine) |
|---|---|---|
| **Dermatophytes** (T.rubrum, T.mentagrophytes, T.tonsurans) | 10 | 10 |
| **Yeast like fungus** (candida albicans) | 7 | 7 |
| **Non Dermatophytes molds** (Aspergillus, acremonium, scopulariopsis, Scytalidium) | 8 | 8 |
| **Total** | 25 | 25 |

In groupA out of 25 patients 10(40%) patients found to be dermtophytes, 8(32%) patients were non dermatophytesmolds and 7(28%) patients were candida albicans. Similar figure were seen in group B.

**Table 5:-** Clinical cure in group A and group B.

| Weeks of follow up | No. of patients showing clinical cure | |
|---|---|---|
| | Group A (Oral Terbinafine) | Group B (Oral Terbinafine + 8%Ciclopirox Olamine) |
| **Week 4** | - | - |
| **Week 8** | - | - |
| **Week 12** | - | - |
| **Week 16** | 2 | 4 |
| **Week 24** | 6 | 6 |
| **Week 36** | 6 | 8 |

Of the 25 patients in group B, 18(72%) showed clinical cure (figure 1,2)and 14(60.87%) in group Aby the end of $9^{th}$ month which is significant statistically ($p<0.05$). (figure 3,4)

**Table 6:-** Clinical cure at the end of $9^{th}$ month as per the fungal variant.

| | Group A (Oral Terbinafin) | Group B (Oral Terbinafine + 8%Ciclopirox Olamine) |
|---|---|---|
| **Dermatophytes** (T.rubrum, T.mentagrophytes, T.tonsurans) | 10 | 12 |
| **Yeast like fungus** (candida albicans) | 2 | 5 |
| **Non Dermatophytes molds** (Aspergillus, acremonium, scopulariopsis, Scytalidium) | 4 | 1 |
| **Total** | 14/25 (60%) | 18/25 (72%) |

**Adverse effects:**

Adverse effects were seen in 5 patients with terbinafine (headache seen in 2 patients, gastric upset seen in 2 patients, altered taste in 1 patient) there is no adverse effects with ciclopiroxolamine nail lacquer in present study.

## Discussion:-

Onychomycosis can no longer be considered a simple cosmetic nuisance confined to the nails. It is significant and impotance disease which can generate many physical, psychosocial and occupational problems, considerably imparing patients quality of life.

Onychomycosis is known to be difficult to treat and often exerts a significant negative impact on the quality of life. The agents most commonly used for treatment of onychomycosis are fluconazole, itraconazole, terbinafine as oral agents and ciclopirox, and amorolifine as topical agents. These newer antifungal agents have better pharmacokinetic profiles, such as prompt penetration of the nail and nail bed, persistence in the nail for several months even after the discontinuation therapy and fewer adverse reactions. Terbinafine hydrochloride is a synthetic antimycotic agent that belongs to family of compounds known as allylamines. It is a fungicidal agent and highly active against dermatophytes, less active against molds,dimorphicfungi,and various yeasts.In general tebinafine is safe for the general population as well as children, diabetics andHIV patients[8].

Terbinafineis well absorbed from gastrointestinal tract, mostly in chylomicrons. The distribution half life is 1.5 hours,and the elimination half life is approxmately 22 hours.Terbinafine is highly lipophilic and keratinophilic in nature.It is biotrasformed by liver ,mostly through oxidation by very small fraction of $p_{450}$isoenzymes predominantly by 2D6 isoform. Terbinafine is approved by FDA for the treatment of onychomycosis by dermatophytes. The contraindications includehypersensitivity to terbinafine or vehicle componants, hepatic disease, renal impairment, pregnancy and lactation.
The dose as per weight is:
Children:10-20 kg weight - 62.5mg/day
20-40 kg weight - 125mg /day
>40 kg -250mg /day

Combination therapy refers to the use of combination of oral and topical antifungals simultaneously or in the sequence.In parallel therapy the oral and topical anti fungals are used simultanously,while in sequential therapy topical therapy follows oral therapy.

