

Efficacy, Safety, and Cost Evaluation of the Topical Luliconazole Therapy versus Topical Clotrimazole Therapy in Patients with Localized Dermatophytosis in a Tertiary Care Hospital: An Observational Study

Abstract

Background: Dermatophytosis is a superficial fungal infection that has high affinity for keratinized tissues of the body. The treatment of localized dermatophytosis is a major concern for the dermatologist especially in tropical countries like India. Various topical antifungals are available for the treatment of localized uncomplicated dermatophytosis. Luliconazole is an azole antifungal available that has potent activity against dermatophytes. **Objectives:** The objective of this study was to compare two treatment modalities for the treatment of localized dermatophytosis in terms of efficacy, safety, and cost evaluation. **Materials and Methods:** This was a prospective and observational study carried out for 6 months and included 200 patients (luliconazole group [$n = 94$] and clotrimazole group [$n = 106$]). Patients were followed up for 2, 4, and 6 weeks. Outcome parameters such as pruritis, erythema, scaling, vesiculations, and global assessment score were noted at 2, 4, and 6 weeks for the assessment of efficacy. The statistical analysis was done using Chi-square and Student's *t*-test. **Results:** Luliconazole and clotrimazole showed 56.38% and 23.58% cure rate at the end of two weeks respectively ($P < 0.05$). At the end of treatment, the cure rates were 98.93% and 95.28% in luliconazole and clotrimazole, respectively ($P > 0.005$). Both the drugs were equally safe. On cost-effective analysis, luliconazole was found to be more cost-effective than clotrimazole at the end of 2 weeks. **Conclusion:** Therapeutic efficacy of luliconazole was more as significant proportion of patients achieved complete clearance of lesions at faster rate within 2 weeks with convenient once daily application.

Keywords: Clotrimazole, cost-effective ratio, global assessment score, luliconazole, tinea corporis

Introduction

Dermatophytosis is the fungal infection that invades the keratinized tissue (skin, hairs, and nails) of human beings. It is the most common superficial fungal infection being encountered by dermatologists in routine practice.^[1] According to site, these infections are classified as tinea pedis (feet), tinea corporis (body), tinea cruris (groin), and so on.^[2] It has high prevalence in country like India where prevalence ranges from 36.6% to 78.4%.^[3] Tropical climate characterized by high humidity and varying degree of temperature with low socioeconomic status and conditions such as overcrowding, poor personal hygiene are the various risk factors contributing toward increasing prevalence of disease in India.^[4,5]

Dermatophytosis also known as ring worm infection is characterized by the

erythematous scaly plaques giving it a ring like morphology and is associated with intense pruritis.^[2] Direct microscopic examination is done for the diagnosis of the fungal infection where 10% potassium hydroxide mount is prepared from the skin scrapings.^[6] The treatment of dermatophytosis demands the use of topical or systemic antifungal therapy depending on the site and extent of involvement. Topical antifungal therapy remains the mainstay of treatment for the patients with localized and uncomplicated dermatophytosis owing to their potential lower adverse effects and high efficacy.^[7] However, systemic therapy is required in the severe cases of dermatophytosis.^[2] Clotrimazole and luliconazole are the imidazole antifungal drugs being commonly used in the skin outpatient department (OPD) for the treatment of localized dermatophytosis. Clotrimazole is one of the oldest known

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broad spectrum topical antifungal agent that requires twice daily application.^[1] Luliconazole is also a broad spectrum antifungal and relatively newer agent that is found to be more active than other azole antifungals in several studies and requires single daily application for localized dermatophytosis.^[8] Due to scarcity of the data available on the head on comparison between these two commonly used topical antifungal therapies, this observational study was undertaken with the primary objective to determine the efficacy of the topical luliconazole and clotrimazole therapy in the treatment of uncomplicated and localized dermatophytosis. The secondary objective was to determine the safety and cost-effectiveness of above two therapies.

Materials and Methods

Study design

This study was a prospective and observational study conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki for 6 months. The approval for the protocol of the study was sought from the Institutional Research and Ethical Committee. The study was initiated after the clearance from Ethical Committee and written informed consent was obtained from the patients prior to the enrollment of each of the study participants. The patients were advised to bring the tubes of the medications at every visit to ensure consent in accordance with the established protocol, compliance with medication, and to report immediately on experiencing any adverse event during the study.

