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Original Research Article

Prospective study on comparison of efficacy of topical anti-fungal agents: clotrimazole 1% and sertaconazole 2% in treatment of tinea cruris

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ABSTRACT

Background: Tinea cruris is a common superficial dermatophytic infection of the skin occurring in 20-25% population worldwide. The various types of antifungal agents are available for topical use in treatment of tinea cruris. Clotrimazole is conventional imidazole antifungal drug whereas sertaconazole is newer imidazole antifungal claimed to be superior to clotrimazole in tinea infection. The aim of the study was to determine and compare the efficacy of potent topical azole agents 1% clotrimazole and 2% sertaconazole in patients diagnosed with tinea cruris attending out-patient department of skin and VD of tertiary care hospital in Vadodara.

Methods: A total of 71 patients diagnosed with tinea cruris were divided into two groups. Group A received topical clotrimazole (1% cream), and Group B received topical sertaconazole (2% cream). Outcome parameters such as erythema, scaling, itching, margins of lesions and size of lesions were noted atthe time of hospital visit, by 3rd week and by 6th week for the assessment of efficacy. The statistical test used was independent student t-test and software used was SPSS 20.0.

Results: At the end of follow-up phase, both the drugs were found to be effective with no recurrence or relapse of tinea cruris. However, compared to clotrimazole 1% cream, sertaconazole 2% cream had statistically significant rapid relief in terms of reduction in clinical parameters such as erythema ($p<0.001$), scaling ($p<0.001$), itching ($p<0.001$), size of lesion ($p<0.001$) and margin of lesion ($p<0.011$).

Conclusions: Topical sertaconazole 2% cream was found to be highly efficacious and superior to clotrimazole 1% cream in improvement of clinical parameters of tinea cruris.

Keywords: Tinea cruris, Antifungal, Topical azole, Sertaconazole, Clotrimazole

INTRODUCTION

The skin is the largest organ of the human body. The skin consists major two layers, i.e., the upper one is epidermis which is followed by dermis. Skin provides physical barrier against external environment and its main function is to protect our body from foreign micro-organisms and ultimately from infection.[1] Among the microorganisms fungi are very commonly infecting the cutaneous tissue and in fungi one of the groups of fungi known as dermatophytes are quite frequently responsible for cutaneous skin infection. Dermatophytes can be defined as group of taxonomically related filamentous fungi which have a unique enzyme capacity that enable them to utilise keratin as a nutrient source. The infections caused by dermatophytes are known as dermatophytosis

(also known as tinea infection or superficial mycosis) are major health issue nowadays. There are mainly three classes of dermatophytes which are microsporum, epidermophyton, and tricophyton. They usually grow in keratinised environments such as nails, hair and skin.[2,3]

The classification of the tinea depends on the anatomical location of the infection, such as tinea corporis (trunk), tinea capitis (scalp), tinea cruris (groin area), tinea pedis (feet), tinea barbae (beard area), tinea unguium (nails), and tinea manuum (hands).[4] For the treatment of mild to moderate tinea infection, topical antifungals are most of the time sufficient for cure and symptomatic relief. However, systemic therapy may be required when the infection gets severe. As per the route of administration antifungals are classified into topical, oral, intravenous and intravaginal antifungals. Chemically and therapeutically, antifungals are classified into major four classes as antibiotics, antimetabolite, azoles and allylamine. Among these agents, azoles are commonly used to treat various fungal infections. As per the chemical ring present in the structure, there are two types of azoles which are imidazole and triazole. In imidazole class, the commonly used drugs are clotrimazole, econazole, miconazole, oxiconazole, sertaconazole, luliconazole, ketoconazole which are mainly used topically. In triazole class, the commonly used drugs are fluconazole, itraconazole, voriconazole, posaconazole which are mainly used systemic therapy.[6]

Tinea cruris is the dermatophytic infection of groin area, present with erythematous scaly plaques associated with pruritis. The most common causes for tinea cruris include *Epidermophyton loccosum* and *Trichophyton rubrum*; less commonly *Trichophyton mentagrophytes* and *Trichophyton verrucosumare* involved.[7] Tinea cruris infections may present as an annular erythematous plaque with a raised leading edge and scaling. For the diagnosis, a mycologic examination, consisting of a 10 to 15% potassium hydroxide (KOH) preparation, from skin scrapings, and a fungal culture on Sabouraud's agar media is usuallyperformed.[5] Tinea cruris can be treated with topical allylamines or azoles. As extensive or severe infection cannot be managed solely topical application, usually systemic allylamines or azoles are added to therapy. This study was undertaken to compare two commonly utilized topical azoles (clotrimazole and sertaconazole) on the basis of efficacy, safety and cost effectiveness; in patients suffering from tinea cruris infection.