Ciclopiroxolamine is a hydroxypyridone antifungal with a unique structure.The chemical name of ciclopiroxolamine is 6-cyclohexyl-4methyl-2(H)-pyridone with empirical formula $C_{12}H_{17}NO_{2.}$

Ciclopiroxolamine interrupts active membrane transport of essential cellular precursors, particularly trivalent cations,[9]and subsequent blockade of enzymatic co-factors.Ultimately disrupts cellular fuction,leading to demise of the fungus. Ciclopiroxolamine also has an inherent anti inflammatory activity exerted through inhibition of prostaglandins and leukotriene synthesis with in polymorphonuclear cells. It has broad spectrum antibacterial properties also.

Ciclopiroxolamine penetrates keratine easily, this ability to penetrate keratin recommends use for onychomycosis as the drug is also capable of penetrate the nail plate material. With topical use approximately 10% administration dose is excreted through the urine.Dosing regimen: ciclopiroxolamine is available in a wide range of forms as 0.77% cream or lotion ,1% shampoo or solution and 8%nail lacquer.

8%ciclopiroxolamine nail lacquer has to be applied evenly over entire nail plate at bed time to all affected nail with applicator brush for 9 to 12months.Excess medication removed weekly with alcohol. The adverse effects include localised erythema,rarely burning or tingling sensation. After the application of ciclopirox nail lacquer 8% to the nail, the solvent evaporates and the concentration in the remaining film increases to 34.87 percent, thereby resulting in a high concentration gradient of the antifungal agent in the nail plate.

Avneret al,[10][2005] studied the effectiveness of the combination of oral terbinafine and topical ciclopirox in comparison to oral terbinafine for the treatment of onychomycosis and concluded that combination therapy of oral terbinafine and ciclopirox nail lacquer is a safer and more effective treatment for onychomycosis than terbinafine alone, particularly in younger patients and for a shorter duration of onychomycosis.

Baran et al,studied the efficacy of a combination therapy with amorolfine nail lacquer and oral terbinafine in comparison to oral terbinafine alone for the treatment of onychomycosis with matrix involvement and concluded

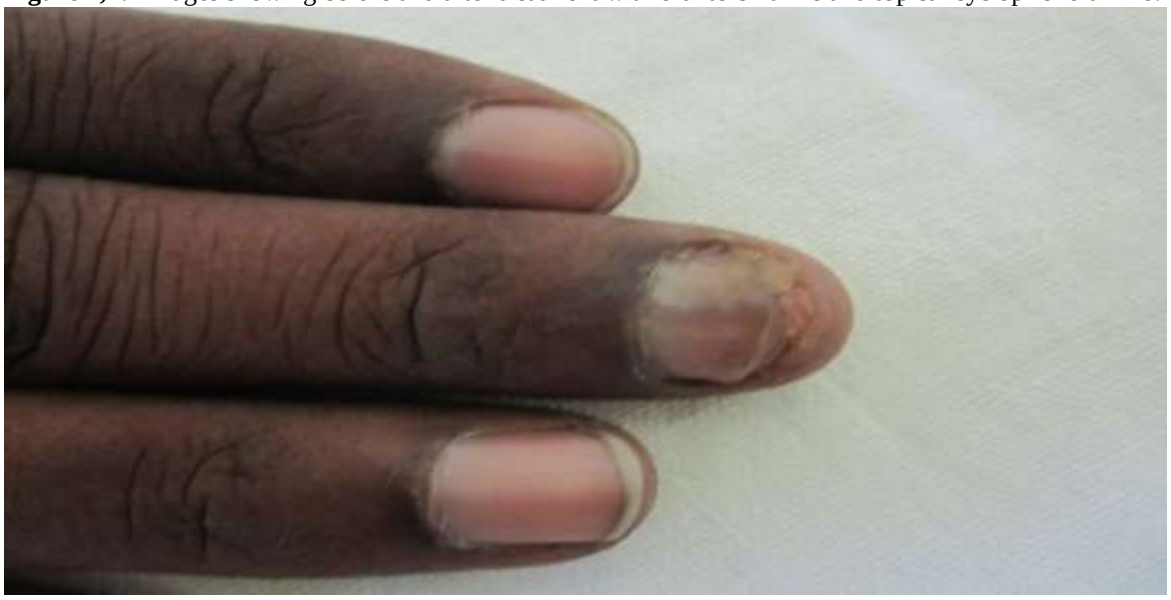
that in the treatment of dermatophytic toenail onychomycosis with matrix involvement, amorolfine nail lacquer in combination with oral terbinafine enhances clinical efficacy and is more cost-effective than terbinafine alone.