Inclusion criteria

All patients above the age of 12 years of either sex who were clinically and mycologically diagnosed of a case of localized dermatophytosis were included in the study.

Exclusion criteria

Patients with extensive dermatophytosis, other forms of tinea infections, superadded bacterial infection, immunocompromised patients, dermatitis such as contact dermatitis, atopic dermatitis, psoriasis, other skin diseases, pregnant and lactating females, patients with a history of hypersensitivity to azole antifungals, patients who received topical antifungal within 1 week before baseline visit and patients who received systemic antifungals within 4 weeks before baseline were excluded from the study.

Treatment

Two hundred and twenty patients who satisfied the inclusion criteria were recruited for the study over a period of 6 months. Of these, 110 patients were prescribed luliconazole by one dermatologist and 110 patients were prescribed clotrimazole by other dermatologist. Sixteen patients were lost to follow-up in luliconazole group ($n = 94$) and four patients were lost to follow-up in clotrimazole group ($n = 106$). Patients in luliconazole group

and clotrimazole group were advised by the dermatologist to apply the drug over the affected area once a day and twice a day, respectively.

Study assessment

Patients were followed up at 2, 4, and 6 weeks. At each clinical visit, clinical response was noted on the basis of pruritus, erythema, vesiculation, and scaling each on the visual analog scale of 0–3 (0: absent, 1: mild 2: moderate, 3: severe signs and symptoms). The Global Assessment score (GAS) was calculated at each follow-up visit by addition of scores on all four parameters (pruritus, erythema, scaling, and vesiculation) in a patient.^[9] Direct microscopic examination was done at the enrollment. Efficacy was determined by the proportion of patients achieving complete clearance of skin lesions. Safety was assessed by the number of adverse events noted at each visit. The cost evaluation was the done to find out the cost incurred per patient for complete treatment.

Statistical analysis

Validated statistical software GraphPad StatMate 2.00 (GraphPad Software) (<http://www.graphpad.com/statmate/upgrade.htm>) was used for the analyses and graphical representation of the data. Chi-square test and Student's *t*-test (paired and unpaired *t*-test) were used for the statistical evaluation. $P < 0.05$ was considered as statistically significant.

Results

Patients who were newly diagnosed with Tinea corporis/ Tinea cruris in the Dermatology OPD during 6 months of the study were screened. Two hundred and twenty patients were recruited for the study and only 200 patients were able to complete the study as 25 patients were lost to follow-up. There were 94 patients in luliconazole group and 106 patients in clotrimazole group who completed the study.

The baseline characteristics of the patients and the four clinical parameters (erythema, scaling, pruritus, and papules) are presented in Table 1. There were no significant differences between groups for these parameters ($P > 0.05$).

Primary efficacy results

The primary outcome was to determine the efficacy of two topical therapies in terms of a number of patients achieving complete clearance.

There was a reduction in the mean score of all the four clinical parameters at the end of two weeks in both the groups including the reduction of GAS score; however, this reduction was more in luliconazole group than clotrimazole group ($P < 0.05$) [Figure 1].

At the end of 6 weeks, significant decrease in pruritus was observed in luliconazole group ($P < 0.05$) while for rest

three parameters (erythema, vesiculation, and scaling) and GAS score, insignificant decrease was found in both the groups ($P > 0.05$) [Figure 2].

At the end of 2 weeks, 53 patients achieved complete clearance in luliconazole group in comparison to clotrimazole group where 25 patients achieved complete clearance. This difference was statistically significant ($P < 0.05$). At the end of 6 weeks, there was insignificant difference between two groups (luliconazole group 98.23% vs. clotrimazole group 95.28%) in terms of achievement of complete clearance [Table 2]. The percentage of patients who achieved complete clearance of lesions in terms of cure rate is summarized in Figure 3.

Secondary efficacy results

The secondary outcome was to determine the safety and cost incurred per patient for complete treatment. The side effect profile was comparable in both the groups and no serious events required the discontinuation of therapy in any of the group. Only two patients in clotrimazole group reported burning sensation which was mild and experienced by patients for just 2–3 days.

Other secondary outcome was the cost effective analysis which was done to find out the cost incurred per patient for complete treatment. Both the drugs were prescribed in the form of creams. In our experience (as the patients were instructed to bring the tubes at each visit), one tube of 10 g cream of luliconazole (requiring once daily application) lasts for about 10–11 days and 30 g tube of clotrimazole (requiring BD application) lasts for about 15–16 days. Cost-effective analysis was carried out at end of 2 weeks and 6 weeks. Cure rate was calculated along with the cost to treat one case in INR at both the end points. Cost of 10 g tube of luliconazole was INR 95 and of 30 g tube of clotrimazole was 96.

