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RESEARCH ARTICLE

Comparative study of the efficacy and safety of topical antifungal agents clotrimazole versus sertaconazole in the treatment of tinea corporis/cruris

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ABSTRACT

Background: Tinea corporis is a common dermatophytic infection affecting 22-25% of the world population. Clotrimazole is conventional antifungal drug whereas sertaconazole is newer antifungal claimed to be superior to clotrimazole. Both are used topically. **Aims and Objective:** To compare the efficacy and safety of topical clotrimazole versus sertaconazole in tinea corporis/cruris. **Materials and Methods:** A total of 60 patients diagnosed with tinea corporis/cruris were randomized into two groups of 30 patients each. Group A received topical clotrimazole (1% cream), and Group B received topical sertaconazole (2% cream). The patients were advised to apply the drug on affected area twice daily for 4 weeks. Outcome parameters such as pruritus, erythema, vesicles and desquamation, and potassium hydroxide mount were noted weekly for the assessment of efficacy. **Results:** There was significant reduction in pruritus ($P < 0.001$), erythema ($P < 0.001$), vesicles ($P < 0.001$), and desquamation ($P < 0.001$) among both the groups. The mean difference and the standard deviation of the total score of all parameters (baseline to 4th week follow-up) for clotrimazole group were 6.39 ± 1.123 and for sertaconazole group were 7.37 ± 0.751, respectively. The P value on the application of students unpaired t-test was $P = 0.115$ (not significant). No serious adverse drug events in both the groups. **Conclusion:** Clotrimazole is as efficacious and safe as compared with sertaconazole in the treatment of tinea corporis/cruris. However, sertaconazole group has showed an early response to therapy compared to clotrimazole group.

KEY WORDS: Sertaconazole; Clotrimazole; Tinea Corporis/Cruris; Potassium Hydroxide

INTRODUCTION

Dermatophytoses' is a most common type of superficial fungal infections affects as many as 20-25% of the world's population.[1] It is a major health problem especially in tropical countries like India due to the hot and humid climate.[2] In India, the most commonly occurring clinical type of dermatophytoses include tinea corporis (36-59%) and tinea cruris (12-27%).[3] Although dermatophytoses does not cause mortality; it does cause morbidity with interference with daily activities, poor quality of life, and health-care expenditure. Treatment strategies to deal with dermatophytoses involve the use of a systemic or topical antifungal agent. However, topical therapy is preferred over oral therapy because of less side effects, avoids drug-drug interactions, better compliance, and less cost.[4-6]

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Clotrimazole has been widely used topically for the treatment of the tinea corporis/cruris for over 25 years. However, it has disadvantages like long duration of therapy, which leads to poor compliance and also a high relapse rate because of rapid development of resistance.[7-9] To manage this growing pathogenicity of superficial fungal infections, development

of newer broad-spectrum antifungals like sertaconazole have opened up new treatment options. Sertaconazole is a newer topical benzothiophene imidazole antifungal, found to be more effective than conventional azoles in several studies. It requires shorter courses of treatment and is associated with lower relapse rates.[3,10] It has both fungistatic and fungicidal activity against dermatophytes.[11-13] It also has additional anti-inflammatory and antipruritic actions that help to provide better symptomatic relief.[14,15] These additional properties of sertaconazole are likely to make an impact on the concomitant symptom control and therefore improve the quality of life of these patients with dermatophytoses.[16,17]

We came across less number of trials reported in literature comparing efficacy, safety and cost-effectiveness of topical antifungals clotrimazole and sertaconazole in the treatment of tinea corporis/cruris. Hence, this study was undertaken to compare two antifungals, conventional clotrimazole and the newer sertaconazole for the treatment of tinea corporis/cruris.