METHODS

This was a prospective, observational comparative study held in dermatology ward at Vadodara, Gujarat, India. In this study, 71 cases were enrolled as per inclusion and exclusion criteria. The samples were divided into two groups i.e., Group A with topical clotrimazole 1% and PO itraconazole 100 mg twice daily 32 patients. And Group B with topical sertaconazole 2% and PO itraconazole 100 mg twice daily 39 patients. The study was conducted for the period of four months starting from 1st August 2018 to 30th November 2018. For this study the material/equipment used were patient information sheet, patient infection record form, informed consent form etc.

Patients diagnosed with tinea cruris infection and prescribed with topical azoles i.e., 1% clotrimazole or 2% sertaconazole were enrolled in the study. Firstly, written informed consent was taken from all the patients after explaining the study. Followed by patients' medical record were collected and major clinical examination suggesting tinea cruris infection such as erythema, scaling, itching, margins, size of lesions and KOH mount; were noted in patient medical record sheets. This study was conducted in two phases; initial 'treatment phase' which was of first three weeks and second 'follow up phase' was for next three weeks.

Selection criteria

In the inclusion criteria, patients with age of >18 years who were visit skin outpatient department or inpatient department with confirmed diagnosis of tinea cruris infection and prescribed with topical clotrimazole or sertaconazole and whenever the patients were not confirmed with tinea cruris; positive for KOH mount test were included in the study. For the exclusion criteria; pregnant and lactating women and for whom regular follow up were not be possible were excluded. The patients with pervious history or known allergy to azoles and who were received topical antifungal and/or the administration of systemic drugs such as corticosteroids, antibiotics, and antifungals within last 2 weeks and the history of administration of immunosuppressive therapy during last 4 weeks were excluded. Patients with extensive skin lesions were excluded because it may take quite long time to get cured. Patients who received some specific drugs which are known to cause significant interaction with itraconazole, were excluded as these drugs may alter the therapeutic response of azole. Examples of drugs which are having significant interaction with azole: lovastatin, quinidine, terfenadine, warfarin, atorvastatin etc. Patients with a history of kidney disease, liver disease and other systemic illness were excluded.

Efficacy outcome

Phase 1

Treatment phase: In this phase, all the relevant clinical data were obtained, scaling was carried out and topical azoles (1% clotrimazole or 2% sertaconazole) were prescribed as per decision of the dermatologist. Oral itraconazole 100 mg twice daily was prescribed to each patient for the better response and through this homogeneity within both the groups of the patients were

maintained. Oral levocetrizine 5 mg SOS was given for the pruritus.

Phase 2

Follow-up phase: In this phase, the improvement in disease condition was observed and on that basis, the efficacy of particular azole was determined.

At the end of these phases, the parameters like erythema, scaling, itching, margins, size of lesions were determined as the clinical outcomes suggesting of efficacy of prescribed azoles.

In both the groups erythema, scaling, itching, margin and size of the lesions were compared at baseline and at each subsequent follow up visit as shown in the Table 1.

Table 1: Clinical parameters for diagnosis of tinea cruris.

Clinical parameters	Standard scale			
Erythema	0 (Absent)	1 (Mild)	2 (Moderate)	3 (Severe)
Scaling	0 (Absent)	1 (Mild)	2 (Moderate)	3 (Severe)
Itching	0 (No itching)	1 (Mild itching not affecting daily act)	2 (Moderate itching affecting daily activities)	3 (Severe itching disturbing the sleep)
Margins of lesion	0 (Regressive)	1 (Stagnant)	2 (Progressive)	-
Size of lesion	1 (<4 cm)	2 (4-7 cm)	3 (7-10 cm)	4 (>10 cm)

Statistical analysis

For conducting the statistical analysis, data were presented in mean and standard deviation (SD). We have applied independent student t-test to find the mean difference between the both study groups and $p<0.05$ has been considered as significance level. The software used in this study was SPSS 20.0.

RESULTS

Patient demographics and clinical characteristics

In this study, total of 71 patients were involved according to the inclusion and exclusion criteria. Two groups were balanced with respect to baseline characteristics. Out of 71 patients, 32 (45.07 %) were included in clotrimazole group and 39 (54.93%) were included in sertaconazole group.