Cost to treat one case successfully at the end of 2 weeks was less for luliconazole group as compared to clotrimazole group [Table 3].

Considering the cure rates at the end of 2 weeks, cost incurred to 100 participants for both the groups was calculated as:

Total cost of treatment = INR for participants cured with 2 week treatment + INR for participants who were treated for 6 weeks^[10]

Luliconazole = $(190 \times 56.38) + (380 \times 43.62) = 27287.80$
 (*380 = 4 tubes \times 95 INR)

Clotrimazole = $(96 \times 23.58) + (288 \times 76.42) = 24272.64$
 (#288 = 3 tubes \times 96 INR)

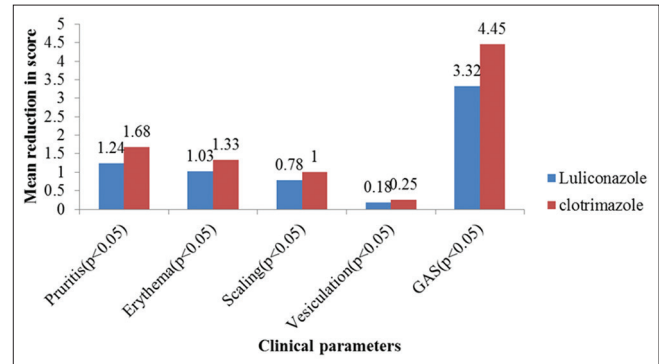


Figure 1: Comparison of efficacy of luliconazole and clotrimazole at end of 2 weeks

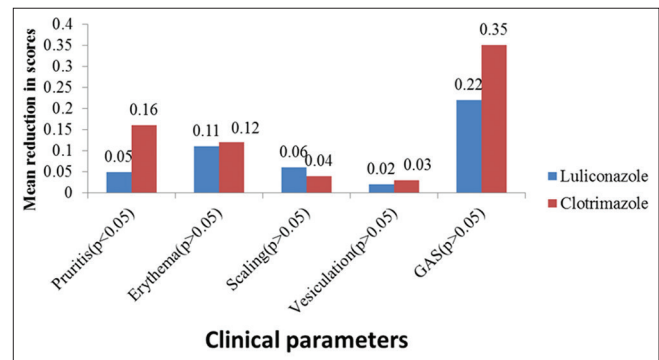


Figure 2: Comparison of efficacy of luliconazole and clotrimazole at end of 6 weeks

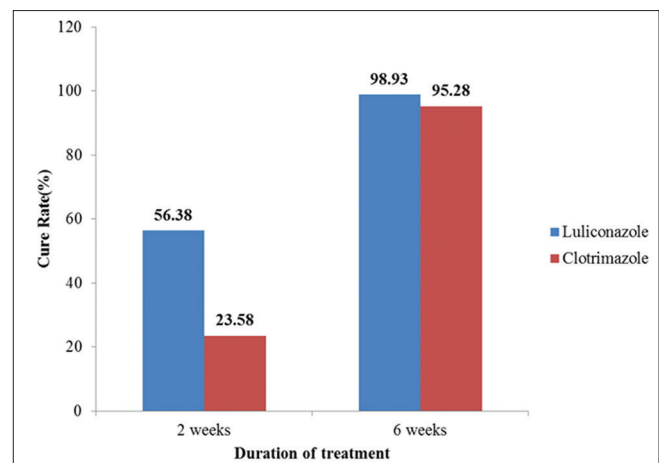


Figure 3: Cure rate in each group at the end of 2 weeks and 6 weeks

Table 1: Baseline demographic and clinical parameters

Baseline characteristics	Luliconazole group (n=94)	Clotrimazole group (n=106)	P
Mean age (years)	38.13±15.24	40.98±16.91	0.22
Sex (male:female)	56:38	59:47	0.58
Tinea corporis/tinea cruris	76/18	80/26	0.36
Number of lesions (=1/≥2)	71/25	78/28	0.95
KOH mount positive	94	106	1
Symptoms			
Pruritis	2.62±0.49	2.69±0.49	0.31
Erythema	2.30±0.65	2.19±0.68	0.25
Scaling	1.97±0.71	1.99±0.68	0.84
Vesiculations	0.71±0.84	0.70±0.82	0.01