MATERIALS AND METHODS

Ethical clearance was obtained from the Institutional Ethical Review Board. A written informed consent was obtained from all the patients enrolled in the study. At screening, the eligibility criteria for inclusion in the study were patients of both genders in age group of 18-65 years with clinical manifestations of cutaneous mycoses (tinea corporis/cruris) and confirmation done with skin scraping positive for potassium hydroxide (KOH) mount. The symptoms and signs of pruritus, erythema, vesicles, and desquamation were scored as 0 (nil), 1 (mild), 2 (moderate), and 3 (severe). Patients were eligible for the study if they had a combined score of at least 5. Exclusion criteria of the study were pregnant and lactating mothers, patients with a known history of severe cardiac, pulmonary, gastrointestinal, renal, hepatic, neurological and uncontrolled diabetes mellitus, those with history of hypersensitivity to azole drugs or vehicle ingredients, previous treatment with antifungal, antibiotic or immunosuppresent agents, patients with contact dermatitis, atopic dermatitis, psoriasis or any other disease and those with superficial which are extensive and treatment resistant cases.

Study Design

It is a single-center, prospective, randomized, open-label, and comparative study. Patients with clinical evidence of tinea corporis/cruris attending Outpatient Department of Dermatology, Victoria Hospital attached to Bangalore Medical College and Research Institute, Bengaluru.

Randomization

The estimated sample size for the study was 60 patients (30 in each group). Patients who fulfilled the eligibility criteria were randomized into two treatment groups (1:1 ratio).

Drug Administration

One group was treated with topical clotrimazole 1% cream while other received topical sertaconazole 2% cream. The test medication in each group was advised to apply twice daily on affected lesion. The total duration of the study was 4 weeks. Patient's demographic data including age, sex, baseline clinical parameters such as pruritus, erythema, vesicles, and desquamation were noted at base line. All patients were followed up on 1st week, 2nd week, and 4th week. Outcome of the treatment was assessed by the clinical and mycological care.

Efficacy and Safety Assessments

The primary efficacy parameter was change in the signs and symptoms severity score of the target lesion. The signs and symptoms that were evaluated were pruritus, erythema, vesicles, and desquamation. These signs and symptoms were graded as absent (0), mild (1), moderate (2), and severe (3). The change in total score of all the signs and symptoms (varying from 0 to 12) was also assessed.

The secondary efficacy outcome was mycological cure based on KOH test: A negative KOH preparation at the end of the study period was considered as mycological cure.

The safety of study medication was assessed in all patients by recording adverse drug reactions (ADRs) as reported by them. The details of occurrence, intensity and causal relationship to the study drug along with the findings of physical and clinical examination were considered.

Statistical Analysis

Analyses for all the variables were performed using last observation carried forward method. Descriptive statistics were reported as percentages, mean ± standard deviation (SD) for continuous parametric variables. Categorical variable was expressed in actual numbers and percentage. Differences in clinical score within group were compared by one-way analysis of variance. Unpaired *t*-test was employed to find the significance in between the group. A difference was considered as significant if the $P < 0.05$.

RESULTS

Study Profile and Baseline Characteristics

Out of 60 patients enrolled in the study (30 in each group), 1 patient from clotrimazole group and 3 patients from sertaconazole group were lost to follow-up and 56 patients completed the study. The study profile of enrolled patients is presented in Figure 1. The demographic and baseline clinical characteristics of study patients were similar between the two groups as presented in Table 1.

Efficacy Parameters

Both groups of patients showed a significant reduction in pruritus, erythema, vesicles, and desquamation from baseline across time at the end of 4 weeks ($P < 0.001$). There was a faster reduction in mean scores of pruritus, erythema, and desquamation by sertaconazole ($P < 0.001$) compared to clotrimazole ($P < 0.01$) from baseline to 1st week (first follow-up) and reduction in vesicle was comparable in both groups ($P < 0.01$). However, no significant difference was found when 2nd week was compared to 4th week in both treatment groups (Table 2). The reduction in total score by sertaconazole was steep and faster compared to clotrimazole from baseline to 4th week as presented in Figure 2.

