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A Clinicoepidemiological study of dermatophytoses with comparative efficacy of topical antifungals (1% terbinafine vs 0.5% fluconazole vs 2% miconazole) at a rural based tertiary care center.

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Abstract:
***Background*:** *Because of the widespread prevalence of dermatophytosis in India, it is important to know their regional prevalence and clinical presentations along with the efficacy of the commonly prescribed topical medications.*
Aims: *To study the prevalence, clinical presentation, age and sex distribution of superficial dermatophytic infections in a rural area along with clinicomycological correlation with the efficacy, safety and tolerability of topical terbinafine 1% vs topical fluconazole 0.5% vs topical miconazole 2%.*
Material and methods: *The study a randomized controlled clinical trialwas carried out in the department of dermatology for the duration of one year after ethical clearance, in patients with a confirmed diagnosis of dermatophytosis. A total of 588 patients were recruited in our study and their data was recorded in a predesigned proforma. Out of which, 120 patients who gave consent to participate in the study were enrolled randomly in one of the 3 groups (40 in each group) receiving one of the three topical medications (Miconazole 2%, Fluconazole 0.5% and Terbinafine 1% cream).*
Results: *Out of 588 patients, 412 patients (70.1%) patients were males and 176 patients (29.9%) patients were females. Patients belonging to the age group of 31 – 50years were having highest incidence of dermatophytic infection. The commonest pattern was tinea corporis (40.4%) followed by tinea cruris (18.4%). Of the total 120 patients treated with topical anti fungals, there was no actual difference in the efficacy of the three topical medications at the end of four weeks.* ***Conclusions:*** *The present study gives an insight about the prevalence and clinical profile which would help in estimation of the problem and hence in the prevention and treatment of dermatophytoses with adequate control measures.*
Key-words*: Dermatophytosis, terbinafine, fluconazole, miconazole*

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I. Introduction

Superficial mycoses are infections of skin, hair and nails caused by dermatophytes, yeasts and non-dermatophyte molds. Among these, dermatophytes are responsible for the largest number of cases. Dermatophytes are divided into three genera: Trichophyton, Epidermophyton and Microsporum.[1] Distribution of the dermatophytes varies with the geographical area and course of time.[2]. Dermatophytes are aerobic fungi that produce proteases that digest keratin and allows colonization, invasion and infection of the stratum corneum of the skin, the hair shaft, and the nail.[3] Infection is generally cutaneous and restricted to the nonliving cornified layers because the fungi is not able to penetrate the deeper tissue or organs of healthy immunocompetent host. The infection is commonly designated as ring worm or "tinea". Dermatophytoses is one of the most common diseases in human beings,[4] the prevalence of which varies in different parts of the world. It is common in tropical regions in areas of high heat and humidity. Factors such as overcrowding, lack of personal hygiene and exposure to animals play a role in the frequency of dermatophytoses in different individuals. It has become a significant health problem affecting children, adolescents and adults. This infection although trivial, has a lot of psychological effect and requires effective therapy which is often costly. Many antifungals which are being used commonly nowadays have developed resistance, so hereby we compare the efficacy of commonly used topical antifungal drugs in the treatment of dermatophytoses.

II. Aim and objective

To study the prevalence, clinical presentation, age and sex distribution of the superficial dermatophytoses in a rural area. To study the clinico- mycological correlation along with the efficacy of topical antifungals and evaluate the safety and tolerability of topical Terbinafine (1%) vs topical Fluconazole(0.5%) vs topical Miconazole 2%.

III. Material And Methods

A randomized controlled clinical and observational study was carried out in the department of dermatology after ethical clearance for the duration of one year. (Oct 2013-Sep 2014). Patients with a confirmed diagonasis of dermatophytoses were included. Dermatophytic infection was diagnosed by clinical assessment which included pruritus, typical morphology and distribution in different parts of body and later confirmed by 10% KOH examination and fungal culture.HIV positive patients , pregnant women, lactating women ,women using unreliable methods of contraception ,patients with drug hypersensitivity to imidazole derivative, patients with concurrent treatment with rifampicin, phenytoin, digoxin, oral anticoagulants and H2 receptor antagonists were excluded. The data was recorded in a predesigned proforma and analysed. A total of one hundred and twenty patients were chosen for randomized control clinical trial for comparison of the efficacy of three topical drugs. The selected patients did not have any indication for systemic therapy. They were divided in three groups, with 40 in each group. (Miconazole 2% cream, Fluconazole 0.5% gel, Terbinafine 1% cream respectively). Of 40 each, in one group miconazole twice daily 2% cream was advised. In another group Fluconazole 0.5% gel, once daily application was advised. In third group Terbinafine 1% cream, once daily application was advised. After explaining the entire study procedure, the patients were enrolled with written consent, who fulfilled the selection criterion. Before treatment, a KOH smear was done and follow up (during treatment) was done weekly upto four weeks. At each visit (weekly) KOH smear and clinical evaluation was done and post treatment assessment was done accordingly.Fungal culture (Dermatophyte test medium) was done in all the patients.

