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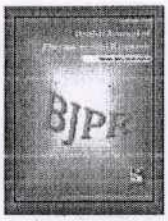

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Clinical Efficacy of Topical Terbinafine Versus Topical Luliconazole in Treatment of Tinea Corporis/Tinea Cruris Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author CPVL designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author GMB reviewed protocol, literature searches, and statistical analysis. Author VSK managed the collection of sample data and review manuscript literature search. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: Tinea corporis & cruris of skin respond well to topical antifungal therapy, but there is a need to apply cream 2- 3 times daily for up to four weeks will impair compliance & lead to treatment failure. Luliconazole is one of those drugs offering good efficacy & tolerability with a short duration of treatment. Terbinafine, an allylamine antifungal agent, acts by selective inhibition of fungal squalene epoxidase.
Luliconazole, an imidazole antifungal agent is considered to be more effective in inhibition of ergosterol biosynthesis and its reservoir property in stratum corneum is greater than that of terbinafine. As there are lack of studies between terbinafine & luliconazole, the present study was undertaken to compare the clinical efficacy in tinea corporis/tinea cruris patients.
Study Design: Prospective parallel study.
Place and Duration of Study: Study was conducted on 60 patients presenting to the Dermatology out-patient department of RL Jalapa Hospital, Kolar, from 1st December 30th April 2012.

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Methodology: Patients alternatively assigned to either terbinafine or luliconazole & advised to apply test drugs topically for 14 days. Clinical symptoms & signs were assessed using 4-point (pruritus, erythema, scaling) scale & 10% KOH mount at base line, end of treatment visit (15th day) & later 30th day. The data was analysed based on age, gender distribution, duration of lesion, clinical score & KOH mount.
Results: Of the 60 patients recruited, all came for 1st follow up (14th day) & 51 patients for 2nd follow-up (30th day). Mean age of the patients was 33.80± 9.58 years in terbinafine & 33.90 ± 9.58 years luliconazole group. Majority of patients were in 12- 40 years aged in both group. Sixty patients and 51 patients were negative for KOH mount preparation on 15th & 30th day respectively. At the end of first follow-up, the clinical score was reduced from 3 to zero (P=0.0001) in both the treatment groups. Mycological cure was 100% in both the drug groups. There was no relapse in 51 patients who came for 2nd follow-up. Four in terbinafine and 5 in luliconazole group were lost to follow up.
Conclusion: Only mild forms of tinea infections were included as compared to other studies where moderate to severe (pustules, incrustations, vesiculation). Hence the onset of illness, treatment duration and severity of illness were favorable in this study for two weeks. In both the treatment arms, clinical & mycological cure was comparable, hence once a day application for two weeks of terbinafine & luliconazole were equally effective for treatment of tinea corporis/cruris infection.

Keywords: Topical terbinafine 1% cream; topical luliconazole 1% cream tinea corporis; tinea cruris.

1. INTRODUCTION

Superficial fungal infections of skin caused by dermatophytes constitute an important public health problem [1,2]. Tinea corporis and tinea cruris are commonly seen in day to day outpatient basis in Dermatology centers throughout the world and an important clinical problem that may at times be a therapeutic challenge [3]. All species of dermatophyte belonging to genera Trichophyton, Microsporum, or Epidermophyton is capable of producing tinea corporis and cruris, most common causative organisms are *T. rubrum, M. canis* and *T. mentagrophytes* [4,5]. Pruritus is a common symptom, 6 the most common presentation is the typical annular lesion, scaling with an active, erythematous, central clearing, and sometimes vesicular border [6,7]. As it's a contagious infection which spreads, produces itching and disturbs activity and sleep, will have an impact on their day to day life, hence the infection has to be treated.

The treatment for tinea corporis & tinea cruris is extremely varied; current treatment includes topical antifungal agents such as clotrimazole, sertaconazole, lanoconazole, miconazole, bifonazole, ketoconazole, terbinafine, which achieve high cure rates but require almost 2-3 times daily application, for up to 4-6 weeks which can impair patient compliance & lead to treatment failure [8]. An antifungal drug with good efficacy & tolerability with the advantage of providing a complete cure in a short duration of treatment may be preferred by the patients and the dermatologists.