Table 3 shows the intergroup comparison of mean difference of pruritus, erythema, vesicles, and desquamation scores at 1st week, 2nd week, and 4th week from the baseline score in both treatment groups. Symptoms of pruritus and desquamation have shown a statistically significant reduction ($P < 0.05$) in sertaconazole group when compared with clotrimazole group at the end of 1st week. There was no statistically significant difference in reduction in the scores of erythema and vesicles in between the groups. The mean difference of baseline to 2nd week's score was highly significant ($P < 0.01$) in pruritus, significant ($P < 0.05$) in vesicles and nonsignificant in erythema and desquamation when sertaconazole 2% cream was compared with clotrimazole 1% cream. However, mean difference of the baseline to 4th week's score was statistically significant only for pruritus, but nonsignificant for erythema, vesicles and desquamation score when the two group drugs were compared.

Figure 3 represents mean difference in the total score of all symptoms from baseline to 1st, 2nd, and 4th week follow-up. Although the mean reduction of total score was faster in sertaconazole group than clotrimazole group, there was no statistically significant difference between both groups at the end of 4th week follow-up ($P = 0.115$).

Figure 4 shows the comparison of mycological cure in between the groups. At the end of 2nd week follow-up, 41% and 7% cases were positive on KOH mount in clotrimazole and sertaconazole groups, respectively. There were no (0%) positive cases by the end of study period in both the treatment groups.

Table 1: Baseline demographic and clinical characteristics of patients

Characteristic	Clotrimazole	Sertaconazole
Number of patients	30	30
Number of patients completed trial	29	27
Age (years) (mean±SD)	32.26±11.16	30.76±10.35
Male	19	18
Female	11	12
Tinea corporis	20	18
Tinea cruris	10	12

SD: Standard deviation

Table 2: Intragroup comparison of mean scores of primary efficacy parameters at 1st week, 2nd week, and 4th week

Parameter	Baseline	1st week	2nd week	4th week
Clotrimazole				
Prurirtis	2.73±0.80	2.06±0.57*	1.73±0.69***	1.43±0.56***
Erythema	2.63±0.71	1.8±0.71**	1.23±0.5***	0.6±0.49***
Vesicles	1.36±1.12	0.66±0.71**	0.23±0.43***	0***
Desquamation	1.9±0.99	1.16±0.83**	0.46±0.57**	0.2±0.4***
Sertaconazole				
Prurirtis	2.70±0.66	1.73±0.77***	1.46±0.75***	1.26±0.63***
Erythema	2.6±1.27	1.6±1.16***	0.9±0.75***	0.3±0.46***
Vesicles	1.73±1.2	0.73±0.9**	0.1±0.3***	0***
Desquamation	2.13±0.93	1.06±0.86***	0.63±0.8***	0.23±0.43***

All values are expressed in mean±SD. One-way ANOVA was used. *P<0.05, **P<0.01, ***P<0.001, SD: Standard deviation, ANOVA: Analysis of variance

Safety Parameters

Both drug treatments were well-tolerated. However, two patients complained of burning with clotrimazole and

