

Comparison of efficacy, safety, and cost-effectiveness of sertaconazole and luliconazole cream in patients with dermatophytoses: A prospective, randomized, open-label study

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Abstract

Objective: To compare efficacy, safety, and cost-effectiveness of sertaconazole (2%) and luliconazole (1%) cream in patients with dermatophytoses.

Materials and Methods: Sixty-four patients with tinea corporis and tinea cruris infections were enrolled in this single-center, randomized, open-label, parallel study. Following inclusion and exclusion criteria, patients were randomly divided into two treatment groups and received either sertaconazole 2% cream applied topically twice daily for 4 weeks and luliconazole 1% cream once daily for 2 weeks. At follow-up, efficacy was assessed clinically using 4-point physician global assessment (PGA) scale, composite score, and mycologically by KOH mount. Safety was assessed by monitoring adverse drug events at each visit.

Results: The primary efficacy variables including changes in pruritus, erythema, vesicle, and desquamation (4-point PGA) were significantly ($P < 0.0001$) improved in both the groups, at the end of treatment. There was a significant reduction in mean total composite score (pruritus, erythema, vesicle, and desquamation) after the end of treatment in the sertaconazole group ($P = 0.0002$) compared to the luliconazole group. Both the groups showed equal negative mycological assessment. Both the study drugs were well tolerated. Only one patient in the sertaconazole group showed allergic contact dermatitis.

Conclusion: Sertaconazole was better than luliconazole in relieving signs and symptoms during the study and follow-up period, but cost-effectiveness wise, luliconazole was better than sertaconazole.

Keywords: KOH mount, physician global assessment, tinea corporis, tinea cruris

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INTRODUCTION

Superficial mycotic infections which include dermatophytoses are an extremely common infection occurring throughout the world. It is a superficial fungal infection of keratinized tissue (i.e., hair, skin, and nails),

because of keratinophilic fungi known as dermatophytes. The disease is caused by dermatophytes belonging to genera of *Trichophyton*, *Microsporum*, and *Epidermophyton*.^[1,2] The fungal infections of the skin are more common in tropical countries like India due to environmental factors

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such as heat and humidity. The incidence of topical fungal infections has increased in recent years because of an improper hygiene, socioeconomic status, and increased number of immunocompromised patients.^[3,4] *Trichophyton rubrum* is implicated as the most common causative agent of dermatophytosis in India. The two varieties of tinea generally encountered are tinea corporis (affecting trunk and limbs) and tinea cruris (affecting the inguinal region).^[5] Tinea of the skin presents clinically as well-demarcated, scaling, and inflamed lesions, which are often accompanied by an itching or burning sensation.^[6]

Imidazoles, allylamines, and triazoles are most effective agents for dermatophytoses. However, the antifungal therapy is often fraught with numerous clinical challenges including high relapse rates and recurrences.^[3,6] Luliconazole 1% and sertaconazole 2% cream is a newly broad-spectrum topical antifungal agent that belongs to the azole class of drugs. Its antifungal activity is due to inhibition of the ergosterol biosynthesis and disruption of the cell membrane.^[7] Luliconazole is approved for the treatment of tinea pedis, tinea corporis, and tinea cruris.^[8,9] It showed broad-spectrum activity against dermatophytes, yeasts, and dimorphic fungi.^[2,10] Sertaconazole has both fungistatic and fungicidal activities against dermatophytes, candida species, and *Cryptococcus* fungal infections.^[11,12] It has anti-inflammatory and antipruritic actions additionally.^[3,13]

Although individually luliconazole and sertaconazole are efficacious in tinea infections, data on the head-to-head study of these drugs in Indian population are scanty. In spite of extensive literature search, we could not find any study comparing the cost-effectiveness of these drugs. Therefore, we aimed to compare the efficacy and safety of luliconazole with that of sertaconazole and to determine the cost-effectiveness, so that better option will be offered for the treatment of dermatophytoses.

MATERIALS AND METHODS

Study design

This was a prospective, randomized, open-label, parallel study conducted in 64 newly diagnosed patients of tinea corporis and tinea cruris attending the Dermato-Venereo-Leprology outpatient department (OPD) in a tertiary care teaching hospital. Patients were randomly divided into two groups with 32 patients in each group to receive either luliconazole 1% cream once daily for a period of 2 weeks or sertaconazole 2% cream twice daily for a period of 4 weeks. The study was conducted during January 2017–August 2018. The study was approved by the institutional ethics committee. After written informed consent was obtained, patients were enrolled in the study. The Clinical

Trials Registry-India (CTRI) registration number for trial is CTRI/2017/11/010418.