Luliconazole is one of those drugs offering good efficacy & tolerability with a short duration of treatment [9]. Terbinafine, an allylamine antifungal agent, acts by selective inhibition of fungal squalene epoxidase [10]. Luliconazole, an imidazole antifungal agent is considered to

be more effective in inhibition of ergosterol biosynthesis, and its reservoir property in the stratum corneum is greater than terbinafine [11].

Since there are no published clinical studies till date that evaluated the efficacy of topical terbinafine compared to topical luliconazole in mild tinea infections (tinea corporis & tinea cruris), the present study was undertaken.

2. MATERIALS AND METHODS

2.1 Source of Data

The study was conducted on 60 patients presenting to Dermatology OPD of Sri. R. L. Jalapa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, and Karnataka. The study recruited patients on outpatient basis from December 2010 to April 2012. The study was started after obtaining ethical clearance from institutional ethical committee.

2.2 Inclusion Criteria

1. Patients of either gender over 12 years of age.
2. Patients with a mycological diagnosis of tinea corporis/tinea cruris Confirmed by microscopic KOH wet mount.

2.3 Exclusion Criteria

1. Pregnant and lactating females.
2. All other clinical types of tinea infections.
3. Patients who are immunocompromised (due to diseases Ex: HIV or medication).
4. Patients with a history of intolerance or hypersensitivity to imidazole and allylamine compounds.
5. Patients using the following medications:

    a. Topical antifungal agent / topical corticosteroids in treatment area (s) within 30 days of base line visit.
    b. Systemic antifungals within eight weeks of base line visit (8 months for oral terbinafine).
    c. Systemic corticosteroid within 30 days of base line visit.

2.4 Method of Collection of Data

60 patients were recruited for this prospective study and patients were alternatively assigned to two groups of 30 patients each.

Group A: Patients was receiving topical terbinafine
Group B: Patients was receiving topical luliconazole

Clinical history was taken and clinical evaluation done (after examination) by Dermatologist as per the proforma attached. Informed consent was taken from each patient after explaining the details of the study, then patients were assigned to either Group A/Group B and were advised to apply either topical 1% luliconazole cream / topical 1% terbinafine cream at bed

time once daily for 14 days. Complete clinical assessment of main symptoms and signs and mycology screening test (KOH mount) were performed at first visit (base line), at end of the corresponding treatment visit (its end of 14th day for both groups) and 15th day and later 30th day.

Improvement in clinical symptoms and signs (pruritus, erythema, scaling) were assessed by toal composite score using the 4-point scale [12] done by the investigator.(0=absent, 1=mild, 2=moderate,3=severe).

2.4.1 Procedure for KOH mount [13,14]

Scraping - Infected lesions are scraped from the edge of lesion using scalpel blade no :15 (with pre-flamed blunt scalpel), scrapings may be collected in a black paper or directly on to the slide, KOH 10% (2-3 drops) is added to the collected material, covered by a cover slip and gently preheated before examining for fungi.

2.4.2 Microscopic examination

Slides were microscopically examined first under low power (10x), then under high power (40x) objective, for presence of thin filamentous forms (hyphae).

At the end of treatment & 2-week follow up examination, therapeutic response in each patient was categorized as follows: complete cure- normal microscopy findings, no residual signs & symptoms; mycological cure – normal microscopy findings & mild residual erythema &/or desquamation & /or pruritus (total score ≤ 2), but no other signs & symptoms; improvement – significant reduction in signs & symptoms, but residual signs & symptoms (total score more than 2) & /or presence of pathogen; failure – no significant response to therapy or exacerbation of signs & symptoms.

If a patient achieved a complete cure or a mycological cure with mild residual signs or symptoms, the response to treatment was considered to be "effective." Therapy was defined as "ineffective" if any other response occurred [15].

2.5 Statistical Analysis

The data was analyzed for age, sex, duration of lesion, score pattern & KOH mount. Descriptive statistic was used to analyze demographic data. Duration of lesions between the groups was compared using Unpaired't test. Clinical parameters (pruritus, erythema, scaling) was compared by using Kruskal-Wallis test (within the group) and Mann-Whitney test for comparing the groups at base line / 15th day / 30th day. P value <0.05 will be considered statistical significant.

3. RESULTS

Of the 60 patients, all were available for 1st follow up (15th day) & 51 patients for 2nd follow up (30th day). All 51 patients were negative for KOH mount preparation on 15th & 30th day.