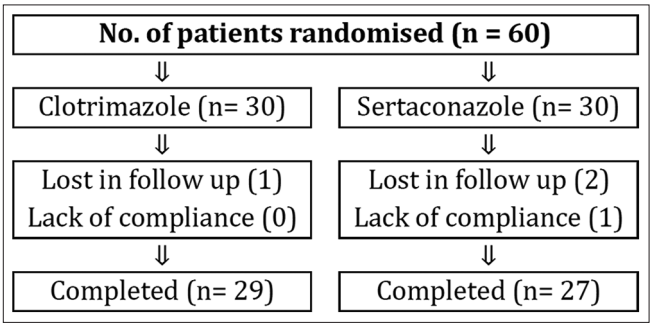

Figure 1: Flow diagram of patient enrolment, treatment allocation, and follow-up

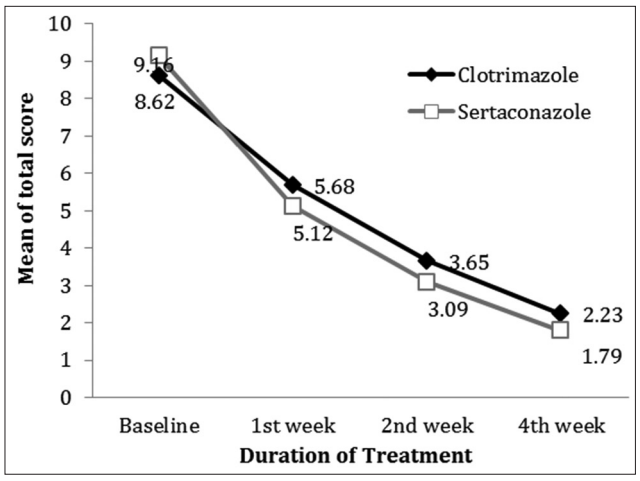

Figure 2: Changes in mean of total score in both groups for 4 weeks

Table 3: Intergroup comparison of mean differences in scores of signs and symptoms at 1st, 2nd, and 4th week from baseline score

Duration	Baseline to 1st week		Baseline to 2nd week		Baseline to 4th week	
Parameters	**Clotrimazole**	**Sertaconazole**	**Clotrimazole**	**Sertaconazole**	**Clotrimazole**	**Sertaconazole**
Prurirtis	0.67±0.23	0.97±0.21*	1±0.25	1.24±0.22*	1.3±0.22	1.44±0.26**
Erythema	0.83±0.17	1±0.21	1.4±0.27	1.7±0.28	2.03±0.26	2.3±0.4
Vesicles	0.7±0.28	1±0.27	1.13±0.35	1.63±0.42*	1.36±0.42	1.73±0.44
Desquamation	0.73±0.21	1.07±0.19*	1.43±0.32	1.5±0.27	1.7±0.34	1.9±0.31

All values are expressed in mean±SD. Unpaired *t*-test was used. *P<0.05 and **P<0.01, SD: Standard deviation

redness was reported in one patient with sertaconazole. All three ADRs were mild, self-limiting, and did not require the discontinuation of therapy.

All values are expressed in mean ± SD. Unpaired *t*-test was used $P = 0.115$.

DISCUSSION

Dermatophytes are group of taxonomically related fungi that invade the keratinized tissue (skin, hair, and nails).[4] The disease is most common in tropical countries like India. The incidence of tinea infections has progressively increased since the 1970s owing to increase in the population of immunocompromised individuals.[18] Clotrimazole which belongs to azole group is the most commonly encountered broad-spectrum topical antifungal agent.[7,9] Sertaconazole is a newer topical benzothiophene imidazole antifungal, found to be more effective than conventional azoles in several studies.[3,10]

In this study, the efficacy of topical therapy with clotrimazole 1% cream and sertaconazole 2% cream, twice daily application for 4 weeks was compared in patients suffering from mild to moderate tinea corporis/cruris. There was a significant reduction in clinical features (pruritus, erythema, vesicles, and desquamation) as compared to baseline in both the study groups. However, sertaconazole group has showed an early response to therapy compared to clotrimazole group. Similar results were seen in studies conducted by Khan et al.,[3] Shivamurthy et al.,[7] and Jerajani et al.[10] The probable reason may be attributed to its wide range of action. It is an effective fungistatic and fungicidal agent. Its fungistatic action is attributed to its inhibitory action on 14α-demethylase, which converts lanosterol to ergosterol and is required in fungal cell wall synthesis. At high concentrations sertaconazole binds directly to non-sterol lipids on the fungal membrane and interferes with ligands from the intracellular contents, thereby causing cell death which elucidates its fungicidal activity.[11-13] In this study, sertaconazole group showed early response and highly significant reduction in pruritus than clotrimazole group. This explains the additional anti-inflammatory properties of sertaconazole. This has been described by reducing cytokine secretion from activated

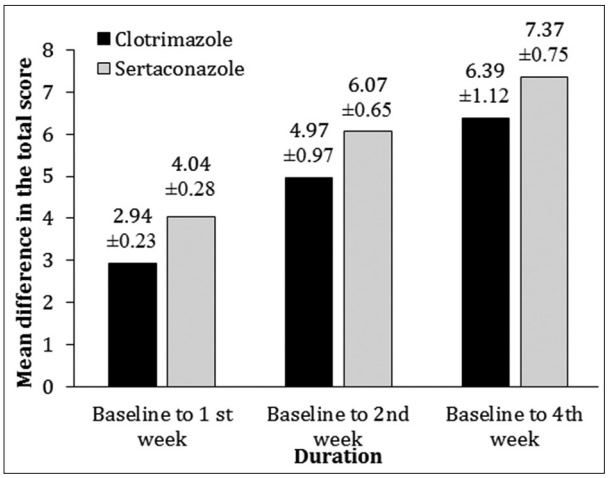

Figure 3: Intergroup comparison of mean differences in total scores of signs and symptoms at 1st, 2nd, and 4th week from baseline score