In our present study combination therapy give high mycological cure rates than oral terbinafinemonotherapy.

Combination therapy(oral terbinafine 250mg daily dose with 8% ciclopiroxolamine nail lacquer) showed 70 % clinical cure rate and 60 % mycological cure .

Onychomycosis due to candida albicans and dermatophytesrespond better to Combination (oral terbinafine 250mg daily dose with 8% ciclopiroxolamine nail lacquer) therapy.

**Figure 1,2:-** images showing before and after treatment with oral terbinafine and topical cyclopiroxolamine.



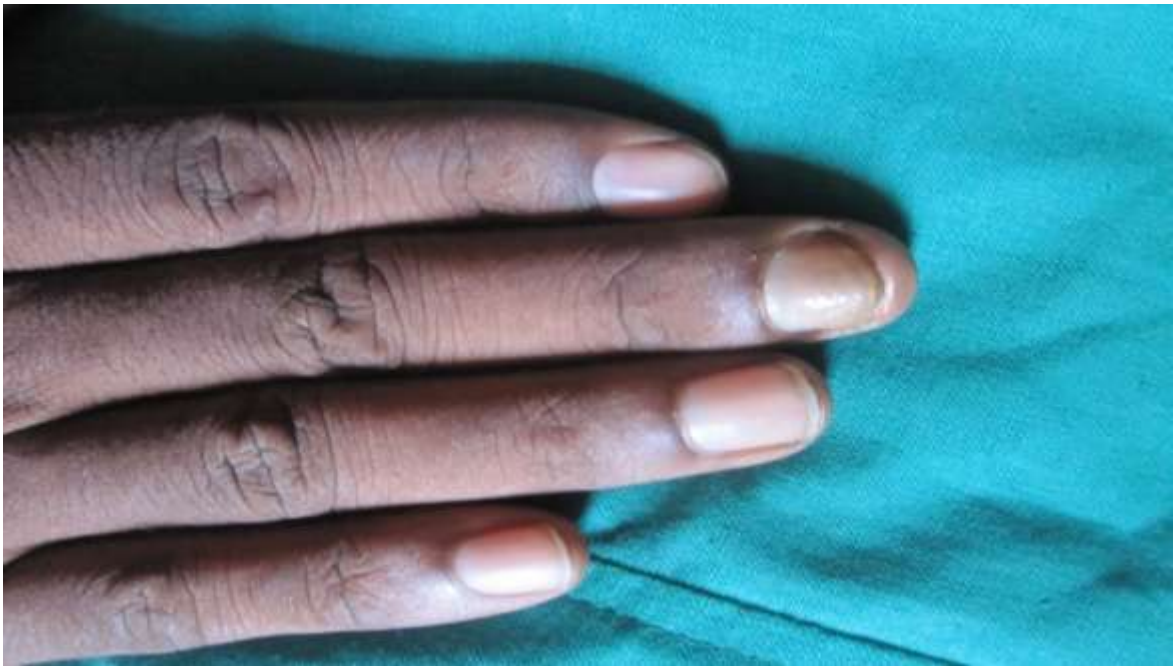
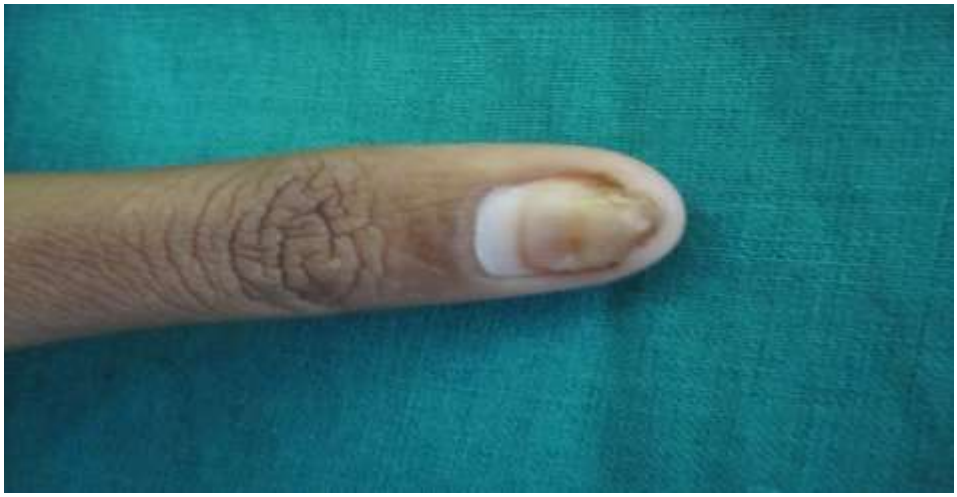
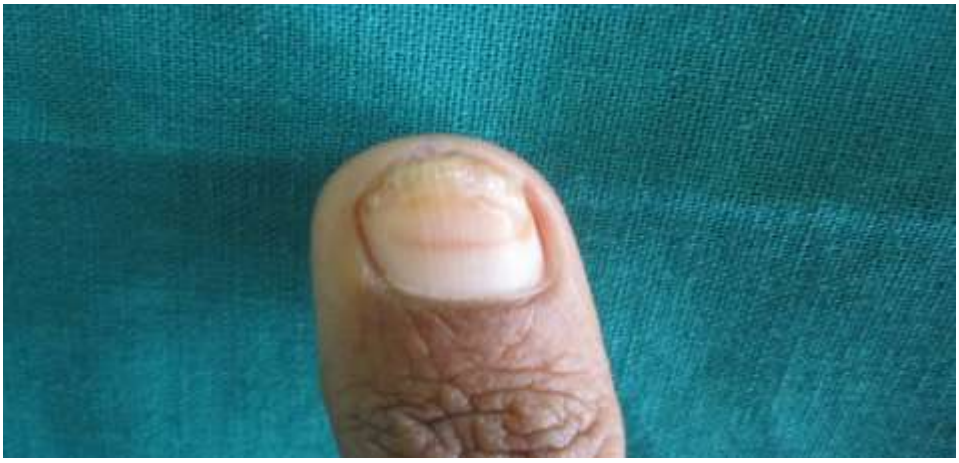