The patients were balanced with respect to baseline characteristics. The mean age was similar in both groups as shown in Table 1. Majority of the patients were aged between 12-40 years. Male patients predominated in both the study groups.

24 patients of terbinafine group had 3-20 days duration of lesion and 6 patients between 21-31 days.

Similarly, among 10 patients of luliconazole group - 5 patients had duration of lesion between 3-10 days and the remaining 5 patients between 21-31 day. Rest of the 20 patients had duration of lesion between 11- 20 days.

Table 1. Demographic details

	1% Terbinafine group n=30	1% Luliconazole group n=30
Age (yrs)	33.80±9.58	33.90±9.58
12-40	24	29
41-60	6	1
Males (%)	19 (63.3)	16 (53.3)
Females (%)	11 (36.3)	14 (46.7)

Table 2 and Fig. 1 represents the number of days; the patient was suffering from tinea cruris/tinea corporis before coming to dermatologist.

Table 2. Duration of lesion at the time of presentation

Duration(days)	No of patients of 1% Terbinafine group	No of patients of 1% Luliconazole group
3-10	12	5
11-20	12	20
21-31	6	5

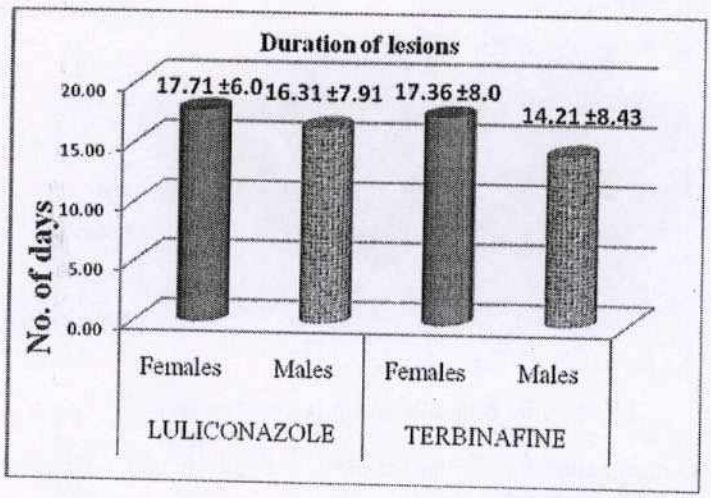

Fig. 1. Duration of lesion

Figs. 2 and 3 Represents the diameter of size of lesions of patients belonging to either terbinafine / luliconazole group.

Terbinafine group: About 80% patients presented with a diameter of 4×5 cm as size of lesion, remaining 20% patients had a diameter ranging between 2×2cm to 7×8 cm.

Luliconazole group: About 40% patients presented with an diameter of 4 ×4 cm as size of lesion; remaining 60% patients had a diameter ranging between 2× 1cm to 5× 5cm.

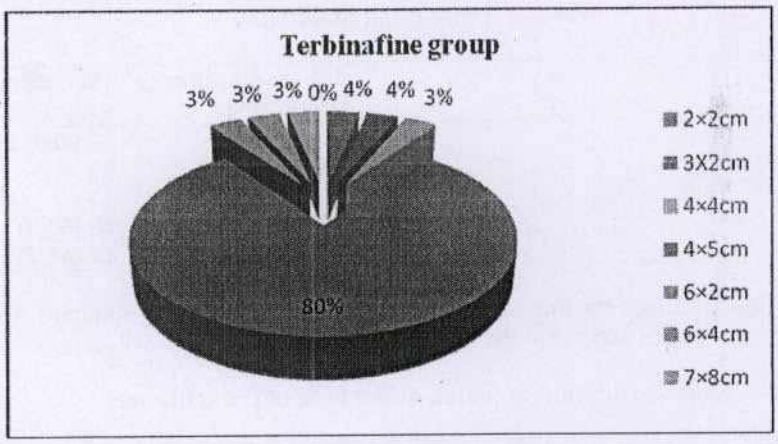

Fig. 2. Terbinafine group (size of lesion)