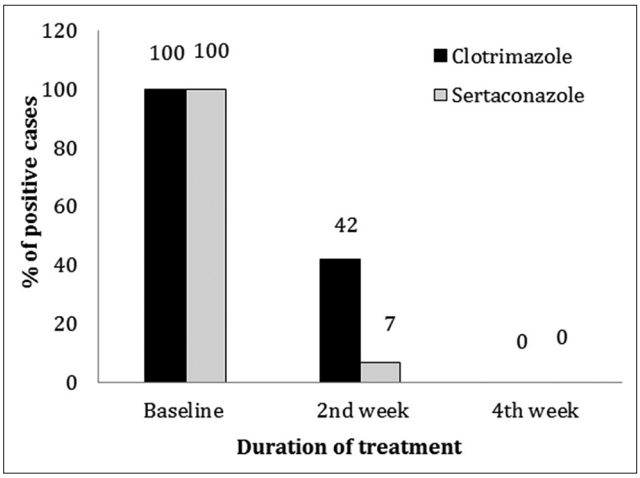

Figure 4: Comparison of mycological cure in both the treatment group at 2nd and 4th week

lymphocytes, histamine release from mast cells and release of prostaglandin E2, all of which control the inflammatory component of dermatophytosis.[14,15]

This study depicts 93% patients treated with sertaconazole 2% cream and 58% patients who received clotrimazole 1% cream were mycologically negative with KOH mount at the end of 2nd week. Although the sertaconazole group had shown early mycological cure than clotrimazole, both the treatment groups had complete mycological cure (100%) at the end of

the last follow-up. The result was very similar with the study conducted by Khan et al., wherein, sertaconazole 2% cream (94%) was superior to clotrimazole 1% cream (62%) in early mycological cure, but at the end of study period both were equi efficacious in mycological assessment.[3] Shivamurthy et al. reported no significance difference between sertaconazole and clotrimazole creams on KOH mount.[7]

There were total of three ADRs reported in this study. Two patients from clotrimazole therapy experienced burning sensation, and one patient in sertaconazole experienced redness. All three were mild and required no discontinuation in the therapy. This is in consistent with a study conducted by Khan et al., where only one patient in sertaconazole group developed burning sensation. It did not require any stoppage of medication, shift to another therapy or withdrawal of the patient from the trial.[3] In another study by Sharma et al., it was reported that five patients in the sertaconazole group experienced mild to moderate adverse events.[19]

There have been a several limitations in our study, e.g., (a) This was an open-label design, (b) smaller sample size, and (c) the diagnosis of tinea was based only on KOH mount but not on culture.

CONCLUSION

The results of this study indicate that sertaconazole was better than clotrimazole in early therapeutic response and mycological cure in the treatment of tinea corporis/cruris. Nevertheless, both the study medications have shown comparable efficacy and safety at the end of 4th week. Thus, sertaconazole 2% cream can be chosen as a first-line agent followed by clotrimazole 2% cream. However, considering the cost factor, clotrimazole is a better choice than sertaconazole.