Table 1 Global Clinical Evaluation

	Clinical Evaluation (Symptoms & Signs) +	Mycological(KOH)
Poor	All findings present (<25% improvement)	+ve
Fair	Reduce (> 25-50% Improvement)	+ve / -ve
Good	Absent (> 50-75% Improvement)	-ve
Excellent	Absent (> 75 - 100% improvement)	-ve

IV. Observations, Analysis

Out of total 15084 outdoor patients seen in the department of dermatology (October 2013-September 2014), 588 (3.89%) patients had dermatophytic infection.The maximum number of patients of dermatophytoses were seen in the month of July and lowest number of patients with dermatophytoses were seen in the month of April.

Table 2. Prevalence of Dermatophytic infection among patients attending skin OPD

Month	Total number of patients who attended skin OPD	No. of patients with Dermatophytic infections
October	1217	40(3.3%)
November	1141	28(2.5%)
December	1230	30(2.4%)
January	1155	35(3%)
February	1072	41(3.8%)
March	1291	33(2.6%)
April	1111	23(2.1%)
May	1183	59(5%)
June	1295	80(6.2%)
July	1397	94(6.7%)
August	1454	54(3.7%)
September	1538	71(4.6%)
Total	15084	588(3.9%)

The demographic profile of the patients attending skin opd in one year duration is given in table 2

Table 3. Demographic and clinical profile

Age	
<10 Yrs.	49(8.3%)
11-30 Yrs.	180(30.61%)
31-50 Yrs.	220(37.41%)
50-70 Yrs.	118(20.06%)
>70 Yrs.	21(0.34%)
Sex	
Males	412(70.1%)
Females	176(29.9%)
Distribution	
T. captitis	53(9%)
T. cruris	108(18.4%)
T. corporis	237(40.3%)
T. cruris + corporis	62(10.5%)
T. unguum	52(8.8%)
T. pedisS	27(4.6%)
T. mannum	11(1.9%)
T.faciei	38(6.5%)

Hence the maximum patients were seen in the age group of 31-50years followed by 11-30 years.The male:female ratio was 2.34. The most common distribution was Tinea corporis followed by Tinea cruris.

Of the total 120 patients who gave consent for the clinical trial ,84patients (70%) were males and 36patients (30%) were females. The most common occupational group being the labourers{41 patients(34.16%)} followed by housewives{ 26 patients(21.66%)}, students and service class patients{25patients (20.83%) and 21(17.5%) patients} respectively. The least affected group was the retired class and business class in {5(4.16)} and 2{(1.66%)} patients respectively.

The correlation of KOH and Culture is shown in table 4.

Table 4. Correlation of KOH and Culture

Drug	KOH +ve Before treatment (n=40)	KOH +ve After treatment	culture Positivity
Group-A Terbinafine (1 %)	26 (65%)	1 (2.5%)	14 (35%)
Group-B Fluconazole(0.5%)	27 (67.5%)	2 (5%)	12 (30%)
Group – C Miconazole (2%)	24 (60%)	1 (2.5%)	16 (40%)

The clinical efficacies of the three drugs are shown in table 5

Table. 5 Comparison of clinical efficacy of the three drugs

Excellent response	1 week	2 week	3 week	4 week
Group-A	18 (45%)	7 (31.81%)	5 (33.33%)	34(85%)
Group-B	13 (32.5%)	5 (18.51%)	5 (27.27%)	34(85%)
Group-C	9 (22.5%)	10 (32.25%)	6 (28.57%)	33(82.5%)

Excellent response at the end of first week of treatment was shown by — 18 patients (45%) in group A (Terbinafine 1%), 13patients (32.5%) in group B (Fluconazole 0.5%) and 9 patients (22.5%) in group C (Miconazole 2%).Good response at the end of first week of treatment was shown by 6patients (15%) in group A (Terbinafine 1%), 5 patients (12.5%) in group B (Fluconazole 0.5%) and 10 patients (25%) in group C

(Miconazole 2%). Fair response at the end of first week of treatment was shown by 8 patients (20%) in group A (Terbinafine 1%), 12 patients (30%) in group B (Fluconazoie 0.5%) and 11 patients (27.5%) in group C (Miconazole 2%).Poor response at the end of first week of treatment was shown by 8patients (20%) in group A (Terbinafine 1%), 10 patients (25%) in group B (Fluconazole 0.5%) and 10 patients (25%) in group C (Miconazole 2%).