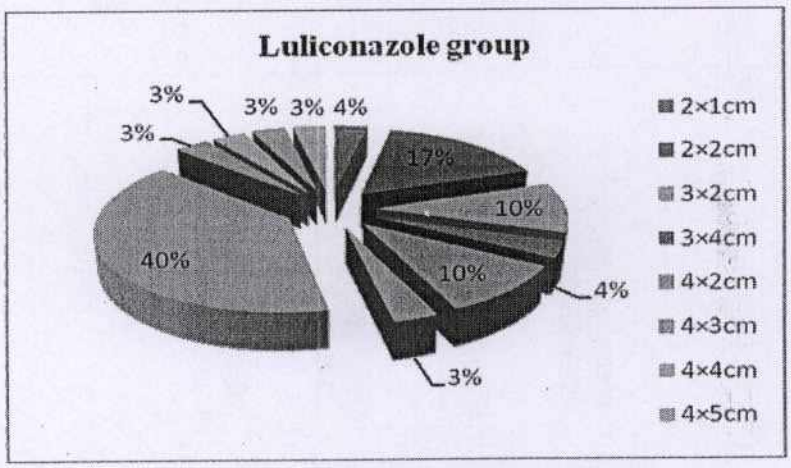

Fig. 3. Luliconazole group (size of lesion)

Table 3 and Fig. 4, represents the number of patients being diagnosed as tinea corporis /tinea cruris in the respective groups.

Table 3. Diagnoses

Group	Tinea corporis (%)	Tinea cruris
Luliconazole 1%	15(50)	15(50)
Terbinafine 1%	11(36.7)	19(63.3)

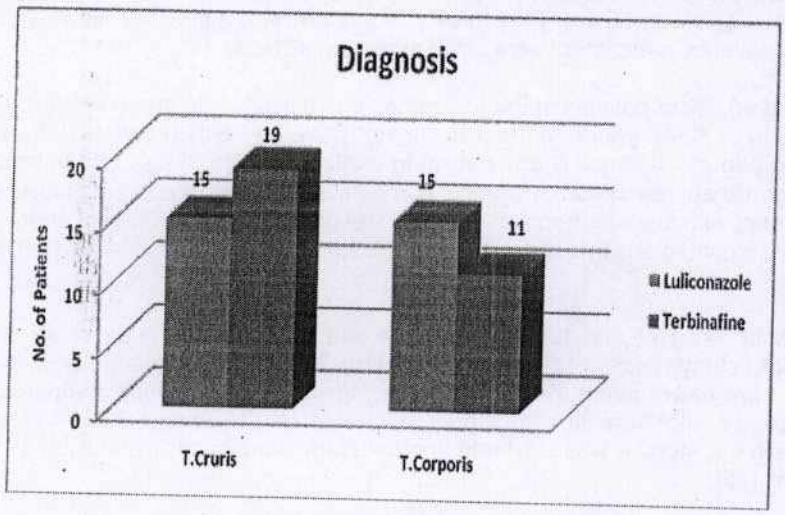

Fig. 4. Diagnosis

In the luliconazole group, 15 patients were of tinea cruris and 15 patients were of tinea corporis as shown in Fig. 4.

In the terbinafine group, 19 patients were of tinea cruris and 11 patients were of tinea corporis as shown in Fig. 4.

When the scores were compared within the group, there was significant improvement on 15th day compared to baseline in both the groups. The total composite score and KOH mount was negative by 15th day in both the groups; the improvement in symptoms and signs were similar in both the groups by the end of 15th day (P>0.05).Types of lesion in both the groups were scaly and erythematous. Complete cure was observed with both the drugs by 15th day (Table 4). None of the patients had relapse when assessed on day 30. None of the patients reported any serious adverse effects during the entire study period in both the groups. About four patients, in the terbinafine group showed mild contact dermatitis, which wasn't troublesome issue for their entire treatment & follow up period. No incidence of contact dermatitis was noticed among patients of luliconazole group (P=0.0001).

Table 4. Response to treatment in both groups

Groups	Baseline score=3, KOH mount-positive	15th day, score=0, KOH mount negative	30th day, score=0, KOH mount negative
Terbinafine	30	30	2l
Luliconazole	30	30	25

4. DISCUSSION

In our study, the mean age of patients was 33.80± 9.58 & 33.90± 9.58 years in terbinafine and luliconazole group respectively, which was similar to study done by Budimulja U et al. [16] where mean age was 35 yrs. Fifty three patients presented in 2nd, 3rd & 4th decades of life and seven patients in the later years of life as shown in Table 1.