Selection of subjects

Inclusion criteria

1. Adults between the age group of 18 and 70 years of either gender, with clinical diagnosis and mycological confirmation (positive KOH test) for tinea corporis and tinea cruris infections
2. Patients having a physician global assessment (PGA) composite score of at least 5 (composite score is a combined score of all clinical signs and symptoms of tinea infection)
3. Patients willing to give written informed consent.

Exclusion criteria

1. Patients having clinical diagnosis of tinea infections other than tinea corporis and tinea cruris
2. Patients having extensive fungal infection
3. Patients who had received topical or oral antifungal agents up to 4 weeks before the initiation of the study
4. History of hypersensitivity to the study drugs
5. Immunocompromised patients
6. Patients having superadded bacterial infection
7. Pregnant or lactating women.

Enrolment of subjects

Patients attending the Dermato-Venereo-Leprology OPD were screened by the dermatologist and principal investigator. Diagnosis of tinea infection was made on the basis of patients' chief complaints, history, and mycological assessment. Those meeting the inclusion criteria were briefed about the study. After written informed consent was obtained, patients were enrolled in the study. A patient information sheet was given to all prospective participants.

Treatment details

After initial screening, clinical examination, and baseline investigations, patients were randomized into Group A or Group B according to random number table. Initial treatment phase involved two groups receiving either sertaconazole 2% cream applied topically twice daily for 4 weeks or luliconazole 1% cream applied topically once daily for 2 weeks [Figure 1]. At the end of treatment phase, there was follow-up phase of 2 weeks for assessing the patients clinically and mycologically for relapse (patients who showed successful treatment outcome at the end of treatment but a clinical failure at follow-up). Drugs were purchased by the principal investigator and distributed to the patients free of cost. There was no financial burden on the patients.

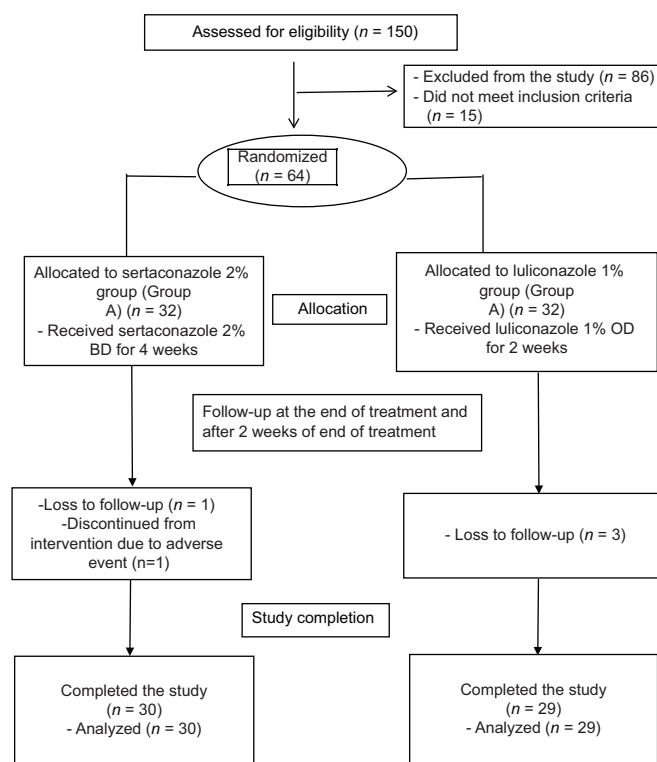


Figure 1: Study flowchart

Investigations

KOH (10%) mount test was performed at the baseline (0 week), end of treatment, and follow-up.

Efficacy assessment

Efficacy was a primary endpoint of the study. It was assessed by 4-point PGA scale at the completion of treatment and follow-up. Completed clearance was defined as both clinical cure (score of 0 on a 4-point PGA scale) and mycological cure (negative KOH). Four-point PGA for clinical assessment was based on the proportion of patients with symptoms and signs of tinea lesions, namely pruritus, erythema, vesicle, and desquamation, and graded as none (0), mild (1), moderate (2), and severe (3) depending on intensity. Mycological assessment was based on KOH mounting for dermatophytes.^[3]

Safety assessment

Safety and tolerability were assessed in patients with dermatophytoses receiving either sertaconazole or luliconazole cream by monitoring adverse drug events at each visit.