KOH: Potassium hydroxide

Table 2: Comparisons of the number of patients achieving complete clearance in both groups

Duration	Group	Complete clearance		P	Percentage of patients
		Achieved	Not achieved		
2 weeks	Luliconazole	53	41	<0.05	56.38
	Clotrimazole	25	81		
6 weeks	Luliconazole	93	1	>0.05	98.93
	Clotrimazole	101	5		

Table 3: Cost effective analysis of the luliconazole and clotrimazole at the end of 2 weeks

Parameters	Luliconazole	Clotrimazole
Cost in INR for 100 participants	190* ×100=19,000	96×100=9600
Cure rate	56.38	23.58
Cost-effectiveness	INR 19,000 for 56.38participants	INR 9600 for 23.58 participants
Cost to treat one case (INR)	336.9	407.12

*190=(2 tubes× 95 INR)

Table 4: Cost-effective analysis at the end of treatment

Parameters	Luliconazole	Clotrimazole
Cost in INR for 100 participants	27,287.80	24,272.64
Cure rate	98.93	95.28
Cost-effectiveness	INR 27,287.80 for 98.93 participants	INR 24,272.64 for 95.28 participants
Cost to treat one case (INR)	275.83	254.74

All the values thus obtained were used for further analysis. The cost at the end of 6 weeks was found to be almost similar for both the groups with luliconazole cream being slightly costlier (approximately 10% higher) than clotrimazole for the patients who needed treatment for more than 2 weeks [Table 4].

Discussion

The mean age of distribution in this study indicates that dermatophytosis is more common in 3rd decade of life. Majority (60%) of the patients were in the age group 21–40 years. The present observation correlates well with the study done by Prasad *et al.*^[11] and Sudha *et al.*^[12] This set of age group is the working population who are more exposed to the physical activities, thus more prone to perspiration which favors the growth of dermatophytes.^[13] Moreover, younger group of patients approaches the dermatologist at an earlier stage because of social stigma associated with this localized dermatophytosis. Majority of the patients were males (121/79) with male female ratio of 1.53:1. This might be due to the fact that males are more engaged in outdoor activities than the females who are commonly homemakers particularly in developing country like India. The most common

dermatophytic infection was tinea corporis followed by tinea cruris. These findings are in accordance with findings by and Nagara *et al.*^[14] and Verma *et al.*^[15] in India.

Complete clearance of skin lesion was higher (56.38%) in luliconazole group than clotrimazole group at the end of 2 weeks. This finding is in contrast to the findings of Prabha *et al.*^[9] and Jerajani *et al.*^[16] where complete clearance was about 100% and 95%, respectively. This might be attributed to the fact that sample size was less ($n = 60$ and 62) respectively in these studies as compared to our study ($n = 200$). Higher cure rate seen in luliconazole group might be due to its unique chemical structure leading to its strong fungicidal activity and favorable pharmacokinetic properties in the stratum corneum. It has shown extremely potent activity against dermatophytes in clinical trials.^[17,18]

Both the group of drugs was found to be safe and well tolerated by the patients. The safety has been quoted by the Prabha^[9] and Satish *et al.*^[19]

On doing cost-effective analysis, treatment modality having low cost-effective ratio (CER) is considered to be superior to the other drug.^[20] It was observed in our study CER was high for clotrimazole drug than luliconazole at the end of two weeks as the cure rate was more in luliconazole group. There is no cost-effectiveness study available on head on comparison between these two study drugs.

Conclusion

From the present study, it can be concluded that topical luliconazole shows better improvement in terms of clinical parameters than topical clotrimazole within a span of 2 weeks in the treatment of localized dermatophytosis. The patient compliance is also better with once daily application of the luliconazole drug as compared to standard two times application and prolonged treatment with clotrimazole drug.

However, at the end of treatment, the proportion of patients achieving complete clearance was same and the difference found was insignificant. Both the topical drugs were well tolerated with none of the patients required discontinuation of therapy. On cost-effective analysis, it was found out that although per gram cost of luliconazole cream was more than clotrimazole, but it is used in half amount than clotrimazole on daily basis and also average number of days used are much less with better results at 2 week. Even for 6 week treatment, the cost was almost comparable in both the groups.

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Conflicts of interest

There are no conflicts of interest.

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