Out of 32 patients in clotrimazole group, 25 (78.13%) were male and 7 (21.88%) were female. Among, 39 patients of sertaconzole group, 23 (58.97%) were male and 16 (41.03%) were female. In this study, 2/3 patients population were male. The mean age was found to be 29.78±11.10 years and 34.82±14.28 years, for the clotrimazole group and sertaconazole group, respectively.

The clinical presentation for the study populations was a presence of erythema, itching and development of scales over the skin. All these signs and symptoms were present included in both the study groups and thus comparison of various infection parameters was practically feasible.

Comparison of infection parameters

Our main objective was to compare the therapeutic efficacy of sertaconazole 2% cream and clotrimazole 1% cream for patients of tinea cruris. The five disease related parameters considered while doing comparison were erythema, scaling, itching, margins of lesion and size of the lesion. We have obtained a score for each clinical parameter for each patient as per the standard scaling method.

Then, we took the mean and SD for the entire group of A and B in a view to compare the effect of two different topical azoles. The values of Mean and SD were obtained at baseline, on 3rd week of follow up and on 6th week of follow up. The p-value was also obtained for the same.

Table 2: The comparison of relieve in erythema by topical clotrimazole 1% cream and sertaconazole 2% cream.

Erythema	Clotrimazole		Sertaconazole		P value
	Mean	SD	Mean	SD	
Baseline	2.75	0.44	2.69	0.47	0.595
F. Up 1	1.53	0.51	1.03	0.16	0.001
F. Up 2	0.53	0.51	0.05	0.22	0.001

One of the major clinical consequences of tinea cruris is erythema. Thus, it is important to compare the effective and quick relief in it. In a view to compare the effect of topical clotrimazole 1% and sertaconazole 2% on erythema induced by tinea cruris infection, we had first given the score of erythema to each and every patient of both of the groups on the basis of clinical examination. Then, for the purpose of comparison, we took the mean score of erythema as well as SD for the group A and group B and derived p value.

At the initial, the baseline mean values for group A and B were not having statistically significant difference as at that point, no therapy was initiated. But, we found statistically significant different among the mean values of scores of erythema obtained for group A and group B after completion of 3 weeks of follow up ($p<0.001$). Similarly, statistically significant difference was observed

in mean values after completion of 6 weeks of follow up (p<0.001).

Table 3: The comparison of relieve in scaling by topical clotrimzaole 1% cream and sertaconazole 2% cream.

Scaling	Clotrimazole		Sertaconazole		P value
	Mean	SD	Mean	SD	
Baseline	2.66	0.48	2.64	0.49	0.896
F. Up 1	1.50	0.51	1.03	0.16	0.001
F. Up 2	0.47	0.51	0.03	0.16	0.001

The other clinical consequence of tinea cruris is scaling. Mean value and SD for the scaling were obtained for both groups in a similar manner as it was obtained for erythema.

Initially, the baseline mean values for group A and B were not having statistically significant difference as at that point, no therapy was initiated. But, we found statistically significant different among the mean values of scores of scaling obtained for group A and group B after completion of 3 weeks of follow up (p<0.001). Similarly, statistically significant difference was observed in mean values after completion of 6 weeks of follow up (p<0.001).

Table 4: The comparison of relieve in itching by topical clotrimzaole 1% cream and sertaconazole 2% cream.

Itching	Clotrimazole		Sertaconazole		P value
	Mean	SD	Mean	SD	
Baseline	2.91	0.30	2.77	0.43	0.116
F. Up 1	1.75	0.44	1.05	0.22	0.001
F. Up 2	0.81	0.47	0.05	0.22	0.001

Itching is very common among the tinea cruris patients. Thus, to compare the reduction in itching, firstly mean value and SD for the itching score were obtained for both groups in a similar manner as it was obtained for erythema.

Table 5: The comparison of relieve in margin of lesion by topical clotrimzaole 1% cream and sertaconazole 2% cream.

Margins of lesions	Clotrimazole		Sertaconazole		P value
	Mean	SD	Mean	SD	
Baseline	1.88	0.34	1.72	0.46	0.110
F. Up 1	0.88	0.34	0.62	0.49	0.011
F. Up 2	0.03	0.18	0.00	0.00	0.325

Initially, the baseline mean values for group A and B were not having statistically significant difference as at that point, no therapy was initiated. But, we found statistically significant different among the mean values of scores of itching obtained for group A and group B after completion of 3 weeks of follow up (p<0.001). Similarly, statistically significant difference was observed in mean values after completion of 6 weeks of follow up (p<0.001).