Excellent response at the end of forth week was shown by 34 patients 85% in group A (Terbinafine 1%), 34 patients (85%) in group B (Fluconazole 0.5%) and 33 patients (82.5%) in group C (Miconazole2%).
The side effects noted with the three drugs were as follows;

2 patients(5%) had dryness, 1 patient(2.5%) had erythema, 1 patient(2.5%) had burning sensation with topical terbinafine.2 patients (5%)had dryness, 1 patient(2.5%) had erythema with topical fluconazole. 4 patients(10%) had dryness, 1 patient(2.5%) had erythema, and 1 patient(2.5%) had burning sensation with topical miconazole but no adverse reactions were seen with any of the antifungals.

Table 6. Statistical Analysis

Drug	1st Week	2nd Week	3rd Week	4th Week
Group-A Terbinafine (1 %)	18 (45%)	7 (31 .81%)	5 (33.33%)	4 (40%)
Group-B Fluconazole(0.5%)	13 (32.5%)	5 (18.51%)	6 (27.27%)	10 (62.5%)
Group – C Miconazole (2%)	9 (22.5%)	10 (32.25%)	6 (2e.57%)	8 (53.33%)

p=0.28 using chi square test.

The data obtained was analysed using the analysis techniques generally used for randomized clinical trials study design. Chi square test was used to find out a significant difference between the efficacies of the three topical antifungal drugs. The p values were computed at 95% of Confidence intervals. The data was analysed by using the SPSS - 15 statistical software and the p value was not found significant inferring that there is no actual difference in the efficacy of three topical antifungals at the end of four weeks of clinical trial.

V. Discussion

Superficial mycotic infections such as 'Dermatophytoses' is an extremely common infection occurring throughout the world with up to 20% of the population infected at any given time.[5] Its prevalence varies in different countries.[6,7] It is more prevalent in tropical and subtropical countries like India where heat and humidity is high for most part of the year.[8] along with other risk factors like overcrowding and poverty leading to poor personal hygiene. We also found similar findings where maximum number of patients presented in the month of july.

The type and severity of the host response is often related to the species and strain of the dermatophyte causing the infection.The dermatophytes are the only fungi that have evolved a dependency on human or animal host for the survival and dissemination of their species. The infection may spread from person to person (anthropophilic), animal to person (zoophilic), or soil to person (geophilic).The incubation period in humans is usually 1 to 2 weeks. Dermatophytes generally grow only in keratinized tissues and usually stop spreading where it contacts living cells or areas of inflammation.

The type and frequency of dermatophytoses may change with time, due to changes in living standards and application of preventive measures like personal hygiene.[9] Outbreak investigations are an important and challenging component of public health.[10]Careful investigation of outbreaks has increased our understanding of fungal diseases, their sources and modes of transmission and the risk factors for infections and, in so doing, has resulted in design of improved control measures for these infections. Several species of dermatophytes commonly invade human keratin, and these belong to the Epidermophyton, Microsporum, and Trichophyton genera.[11]

Out of total 15084 outdoor patients attending the department of dermatology (October 2013-September 2014), 588 (3.89%) patients had dermatophytic infection. Out of 588 patients ,412 patients (70. 06%)patients were males and 176 patients (29.93%) patients were females with M:F ration of 2.34 which was consistent with Singh et al and bindu et al [12,13].Patients among 31 – 50years were found to have highest incidence of Dermatophytic infection followed by 11-30yrs of age. Similar findings were observed by other workers.[11,12]. The higher incidence in males could be due to greater physical activity and increased sweating and are usually less concerned about the personal hygiene.

The commonest dermatophytic distribution or pattern in our study was Tinea corporis (40.36%) followed by Tinea cruris (18.36%) which is consistent with kanwar et al.[1].Tinea capitis is less common in India than in other countries. This may be attributable to the use of hair oils (particularly mustard oil) which are customarily used by Indians and have been shown to have an inhibitory effect on dermatophytes in vitro. The

predominance of tinea pedis in western countries could be because of the regular use of shoes and socks, predisposing to perspiration and maceration[13].

Dermatophytes can often be detected by microscopic examination of infected hairs and skin or nail scrapings. Fungal cultures, which identify the species of dermatophytes, can be useful in understanding the source of the infection and targeting preventive measures appropriately. Culture may also be necessary if the diagnosis is uncertain, or the infection is resistant to standard treatment. Controlling dermatophytes in animals can prevent some cases of zoonotic dermatophytoses in humans.

Better surveillance, improved living conditions and improved treatment can decrease the overall prevalence of anthropophilic dermatophytes, while hygiene, and prevention of contact are helpful in individual cases. Measures such as moisture control (e.g., in tinea pedis) are important in reducing susceptibility to some forms of tinea.