Assessment of cost-effectiveness

For cost-effectiveness analysis, cost-effectiveness ratio of both the treatment groups was calculated based on the formula.

Cost-effectiveness = Cost/outcome^[14]

where the cost of the topical agents was calculated by averaging the costs of cream. For that, cost of each cream (10 gm) of luliconazole and sertaconazole and the cost of total treatment on both the groups were considered, and for outcome, change in composite score (by 4-point PGA) from the baseline to the end of treatment in both luliconazole and sertaconazole groups was considered.

Statistical analysis

Calculation of sample size

By considering power 80%, significance level of 0.05, standard deviation of 0.40, and expected mean difference of 0.30, the calculated sample size was 29 in each group.^[3] Hence, after considering dropouts and noncompliance of the patients, the study sample size was rounded to 32 in each group. Sample size was calculated using PS: Power and Sample Size Calculation software Version 3.1.2.

Statistical analysis

All randomized patients who received study medication and completed the study were included for analysis. The difference in change in 4-point PGA score of pruritus, erythema, vesicle, and desquamation was assessed. Parametric data were done by unpaired *t*-test. Nonparametric data were done by Fisher's exact test, Wilcoxon signed-rank test, and Mann-Whitney test. $P < 0.05$ was considered statistically significant in all the statistical analyses. Mycological assessment was done by scraping of skin scales and examination by 10% KOH mount.

RESULTS

In total, 64 patients were recruited. Fifty-nine patients completed the study (30 in the sertaconazole group and 29 in the luliconazole group). Five patients, i.e., one in the sertaconazole group and three in the luliconazole group lost to follow-up and 1 patient discontinued the study due to adverse event in the sertaconazole group by the end of the study. Patients were randomly assigned to the treatment with sertaconazole 2% (Group A) or luliconazole 1% (Group B) [Figure 1]. The percentage of male patients was relatively more than female patients, 61.76% in the sertaconazole and 55.88% in the luliconazole group. Demographic parameters, clinical characteristics, and composite score of clinical characteristics were comparable between the two groups at the baseline [Table 1]. At the baseline, all patients of both the groups had positive KOH test for dermatophytes.

Efficacy assessment

At the end of treatment phase, both luliconazole and sertaconazole groups showed significant

changes ($P < 0.0001$) in clinical characteristics [Table 2]. At the end of treatment phase, the percentage of patients with change in erythema, pruritus, desquamation of skin, and vesicles was more in the sertaconazole group (86.66%, 90%, 96.66%, and 96.66%, respectively) as compared to the luliconazole group (48.27%, 75.86%, 86.20%, and 89.65%, respectively) [Figure 2].

Change in composite score

At the end of treatment phase, sertaconazole showed significant decrease in composite score ($P = 0.0002$) compared to the luliconazole group [Table 3].

Mycological assessment

At the end of treatment and follow-up phase, all patients showed negative mycological assessment in both the groups.

Complete clearance

At the end of treatment phase, the complete clearance was seen in higher proportion of patients in the sertaconazole group (70%) as compared to the luliconazole group (27.58%).

Safety assessment

Both the study drugs were well tolerated. Only one patient in the sertaconazole group showed allergic contact dermatitis.

Relapse rate

Sertaconazole did not show any relapse case compared to luliconazole which had two patients of relapse after the end of treatment.

Cost-effectiveness

For cost-effectiveness analysis, only direct health cost of drug treatment was taken into consideration. The cost of each 10 g cream of luliconazole (1%) was Rs. 150, and

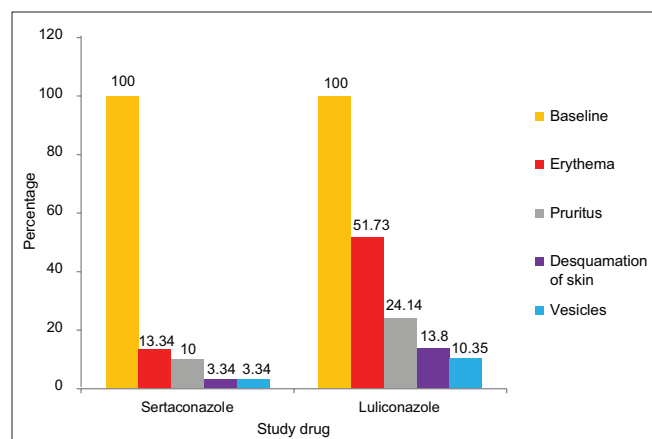


Figure 2: The percentage of patients with change in erythema, pruritus, desquamation of skin, and vesicles was significantly ($P < 0.05$) more in the sertaconazole group as compared to the luliconazole group

