Comparative Assessment of the Effectiveness and Safety of Sertaconazole Cream Versus Terbinafine Cream Versus Luiliconazole Versus Clotrimazolecream in Patients with Tineacruris

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ABSTRACT

Introduction: Dermatophytosis is an infection of keratinized tissues, epidermis and its appendages hair and nails.Topical treatment of dermatophytosis has advantages like targeting the site of infection which minimizes systemic side effects, and enhanced efficacy of treatment. Topical therapy is also considered to improve patient compliance. So to assess the effectiveness and safety of sertaconazole cream versus terbinafine Cream versus luiliconazole versus clotrimazolecream in patients with a form of dermatophytosis i.e.tineacruris (dermatophytosis of groin and adjacent areas).

Material and Method: A randomized, open-label, cohort study was performed over a period of 18 months, from January 2014 to June 2015.

Results: The study was continued till 30 participants in each group were available for analysis; a study population of 120 participants was achieved. Age group obtained in this study was indeed ranged from 18 years to 50 years. There were 64 (53.3%) males and 56 (46.7%) female participants in this study. The participants were randomized into four study groups: (A) Sertaconazole, (B) Luliconazole, (C) Terbinafine, (D) Clotrimazole.

Conclusion: Response to the topical monotherapy with and sertaconazole 2%, luliconazole 1%, terbinafine 1% and clotrimazole 1% cream was safe and well tolerated in the treatment of tineacruris. Treatment with sertaconazole 2% cream and luliconazole 1% cream was early in the onset with tolerable side-effects.

Keywords: Dermatophytosis; tineacruris; sertaconazole; luliconazole; terbinafine; clotrimazole; effectiveness.

INTRODUCTION

Dermatophytosis is an infection of keratinized tissues, epidermis and its appendages hair and nails. Mycotic agents belonging to three genera, *Epidermophyton, Microsporum* and *Trichophyton* are implicated in dermatophytosis. The dermatophytosis causes superficial infections because they produce keratinases, which degrade the keratin and thus are restricted to part of skin containing this protein.These infections are also known by misnomer 'tinea infections'.[1] The prevalence of fungal infections of skin has increased rapidly, affecting approximately 40 million people across the globe; prevalence of dermatophytosis has been estimated to affect close to 25% of world's population, making them most frequent form of infection.[2] Also, these infections are common in tropics and may reach epidemic proportions in geographical areas with hot and humid climatic condition, or with population overload, or with living conditions characterized by poor hygiene.[3,4] Topical treatment of dermatophytosis has advantages like targeting the site of infection which minimizes systemic side effects, and enhanced efficacy of treatment. Topical therapy is also considered to improve patient compliance.[5]

Commonly available topical antifungals are Allylamines (Terbinafine), Imidazoles (Bifonazole,Clotrimazole, Econazole, Ketoconazole, Miconazole, Sertaconazole, Tioconazole, luliconazole), Morpholine derivative (Amorolfine HCl), Polyenes (Nystatin, Amphotericin B, Natamycin), Pyridone derivative (Ciclopiroxolamine) and Thiocarbamate (Tolnaftate).[6]

In our setting clotrimazole, terbinafine, sertaconazole and luliconazole are most commonly used topical antifungal agents. So a study was planned to compare relative efficacy of these four agents when given as single topical therapy.

Clotrimazole blocks sterol synthesis by interfering cytochrome p-450 dependent enzyme, lanosterol14α-demethylase which catalyses conversion of lanosterol to ergosterol. Clotrimazole is well tolerated drug, with isolated reports of erythema, burning, irritation, stinging, peeling, blistering, edema, pruritus and urticaria at the site of application.[6]

Terbinafine is an allylamine which inhibit the enzyme sqaleneepoxidase, one of the steps in synthesis of ergosterol. It is well tolerated drugs; rarely pruritus, irritation,burning,tingling,dryness at the site of application have been reported.[6]

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Sertaconazole induces inhibition of 14α-demethylase and also binds to nonsterol cell membrane lipid, leading to altered membrane permeability and leakage of intracellular content. Sertaconazole has excellent saftey records, however rare cases of allergic contact dermatitis have been reported.[6] Luliconazole belongs to azole class, inhibits lanosterold-emethylase finally decrease fungal cell wall component ergosterol. Side effects are very rare comparable to placebo. Pruritus, burning, tingling at the site of application have been reported.[6]

Objectives

Comparative assessment of the effectiveness and safety of sertaconazole cream versus terbinafine Cream versus luiliconazole versus clotrimazolecream in patients with tineacruris.