Dermatophyte infections are treated with a variety of topical and oral antifungal drugs. In immunocompetent patients, topical agents are usually effective in cases that are limited to glabrous skin (e.g., tinea corporis, tinea cruris, and tinea pedis). Systemic (oral) antifungal drugs may be necessary in severe cases, or if the infection does not respond to treatment or reappears. Topical agents are ineffective against organisms that infect the hairs. These infections are usually treated with systemic antifungals, although topical lotions or shampoos are sometimes used concurrently to decrease shedding of fungi and spores, or to help treat kerion. Topical agents may also be used to treat asymptomatic carriers or prevent reinfection. Dermatophyte infections of the nails (tinea unguium) are usually treated with oral antifungal drugs. Treatment should consider sources of reinfection, such as pets, family members or other close contacts. Some authors suggest treating all family members when the case is caused by certain anthropophilic organisms.

Imidazoles, allyalamines and triazoles are the most effective agents for dermatophytoses. Topical daily antifungal therapy usually involves imidazoles and allylamines.

Terbinafine is a broad spectrum lipophilic antifungal agent which inhibits ergosterol synthesis by inhibiting squalene epoxidase, an enzyme that is part of the fungal cell membrane synthesis pathway. Miconazole is an imidazole antifungal agent, which works by inhibiting the synthesis of ergosterol,a critical component of fungal cell membranes. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system. Fluconazole is a first-generation triazole antifungal agent with spectrum of activity against most Candida species, Cryptococcus neoformans, some dimorphic fungi, and dermatophytes.

Out of the 120 patients included in the trial selected randomly,the most common occupation affected was the labourers and the least affected was the business class. Agarwal et al, however noted the commonest occupation group as students (37.3%) [14]. On the other hand, Sarma and Borthakur[15] found the disease most commonly in occupations related to agriculture (39%), followed by students and unskilled laborers (15%)

84 patients (70%) were males and 36 patients (30%) were females. Out of total 40 patients included in Group A (Terbinafine 1%), 26 patients(65%) were KOH smear positive and 14 (35%) were KOH smear negative before treatment. In Group B (Fluconazole 0.5%) 27 patients (67.5%) were KOH smear positive and 13 (32.5%) were KOH smear negative before treatment. In group C (Miconazole 2%) 24 patients (60%) were KOH smear positive and 16 patients (40%) were KOH smear negative before treatment. The negative KOH can be attributed to minimal scaling in some cases.

14 patients (35%) in group A, 12 patients (30%) in group B and 16 patients (40%) in group C were culture positive on dermatophyte test medium. The negative culture can be attributed to contamination and delay in processing in the laboratory. According to Agarwal et al [14]., 84.67% showed dermatophytes on KOH preparation and 80% cases showed the fungus on culture. Sahai and Mishra[16] reported similar dermatophyte demonstration and isolation rates of 89.6% and 83% respectively.

In the present study with topical fluconazole once a day application, 32.5% patients showed excellent response clinically and were mycologically cured at the end of 1st week and 45% patients showed excellent response at the end of 2nd week while 85% patients were mycologically cured at the end of 4 weeks. Kulkarni KR et al reported 42.5% patients showing excellent response at the end of 2 weeks.[17]

With topical miconazole twice a day application,22.5% patients showed excellent response and were mycologically cured at the end of 1 week and 47.5% patients showed excellent response at the end of 2nd week. Rajendra C et al reported 57.3% patients showing excellent response by 15th day of treatment.[18]

With topical terbinafine once a day application, 45% patients were mycologically cured at the end of 1st week and 85% patients were cured after 4 weeks of treatment. Evans et al reported 60% and 86% patients were found to be mycologically cured at the end of first week and fourth week respectively.[19]

Vanheerden etal reported 59% and 84% patients mycologically cured after first and fourth weeks of treatment respectively.[20]

Terbinafine is the only anti fungal agent where MIC (minimal inhibitory concentration) is equal to MFC (minimal fungicidal concentration) which suggests that it is effective over a very short duration. Azoles inhibit fungal growth and they have only fungistatic effect.

So here we conclude that all the three antifungals used topically for superficial dermatophytoses have equal efficacy at the end of 4 weeks treatment.

VI. Conclusion

Accurate assessment of the prevalence and etiologic agent is desirable to estimate the size of the therapeutic problem and to prevent the transmission and spread of such infections with adequate measures. Moreover; awareness of the preventive measures regarding public health and maintenance of personal hygiene could reduce the incidence of Dermatophytoses and hence the burden of this disease in the community as a whole. The results of the present study indicate that Terbinafine is better than miconazole and fluconazole in relieving signs and symptoms of dermatophytoses especially pruritus ,thereby improving patients' quality of life

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