About 80% and 96.6% of patients in the terbinafine and luliconazole group respectively were in the age group of 12-40 years. In the present study, we had only 6 patients of terbinafine group in age group of 41-60 yrs & one patient in the luliconazole group. The patients in the younger age group approach dermatologists in the initial stage of disease because of social stigma associated with tinea corporis and cruris. The disease have an impact on their day to day life, as its an contagious infection which spreads, produces itching and disturbs activity and sleep.

Male:female ratio was 1.75 and 1.15 in terbinafine and luliconazole group in our study and was identical to study results of Budimulja et al. [16]. The routine outdoor activities of men, making them more aware about their skin disorder, their life more difficult compared to their female counterpart who were homemakers. This could be the reason for increased male predominance in our study & was similar to another study done by Millikan LE, et al. [17] and Greer DL, et al. [15].

The mean duration of lesion in terbinafine group was 15.36 ± 8.28 and luliconazole 16.96 ± 7 days. In this study, there was an early presentation of patients to the dermatologist.

The present study shows that about 80% of patients presented within 3-20 days of disease, both in terbinafine & luliconazole group, in other studies the mean duration of disease at time of presentation was 16–20weeks [15]. None of the patients in this study had a history of tinea corporis/tinea cruris. Types of lesion in both the groups were scaly & erythematous, which was similar to study done by Budimulja U, et al. [16].

In our study, about 36.7 % of patients were of tinea corporis & 63.3 % tinea cruris in terbinafine group and 50% were of tinea corporis & 50 % of tinea cruris in luliconazole group. This shows that percentage of patients presenting with tinea cruris seem to be > more than 50% in both the drug group, which was also similar to a study's findings done by Millikan et al. [17].

About 80% of patients presented with a diameter of 4 × 5 cm as size of lesion in terbinafine group & about 40 % of patients with a diameter of 4×4cm in luliconazole group, remaining patients had a diameter ranging between 2 ×2cm to 4×4cm respectively.

We have assessed the response to treatment both by clinical observation(rating by scoring pattern), as well as with mycological study i.e. 10% KOH mount, which was done at base line (zero day), end of 15th day & 30th day respectively for both the drug groups. At the end of 15th day, clinical score was '0' and KOH mount was negative in all patients of both the groups. So 2 weeks of treatment with terbinafine and luliconazole has shown to cure tinea corporis and cruris infection. On day 30, 2nd follow-up was done to assess the relapse in the disease condition. 26 and 25 patients came for 2nd follow-up in terbinafine and luliconazole group respectively, and the clinical & mycological assessment score was zero in both the groups, with no statistical difference (Figs. 5-7 for terbinafine and Figs. 8-10 for luliconazole group). Four patients of terbinafine group and five patients in the luliconazole group were

lost to follow up as they were untraceable or failed to come to hospital after repeated reminders.

TERBINAFINE GROUP

Fig. 5a. Base line (Before treatment)

Fig. 5b. After 4weeks of treatment completion

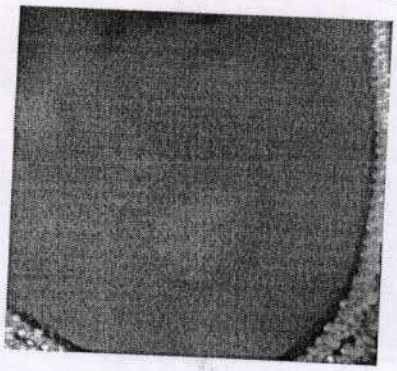

Fig. 6a. Base line (Before treatment)

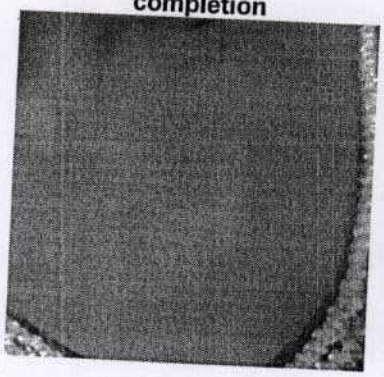

Fig. 6b. After 4weeks of treatment completion

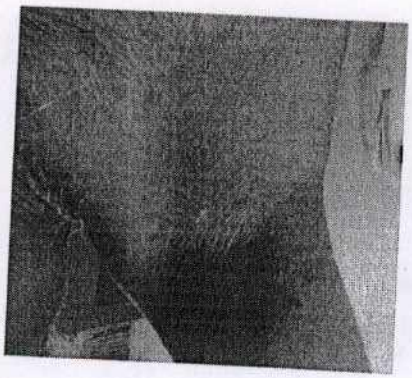

Fig. 7a. Base line (Before treatment)