METHOD AND MATERIAL

A randomized, open-label, cohort study was performed at Out-Patient facility of Department of Dermatology, Venereology and Leprosy of Mahatma Gandhi Memorial Medical College and associated Maharaja YashwantRaoHolkar Hospital, Indore, India; over a period of 18 months, from January 2014 to June 2015.

Study protocol was approved by Institutional Ethics Committee prior to initiation of the study.

Consenting patients affected with only tineacruris of age ranging from 18 years to 50 years were recruited in this study. We have taken only single variant of dermatophytosis, as the efficacy of any topical medication varies with site of involvement. This group had been chosen on the basis of results of several studies, that has found the age group of 21–50 years to be most affected with dermatophytosis.[1,7,8] Only patients with Positive mycological confirmation by positive KOH test and positive lactophenol blue test were included, same were performed at the completion of study period to ascertain mycological cure. To remove inter-observer bias the KOH test and grading of clinical parameters were read by independent observer only (by authors SK and BS, respectively).

Patients with other body site involvement, patients who had received topical and oralantimycotictherapytwoweeks and four weeks, respectively, prior to initiation of the study were excluded. Also patients who were on any kind of immunosuppresive therapy were excluded. Participants with known history of hypersensitivity to study drugs, or with superadded bacterial infection, or pregnant and lactatating female, or immunocompromised patient and chronically ill patients were also not recruited.

All the participants in the study were subjected to the followingdetailed personal and clinical historyrecording, past and present medical history, past and concomittant drug history. Routine blood examination was done to rule out diabetes or any other co-morbid condition in selected cases. The study medication was dispensed to the subject following randomization, provided all inclusion and exclusion criteria were satisfied. The patients were instructed to apply the cream thinly to the affected area.

Participants were randomized with the help of table of random numbers in to four groups containing 30 participants each. Group A, had received sertaconazole2% cream applied twice daily for four weeks; while group B had luliconazole 1% cream applied once daily for two weeks. Group C had 30 patient on terbinafine1% cream applied twice daily for two weeks and group D had 30 patient clotrimazole 1% cream applied twice daily for four weeks. At the end of treatment phase there was a follow up phase at the end of two weeks, where patients were reassessed clinically and my cologically.

Primary efficacy was based on clinical and mycological assessment of tinea lesion at base line, at the end of treatment phase and follow up phase two week following completion of treatment. Clinical assessment was based on the proportion of patients with symptoms and signs of tinea lesions namely pruritus, erythema and desquamation, and graded as none (0), mild (1), moderate (2) and severe (3) depending on intensity. Mycologic assessment was based on KOH mounting for dermatophytes.

Secondary efficacy was assessed on the basis 'Physician Global Assessment' based on three criteria- successful treatment outcome (clinical cure + negative mycology), clinical success (symptomatic relief + clinical cure) and clinical failure (no clinical and mycological improvement), at end of 'Treatment Phase' and 'Follow-up Phase'.

Safety and tolerability was assessed by monitoring treatment related adverse events at each visit.

Patients who failed to follow up for two consecutive visits were considered as being lost to follow up was not included in the analysis.

Medicines

The sertaconazole cream was a gift from Glenmark-Gracewell, India; in the form of their market product Onabet Cream. The supply of luliconazole cream was a gift from Ranbaxy, India; in the form of their market product Lulifin Cream. Terbinafine was obtained as a gift from Abbott, India; in the form of their market product Tyza Cream. Whereas clotrimazole was made available through hospital pharmacy supply.