for sertaconazole (2%), it was Rs. 155. The mean of cost of treatment for per patient of luliconazole group was Rs. 341.40 and for sertaconazole group was Rs. 733.61. Thus, calculating the total cost of treatment at the end of treatment gave us the idea of difference of total cost in the treatment which is more in the sertaconazole group. The cost-effectiveness ratio was calculated as described elsewhere.^[15] In our study, effectiveness parameter was composite score by 4-point PGA scale, i.e., difference in composite score after the end of treatment taking into consideration the change from the baseline values in both the groups, for luliconazole group difference in composite score was 5.51 and for sertaconazole it was 6.30, which was our main parameter. The treatment modality having less cost-effectiveness ratio is considered as superior. In our study, the cost-effectiveness ratio is less in the luliconazole

Table 1: Baseline demographic parameters, clinical characteristics, and composite score of two groups of dermatophytosis patients

Parameters	Mean±SD		P*
	Luliconazole (n=29)	Sertaconazole (n=30)	
Age (years)	33.21±13.49	35.50±14.43	0.5311*
Gender (male:female)	21:8	23:7	0.7710 [§]
Weight (kg)	64.28±7.035	65.77±9.467	0.4963 [#]
Erythema	1.48±0.50	1.60±0.49	0.3749 [#]
Pruritus	2.00±0.00	2.00±0.00	NS
Desquamation of skin	2.00±0.00	2.00±0.00	NS
Vesicles	1.00±0.00	1.00±0.00	NS
Composite score	6.51±0.50	6.60±0.49	0.5303 [#]

*Difference is statistically significant when $P \leq 0.05$. #Unpaired t-test, [§]Fisher's exact test. NS=Nonsignificant, SD=Standard deviation

Table 2: Comparison of changes in proportion of patients with erythema, pruritus, desquamation, and vesicles in the luliconazole group and sertaconazole group

Character	Luliconazole group (n=29), mean±SD		Sertaconazole group (n=30), mean±SD	
	Baseline	End of treatment	Baseline	End of treatment
Erythema	1.48±0.50	0.51±0.50****	1.60±0.49	0.13±0.34****
Pruritus	2.00±0.00	0.24±0.43****	2.00±0.00	0.10±0.30****
Desquamation of skin	2.00±0.00	0.13±0.35****	2.00±0.00	0.03±0.18****
Vesicles	1.00±0.00	0.10±0.30****	1.00±0.00	0.03±0.18****

Difference is statistically significant when $P \leq 0.05$. **** $P < 0.0001$ compared to baseline, #Wilcoxon signed rank test. SD=Standard deviation

Table 3: Difference between changes in composite score in two groups

Changes	Mean±SD		P*
	Luliconazole (n=29)	Sertaconazole (n=30)	
Baseline	6.51±0.50	6.60±0.49	-
End of treatment	1.00±0.75	0.30±0.46	-
Difference in composite score	5.51±0.25	6.30±0.03	0.0002 [§]

*Difference is statistically significant when $P \leq 0.05$. #Mann-Whitney test. SD=Standard deviation

group at the end of treatment and that of the luliconazole group is more cost-effective [Table 4].

DISCUSSION

Dermatophytosis infections are one of the most common fungal infections of the skin.^[15,16] It is known fungal infections and affects the quality of life of patients due to the concomitant inflammatory symptom involving pruritus.^[3] Luliconazole and sertaconazole have already known to be effective in tinea infections in several clinical trials, but this is the first study to compare their efficacy, safety, and cost-effectiveness of these two drugs and help choose the better agent. Moreover, data on such types of studies from the Indian setup are very scanty. Hence, we considered it worthwhile to conduct this study in the Indian setup where patients have less affordability for costly medicines.