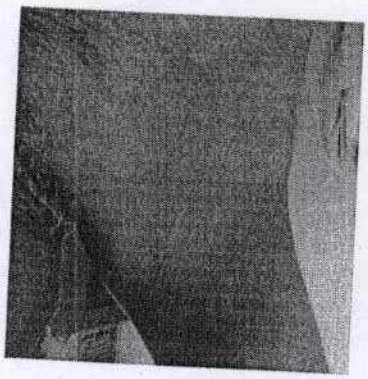

Fig. 7b. After 4weeks of treatment completion

LULICONAZOLE GROUP

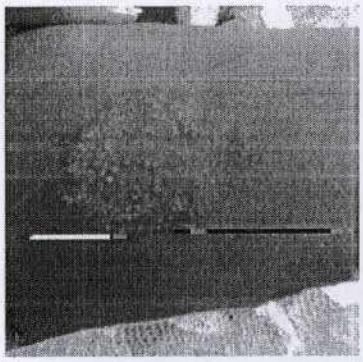

Fig. 8a. Base line (Before treatment)

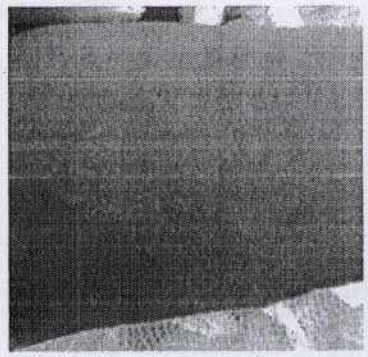

Fig. 8b. After 4weeks of treatment completion

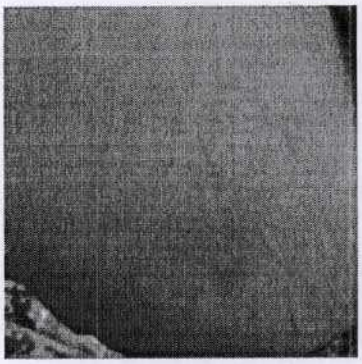

Fig. 9a. Base line (Before treatment)

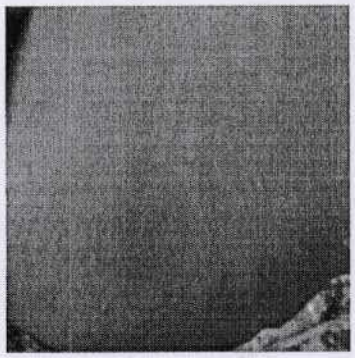

Fig. 9b. After 4weeks of treatment completion

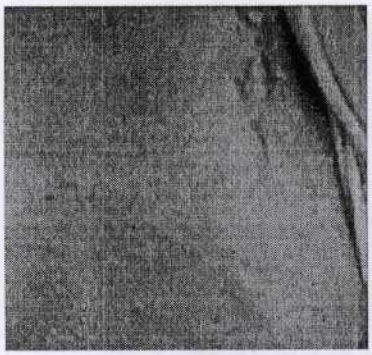

Fig. 10a. Base line (Before treatment)

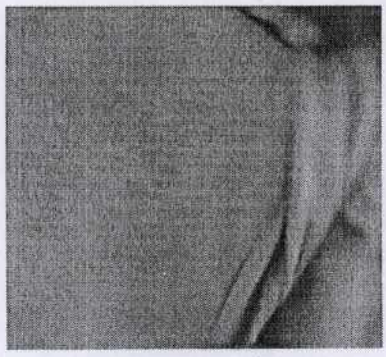

Fig. 10b. After 4weeks of treatment completion

Once a day treatment with terbinafine was effective in tinea cruris and corporis for 7 days and the mycological cure was 90% with moderate and severe lesions as related to a study done by Budimulja et al.[16] Hence this study establishes the need for two-week treatment of terbinafine1% for tinea corporis and cruris.