STATISTICAL ANALYSIS

All randomized patients who received study medication and completed the study were included for analysis. The difference in change in clinical assessment of pruritus, erythema, vesicle and desquamation. Mycological assessment by scraping of skin scales and examination in 10% KOH mount and physician global assessment, within and between the groups were analyzed using Chi-square test. Categorical variable was expressed in actual numbers and percentage,

and compared using Fisher's exact test and intra group comparison performed using paired t-test. Two tailed p<.05 was considered as statistically significant.

RESULTS

The study was continued till 30 participants in each group were available for analysis; a study population of 120 participants was achieved. Age group obtained in this study was indeed ranged from 18 years to 50 years. There were 64 (53.3%) males and 56 (46.7%) female participants in this study. The participants were randomized into four study groups: (A) Sertaconazole, (B) Luliconazole, (C) Terbinafine, (D) Clotrimazole. Baseline characteristics of the study participants have been presented in table 1. The groups were balanced with respect to baseline characteristics.

Clinical Efficacy results

Changes in Pruritus [table 2]: At the end of treatment phase, the resolution of pruritus was seen in 93% of patients in sertaconazole group and 100% in luliconazole group, respectively; however complete resolution of pruritus occured in both groups at the end of follow up phase. In terbinafine and clotrimazole groups, resolution of pruritus was not complete and only 73% in terbinafine group and 33% in clotrimazole group were able to show resolution in pruritus at the end of follow up phase. The reduction in pruritus in luliconazole or setaconazole groups were significantly more than clotrimazole group. Reduction in terbinafine although less but no significant relation was found when compared to rest of the groups.

Changes in Erythema [table 3]: in sertaconazole group, at the end of treatment phase and at the end of folow up phase, the resolution of erythema was 73% and 100%, respectively; these parameters were exactly similar in lulicoanzole group. Terbinafine and clotrimazole appears to be less effective in reducing erythema when compared with sertaconazole/luliconazole.

Changes in desquamation [table 4]: in sertaconazole group, at the end of treatment phase and at the end of folow up phase, the resolution of erythema was 83% and 100%, respectively; again these parameters were exactly similar in lulicoanzole group. Terbinafine and clotrimazole appears to be less effective in reducing desquamation when compared with sertaconazole/luliconazole. In terbinafine group mild desquamation persisted in 33% participants, whereas it was persistent in 87% of participants in clotrimazole group. Sertaconazole and luliconazole, both had significantly level of change in desquamation proportions compared to clotrimazole.

Characteristics	Sertaconazole	Luliconazole	Terbinafine	Clotrimazole
Male	17	12	16	11
Female	13	18	14	19
Age in years (SD)	31.01 (7.7)	33.9 (8.1)	30.2 (7.0)	34.7 (4.9)
Proportion patientswith moderate and severe erythema	80%	83%	80%	77%
Proportion patients with moderate and severe pruritus	77%	77%	77%	77%
Proportion patients with moderate and severe desquamation	57%	57%	57%	63%
KOH positive	100%	100%	100%	100%
SD: standard deviation; KOH: potassium hydroxide mount for microscopic identification of dermatophytes.				

Table-1: Baseline characteristics of study population n=120

	Sertaconazole			Luliconazole			Terbinafine			Clotrimazole		
Pruritus Score	Base-line	End of treat-ment	Follow up	Base-line	End of treat-ment	Follow up	Base-line	End of treat-ment	Follow up	Base-line	End of treat-ment	Follow up
None	0	28	30	0	30	30	1	20	22	0	9	10
Mild	7	2	0	7	0	0	6	10	8	7	16	15
Moderate	12	0	0	13	0	0	13	0	0	12	3	5
Severe	11	0	0	10	0	0	10	0	0	11	2	0

Table-2: Comparison of changes in proportion of patients with pruritus

	Sertaconazole			Luliconazole			Terbinafine			Clotrimazole		
Erythe-ma Score	Base-line	End of treat-ment	Follow up	Base-line	End of treat-ment	Follow up	Base-line	End of treat-ment	Follow up	Base-line	End of treat-ment	Follow up
None	0	22	30	0	22	30	0	19	21	0	15	18
Mild	6	8	0	5	7	0	6	11	9	7	11	11
Moderate	18	0	0	20	1	0	17	0	0	17	4	1
Severe	6	0	0	5	0	0	7	0	0	6	0	0