**Figure 3,4:-** images showing before and after treatment with oral terbinafine.





## Conclusion:-

Combination of oral terbinafine with ciclopiroxolamine 8% nail lacquer, is effective and safe than terbinafinemonotherapy.

## References:-


1. Van der straten MR, HossianMA, Ghannoum M A.cutaneousinfections;Dermatophytosis,onychomycosis and tineaversicolor.Infect Dis clin North Am.2003;17:87-122.
2. Herranz P, GrraciaJ,De Lucas R, et al, Toenail onychomycosis in patients with aquriedimmunedeficency syndrome treatment with terbinafine .Br J Dermatol 1997;137:577-80
3. English MP. Nail and Fungi. Br J Dermatol, 1976; 94 : 697 – 701.
4. Tunzun Y. Microsporum infection of the nails. Arch Dermatol, 1980; 116 – 620.
5. Ellis DH, Watson AB, Williams TG. Non-dermatophytes in onychomycosis of the toe nails. Br J Dermatol 1997; 136 : 490 – 493.
6. Migdley G, Moore MK, Cook J.C. Mycology of nail disorders. Jam AcadDerm 1994; 31:368 – 374.
7. Norton LA:naildisorder:Arebiew,JamAcardDermatol 2:451,1980.
8. Gupta AK,MatzH,Lynch,et al, The use of terbinafine in treatment of onychomychosis in a adults in special population ,a review of the evidence .J Drugs Dermatol 2005,4:302-8.
9. AbramsB,HeinzH,HoehlerT. Ciclopiroxolamine: a hydroxypyridoneanti fungalagent.clindermatol 1990;15:95-100.
10. ShemerAvner,combination of oral terbinafine and ciclopiroxolamine compared to oral terbinafine for the treatment of onychomycosis.JDT ,2005,16,no-5-6,327-330.