In the present study, there was a statistically significant decrease in clinical characteristics such as erythema, pruritus, desquamation of skin, and vesicles ($P < 0.0001$) after 2 weeks of treatment with luliconazole group and 4 weeks of treatment with sertaconazole group. Comparison between luliconazole and sertaconazole groups was done for difference in the mean of composite score at the end of treatment. There was a statistically significant decrease in composite score in the sertaconazole group ($P = 0.0002$) compared to the luliconazole group at the end of treatment. In the present study, the percentages of patients who showed complete clearance in the sertaconazole and luliconazole groups were 70% and 27.58%, respectively. In a meta-analysis, randomized controlled trials, luliconazole 1% cream significantly reduced the clinical signs and symptom at week four.^[17] In another randomized, multicenter, double-blind study, luliconazole showed significantly reduction in the clinical sign and symptoms after 28 days. Complete clearance was obtained in 21.2% of patients treated with luliconazole cream.^[18] Our study showed similar finding of significant reduction in the clinical characteristics.

In a randomized, open-label, 4-week study, sertaconazole significantly reduced baseline signs and symptom score. Complete clearance was obtained 90% in the sertaconazole group.^[19] In a comparative, randomized study, sertaconazole significantly improved clinical signs and symptoms and

complete clearance was obtained 93% in sertaconazole recipients.^[5] Our study observed similar results of significant reduction in the clinical characteristics.

In a randomized, multicenter study, sertaconazole 2% and luliconazole 1% cream significantly improved clinical sign and symptoms and the mean of composite score was greatly reduced in the sertaconazole group (97.1%) as compared to the luliconazole group (92.9%).^[3] Our study supports this finding of significant reduction in clinical characteristics and mean of composite score. Our study also assessed the P value for composite score.

Both sertaconazole and luliconazole belong to the imidazole class of antifungals. They act primarily by inhibiting the cytochrome P450-dependent synthesis of ergosterol. The probable superiority of sertaconazole over luliconazole may be attributed to the following findings. The antipruritic and anti-inflammatory action of sertaconazole over other antifungals would ensure better adherence to treatment and improved quality of life. This antipruritic and anti-inflammatory property of sertaconazole is due to its ability to reduce histamine release and several other proinflammatory cytokines including PGE2.^[3] Because of all these actions, reduction in the mean of composite score may be more significant in the sertaconazole group as compared to the luliconazole group and the percentage of complete clearance was also high in the sertaconazole group.

In the present study, all patients showed negative mycological assessment in both the groups. This observation is in correspondence with previous studies.^[2,3]

In the present study, both the creams were well tolerated and safe; this finding is similar to the previous studies.^[3,5] However, one patient in the sertaconazole group had complained of burning sensation on application, which supports this finding with previous study.^[3] In the present trial, sertaconazole did not show any relapse case compared to luliconazole which had two patients of relapse after the end of treatment. A randomized, open-label study showed no relapse case in both the groups.^[3]

To compare the cost-effectiveness of two drugs, only the direct health cost of the drug treatment was taken into consideration. When we compared the cost-effectiveness ratio of the treatment, i.e., luliconazole and sertaconazole, we found that cost-effectiveness ratio was less in luliconazole. For pharmacoeconomic analysis, treatment modality having less cost-effectiveness ratio is considered as superior. Thus, it suggests that luliconazole is more

Table 4: Comparison between cost-effectiveness of both luliconazole and sertaconazole groups at the end of treatment

	Luliconazole (1%)	Sertaconazole (2%)
Cost-effectiveness ratio at the end of treatment	61.96	116.44

cost-effective than sertaconazole for the treatment of dermatophytoses (tinea corporis/tinea cruris). Thaker *et al.*, compared the cost-effectiveness between sertaconazole and butenafine, and in this study, the total cost of therapy was more with sertaconazole as compared to butenafine treatment.^[19]

Our study allowed direct comparison of the two active substances, both with regard to effect sizes and adverse event profiles. Although the present study was open-label with small sample size and of short duration, the results of the study cannot be ignored. However, double-blind studies with longer follow-up period may yield more meaningful data to compare luliconazole and sertaconazole cream for dermatophytoses. Furthermore, to determine the cost-effectiveness, studies considering direct cost, indirect cost, and incremental cost can provide more meaningful data.

CONCLUSION

The results of the present study indicate that sertaconazole was better than luliconazole in relieving signs and symptoms of dermatophytoses, but cost-effectiveness wise, luliconazole is better compared to sertaconazole. This information can help physicians in treating the patients. Patients who can afford costly treatment may be prescribed more effective sertaconazole, whereas for patients who cannot afford, it may use luliconazole cream.

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Conflicts of interest

There are no conflicts of interest.

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