Table-3: Comparison of changes in proportion of patients with erythema

	Sertaconazole			Luliconazole			Terbinafine			Clotrimazole		
Desquamation Score	**Baseline**	**End of treatment**	**Follow up**	**Baseline**	**End of treatment**	**Follow up**	**Baseline**	**End of treatment**	**Follow up**	**Baseline**	**End of treatment**	**Follow up**
None	0	25	30	1	25	30	0	10	20	1	7	4
Mild	13	5	0	12	4	0	13	20	10	10	15	26
Moderate	6	0	0	6	1	0	9	0	0	11	8	0
Severe	11	0	0	11	0	0	8	0	0	8	0	0

Table-4: Comparison of changes in proportion of patients with desquamation

Physician global assessment

Physician Global Assessment at end of 'Treatment Phase', the 'Successful Treatment Outcome' was 100% in sertaconazole group and luliconazole group as compared to terbinafine (70%) and clotrimazole (35.3%).

Mycologic assessment

At baseline all patients had positive KOH test for Dermatophytes. At end of 'Treatment Phase' and 'Follow-up' Phase, all patients showed negative mycological assessment (negative KOH test).

Safety assessment

All the medicines were well tolerated with mild application site adverse drug reactions (ADR). No severe adverse events were reported, no participants from the study discontinued due to ADR and no case of non-compliance to the therapy was reported. Burning sensation was reported in two participants each in sertaconazole, luliconazole and terbinafine groups.

DISCUSSION

In the present study, all the four study drugs showed significant reduction in signs and symptoms (*pruritus, erythema, vesicles* and *desquamation*) of tinea infections as compared to baseline. Sertaconazole and luliconazole were found to be equally effective, whereas clotrimazole was least effective among the four groups. Jerajani et al,[9] Chandana T et al[10] and A Tamil Selvan et al[11] have found sertaconazole to be more effective than luliconazole and terbinafine, in terms of reduction in pruritus, erythema, vesiculation and desquamation. However in all of these studies luliconazole was found close to sertaconazole in terms of efficacy. A meta-analysis had shown efficacy and safety rates for 2-week treatment of 1% luliconazole were nearly the same as those for 4-week treatment of the 2% sertaconazole; however author notes whether 2% sertaconazolehas more excellent antifungal activity than 1% luliconazole, requires further trials for verification.[11]

In view of lesser efficacy of clotrimazole compared to others, it would have been better to find antifungal susceptibility comparison of clotrimazole versus sertaconazole or luliconazole or terbinafine, however such data is lacking; particularly in literature available from India.

at the end of follow-up phase complete mycological cure (100%) was observed with all the therapies which confirmed absence of recurrence and relapse of tineacorporis, our results are in accordance with Jerajani et al[9] and Khan H et al.[12]

In the present study, all three treatments were well tolerated and found to be safe. Burning sensation was reported in two participants each in sertaconazole, luliconazole and terbinafine groups, however none were considered serious.

The results of this study are likely to be confounded by the study design as it was an open labeled (non-blinded) study with smaller sample size. Also, the therapy duration was different for all the treatment drugs. However since most the clinical trials conducted with sertaconazole and luliconazole employed a four week and two week study design, respectively, so our study also employed similar duration of therapy. Furthermore, diagnosis of tineacorporis was purely on the basis of clinical examination and microscopic finding of KOH mount. We did not identify the causative organism for the tineacruris by culture sensitivity.

CONCLUSION

Response to the topical monotherapy with and sertaconazole 2%, luliconazole 1%, terbinafine 1% and clotrimazole 1% cream was safe and well tolerated in the treatment oftineacruris. Treatment with sertaconazole 2% cream and luliconazole 1% cream was early in the onset with tolerable side-effects. However treatment with luliconazole cream appears more convenient due to shorter course of application as well as once a day frequency. Our study suggests sertaconazole 2% cream and luliconazole 1% cream to be equally safe and effective, whereas it was surprising to observe least performance of the clotrimazole cream.

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