REFERENCES

1. Chandana T, Saritha CH, Shankaraiah P. Comparison of safety and efficacy of luliconazole and other antifungal agents. Int J Pharm Sci Res. 2014;5(1):1-9.
2. Sharma V, Kumawat TK, Sharma A, Seth R. Distribution and prevalence of dermatophytes in semi-Arid region of India. Adv Microbiol. 2015;5(2):93-106.
3. Khan HS, Dudhgaonkar S, Bende MM, Wankhede S. Comparison of efficacy, safety and cost-effectiveness of clotrimazole 1% cream and sertaconazole 2% cream in patients suffering from of mild to moderate tinea corporis, attending tertiary care hospital out-patient department: A randomized, open-labeled, comparative, parallel group trial. Int J Basic Clin Pharmacol. 2015;4(1):75-81.
4. Hay RJ, Ashbee HR. Mycology. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook's Textbook of Dermatology. 8th ed., Vol. 2. Edinburgh: Wiley Blackwell; 2010. p. 1-36, 93.
5. Bennett JE. Antifungal agents. In: Brunton LL, Knollmann BC, Chabner BA, editors. Goodmann and Gillman's the Pharmacological Basis of Theraupetics. 12th ed. New York: McGraw Hill; 2014. p. 1571-91.
6. Jain A, Jain S, Rawat S. Emerging fungal infections among children: A review on its clinical manifestations, diagnosis, and prevention. J Pharm Bioallied Sci. 2010;2(4):314-20.
7. Shivamurthy RP, Reddy SG, Kallappa R, Somashekar SA, Patil D, Patil UN. Comparison of topical anti- fungal agents sertaconazole and clotrimazole in the treatment of tinea corporis-an observational study. J Clin Diagn Res. 2014;8(9):HC09-12.
8. Greenberg HL, Shwayder TA, Bieszk N, Fivenson DP. Clotrimazole/betamethasone diproprionate: A review of costs and complications in the treatment of common cutaneous fungal infections. Pediatr Dermatol. 2002;19(1):78-81.
9. Stary A, Soeltz-Szoets J, Ziegler C, Kinghorn GR, Roy RB. Comparison of the efficacy and safety of oral fluconazole and topical clotrimazole in patients with candida balanitis. Genitourin Med. 1996;72(2):98-102.
10. Jerajani H, Janaki C, Kumar S, Phiske M. Comparative assessment of the efficacy and safety of sertaconazole (2%) cream versus terbinafine cream (1%) versus luliconazole (1%) cream in patients with dermatophytoses: A pilot study. Indian J Dermatol. 2013;58(1):34-8.
11. Pfaller MA, Sutton DA. Review of *in vitro* activity of sertaconazole nitrate in the treatment of superficial fungal infections. Diagn Microbiol Infect Dis. 2006;56(2):147-52.
12. Palacin C, Tarrago C, Agut J, Guglietta A. *In vitro* activity of sertaconazole, fluconazole, ketoconazole, fenticonazole, clotrimazole and itraconazole against pathogenic vaginal yeast isolates. Methods Find Exp Clin Pharmacol. 2001;23(2):61-4.
13. Palacín C, Sacristán A, Ortiz JA. *In vitro* activity of sertaconazole. Arzneimittelforschung. 1992;42(5A):699-705.
14. Sur R, Babad JM, Garay M, Liebel FT, Southall MD. Anti-inflammatory activity of sertaconazole nitrate is mediated via activation of a p38-COX-2-PGE2 pathway. J Invest Dermatol. 2008;128(2):336-44.
15. Liebel F, Lyte P, Garay M, Babad J, Southall MD. Anti-inflammatory and anti-itch activity of sertaconazole nitrate. Arch Dermatol Res. 2006;298(4):191-9.
16. Croxtall JD, Plosker GL. Sertaconazole: A review of its use in the management of superficial mycoses in dermatology and gynaecology. Drugs. 2009;69(3):339-59.
17. Carrillo-Muñoz AJ, Giusiano G, Ezkurra PA, Quindós G. Sertaconazole: Updated review of a topical antifungal agent. Expert Rev Anti Infect Ther. 2005;3(3):333-42.
18. Singh S, Beena PM. Profile of dermatophyte infections in Baroda. Indian J Dermatol Venereol Leprol. 2003;69(4):281-3.
19. Sharma A, Saple DG, Surjushe A, Rao GR, Kura M, Ghosh S, et al. Efficacy and tolerability of sertaconazole nitrate 2% cream vs. miconazole in patients with cutaneous dermatophytosis. Mycoses. 2011;54(3):217-22.

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