Twice a day treatment for 14 days with terbinafine was found to be effective in tinea cruris, with a mycological cure rate of 78% at the end of therapy and 89 % at the end of 4th week, as compared to 100% at the end of therapy and no cases of relapse at the 4th week follow – up in the present study. Possible reason could be that in the present study, only mild forms of tinea were included and duration of illness was 3-20 days, whereas in other studies it was 24 weeks [17], 16 weeks [15], & moderate to severe forms of tinea infections were included.

In present study only mild forms of tinea were included, which brought 100% mycological cure rate in both the drug groups. Hence 2 week treatment with 1% luliconazole cream is effective in treating mild tinea corporis and cruris infection and its efficacy is comparable to 1% terbinafine.

Similarly, the mycological cure was similar in all the sertaconazole, luliconazole and terbinafine at the end of treatment and follow up period. The mean percentage reduction in total composite score was 97.1%, 91.2% and 92.9% for sertaconazole, terbinafine and luliconazole group respectively, suggesting comparable efficacy of the studied anti-fungal agents at the end of follow-up phase [18].

In several invitro studies, it was proved that luliconazole was more efficacious than terbinafine, lanoconazole and bifonalzole against dermatophytoses spp. The MIC obtained for luliconazole was 4,30 and 1000 times lower than above said drugs [19,20,21].

Maheshwari N et al compared efficacy & safety of luliconazole 1% with miconazole 2% cream in tinea cruris, pedis and corporis patients and showed that the clinical resolution of signs & symptoms was seen in 22.3 and 30.6 days respectively. The time to KOH conversion was 12 days versus 15.6 days & complete cure was 62.9% versus 57.1% in luliconazole & miconazole group respectively. In the present study, clinical improvement and KOH conversion was 100% at the end of 2 weeks of therapy with no relapse at 4th week in the luliconazole group [9].

About 4 patients in the terbinafine group showed mild contact dermatitis, which resolved by the end of study period and did not require treatment, which was similar to study done by Greer DL et al. [15]. But there was no contact dermatitis among luliconazole group which was statistically significant (P=0.0001). There were no other serious adverse effects in both treatment arms.

Two tubes were sufficient for two weeks treatment in terbinafine and luliconazole group, costing Rs 140 (each tube cost Rs 70) and Rs 260 (Each tube cost Rs 130) respectively. Emollient derma dew aloe E cream was prescribed to patients after 1st follow up in both the groups for depigmentation from the affected area for two weeks and also to ensure the patient compliance in attending the 2nd follow-up. Cost of therapy for each patient was Rs.110. Cost of treatment in terbinafine and luliconazole was Rs. 250 and Rs.370 respectively. Terbinafine was more cost-effective in treating tinea cruris and corporis infection.

The study was conducted in a tertiary care hospital in Kolar which is in rural area. Hence culture of fungus was not available. Hence KOH mount was used as diagnostic mycological cure. But ideally culture would have been better. So it one of the limitation of this study.

5. CONCLUSION

Two-week treatment with terbinafine 1% cream & luliconazole 1% cream achieved 100% conversion rate (positive KOH mount microscopy to normal microscopy), with lesser number patients in both the groups lost to follow up at the end of their 2nd follow-up visit. Luliconazole is the newer topical azole which has fungisatic action as compared to terbinafine's fugicidal effect. So the equal efficacy of luliconazole has dermatophytoses especially pruritus thereby improving patients' quality of life. No Indian study has been conducted so far comparing the efficacy of luliconazole in T.corporis and cruris. This is the first study to imply that luliconazole is equally efficacious to other group of drugs which acts through other mechanism. Only one patient reported contact dermatitis in terbinafine group suggesting excellent safety and tolerability of luliconazole and terbinafineOnly mild forms of tinea infections were included when compared to other studies where moderate to severe (pustules, incrustations, vesiculation) were included. Hence the onset of illness, treatment duration and severity of illness were in favor in our study for 2 weeks. Hence, two weeks once a day application of terbinafine & luliconazole were equally effective for treatment of tinea corporis/cruris infection.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The study was approved by Institutional Ethics Committee, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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COMPETING INTERESTS

All authors declare that no competing interests exist

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