The other clinical consequence of tinea cruris is margin of lesion. Mean value and SD for the margin of lesion were obtained for both groups in a similar manner as it was obtained for erythema.

Initially, the baseline mean values for group A and B were not having statistically significant difference as at that point, no therapy was initiated. But, we found statistically significant different among the mean values of scores of margin of lesion obtained for group A and group B after completion of 3 weeks of follow up. Similarly, statistically significant difference was observed in mean values after completion of 6 weeks of follow up.

While comparing margin of lesion; reduction was significantly rapid in sertaconazole group, observed in 3rd week of follow up (p<0.011). However the end result observed at the 6th week of follow up was same in both the groups.

Table 6: The comparison of relieve in size of lesion by topical clotrimazole 1% cream and sertaconazole 2% cream.

Size of lesions	Clotrimazole		Sertaconazole		P value
	Mean	SD	Mean	SD	
Baseline	3.63	0.55	3.46	0.55	0.221
F. Up 1	1.91	0.69	1.51	0.56	0.012
F. Up 2	0.69	0.59	0.08	0.35	0.001

The last clinical consequence of tinea cruris, we compared was size of lesion. Mean value and SD for the size of lesion were obtained for both groups in a similar manner as it was obtained for erythema.

Initially, the baseline mean values for group A and B were not having statistically significant difference as at that point, no therapy was initiated. But, we found statistically significant different among the mean values of scores of size of lesion obtained for group A and group B after completion of 3 weeks of follow up (p<0.012). Similarly, statistically significant difference was observed in mean values after completion of 6 weeks of follow up (p<0.001).

DISCUSSION

Tinea cruris is a common superficial fungal infection and also known as "ringworm." For the management of tinea infection, monotherapy of topical antifungals is widely practiced. Among these, topical azoles are quit commonly used. Today, there are many marketed formulations of different molecules of azoles with

different concentration. There are multiple randomized control trials showing the efficacy and safety of these topical azoles. As such, all azoles are found to be quite effective when used topically but the studies related to comparison of efficacy of topical azoles are very few. Two commonly used topical azoles which are clotrimazole and sertaconazole have not been compared yet solely for tinea cruris. Thus, we have carried out this study to identify better topical azole for the management of tinea cruris.

In this study, the effect of topical agents with clotrimazole 1% cream and sertaconazole 2% cream, twice daily application for 4 weeks was compared in patients suffering from tinea cruris. There was a significant improvement in major inflammatory signs and symptoms related to tinea cruris (erythema, scaling, itching, margin of lesions, size of lesions) observed after few weeks for both the study groups.

The initial 3 weeks were "treatment phase" where clinical and mycological outcomes were evaluated, and last 3 weeks were "follow-up phase" where recurrence and relapse of tinea cruris was observed. At end of "treatment phase", group B has showed an early response to therapy compared to group A. At the end of "follow-up phase", significantly better improvement observed in erythema, scaling, itching, margin of lesions and size of lesions in patients treated with topical sertaconazole 2% cream as compared with patients treated with clotrimazole 1% cream. In this study, no adverse drug reactions was found related to treatment.

Moreover, as per the studies conducted by Khan et al, Shivamurthy et al, and Satish et al; topical sertaconazole has shown better therapeutic response in comparison with topical clotrimazole in other types of tinea infections such as tinea corporis.[9-11] In this manner, the study results of this study is quite similar to the previously conducted studies on comparison of topical antifungals in other tinea infections.

Limitations

Short duration of the study was major limitation of this study. Results of the present study cannot be comprehensive as this was an observational study with smaller sample size and proper randomisation was not possible in this study. As per the physician prospective medications was prescribed.

CONCLUSION

For the pharmacological management of tinea cruris, both of the commonly prescribed topical drugs [clotrimazole and sertaconazole] were found to be effective, safe and well tolerated. Yet, if we compare all the infectious parameters (erythema, scaling, itching, margin of lesions and size of lesions) precisely, the topical sertaconazole 2% cream was found to be more efficacious compared to clotrimazole 1% cream. Hence, if it is affordable; the topical sertaconazole 2% cream can be prescribed as first line agent for the management of tinea cruris.

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