Efficacy and tolerability of topical sertaconazole versus topical terbinafine in localized dermatophytosis: A randomized, observer-blind, parallel group study

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Abstract:

Objective: Epidermal dermatophyte infections most commonly manifest as tinea corporis or tinea cruris. Topical azole antifungals are commonly used in their treatment but literature suggests that most require twice-daily application and provide lower cure rates than the allylamines antifungal terbinafine. We conducted a head-to-head comparison of the effectiveness of the once-daily topical azole, sertaconazole, with terbinafine in these infections.

Materials and Methods: We conducted a randomized, observer-blind, parallel group study (Clinical Trial Registry India [CTRI]/2014/09/005029) with adult patients of either sex presenting with localized lesions. The clinical diagnosis was confirmed by potassium hydroxide smear microscopy of skin scrapings. After baseline assessment of erythema, scaling, and pruritus, patients applied either of the two study drugs once daily for 2 weeks. If clinical cure was not seen at 2 weeks, but improvement was noted, application was continued for further 2 weeks. Patients deemed to be clinical failure at 2 weeks were switched to oral antifungals.

Results: Overall 88 patients on sertaconazole and 91 on terbinafine were analyzed. At 2 weeks, the clinical cure rates were comparable at 77.27% (95% confidence interval [CI]: 68.52%–86.03%) for sertaconazole and 73.63% (95% CI 64.57%–82.68%) for terbinafine (P = 0.606). Fourteen patients in either group improved and on further treatment showed complete healing by another 2 weeks. The final cure rate at 4 weeks was also comparable at 93.18% (95% CI 88.75%–97.62%) and 89.01% (95% CI 82.59%–95.44%), respectively (P = 0.914). At 2 weeks, 6 (6.82%) sertaconazole and 10 (10.99%) terbinafine recipients were considered as “clinical failure.” Tolerability of both preparations was excellent.

Conclusion: Despite the limitations of an observer-blind study without microbiological support, the results suggest that once-daily topical sertaconazole is as effective as terbinafine in localized tinea infections.

Key words: Antifungal, dermatophytosis, observer-blind, parallel group study, randomized, sertaconazole, terbinafine, tinea

Tinea” refers to scaly fungal infections of the epidermis and skin appendages caused by a group of keratinophilic fungi known as “dermatophytes” which includes three genera, namely, *Epidermophyton*, *Microsporum*, and *Trichophyton*.¹ The latter begins in the inguinal folds and presents usually as bilateral, scaly, dull red, pruritic plaques whose leading edge advances in a sharply demarcated, raised, scaly border.³ The former presents as radially advancing, flat, scaly, pruritic macules with a raised border and a characteristic central clearing which earns the sobriquet “ringworm” for these lesions.⁴ The traditional azoles (e.g., clotrimazole, miconazole, ketoconazole) are fungistatic and need twice-daily application.⁶ On the other hand, the allylamines (e.g., terbinafine, naftifine) are fungicidal.⁷

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The available topical formulation of terbinafine (1%) forms a reservoir in the upper epidermal layers which enable just once-daily application.\(^7\) Available literature indicates that superior cure rates and better compliance observed with terbinafine are attributable to its fungicidal action and the convenience of once-daily application.\(^8,9\)

Sertaconazole, one of the newer azoles, is structurally unique due to a benzothiophene ring. It is the only azole with a fungicidal action due to its ability to cause direct fungal cell membrane damage.\(^10\) The available topical formulation of sertaconazole (2%) attains fungicidal concentration in the stratum corneum as the lipophilic property of the benzothiophene ring enables prolonged dermal retention.\(^11\) This permits just once-daily application contrary to most other topical azoles.\(^12\) Sertaconazole has additional anti-inflammatory and antipruritic actions.\(^13\) It has shown efficacy even against dermatophyte isolates resistant to other azoles.\(^14\) Its faster and superior cure rates as compared to other azoles are well documented.\(^10,13,14\)

The efficacy profile and dosage convenience of sertaconazole appear to be similar to that of terbinafine. However, few head-to-head comparisons have been done. The present study sought to assess whether these two topical agents differ significantly in their cure rates in case of the common localized dermatophyte infections.

**Materials and Methods**

This study was designed as a randomized, observer-blind, parallel group, controlled clinical trial and conducted in the dermatology outpatient department of a large tertiary care teaching hospital. Permission was taken from the institutional ethics committee before commencement. The study is registered with Clinical Trial Registry India [CTRI/2014/09/005029].

For sample size calculation, the clinical cure rate was taken as the primary outcome measure. Available literature indicates that as much as 15% difference can be expected between the cure rates of the two types of drugs with maximum cure rates in excess of 90%.\(^13,18\) Taking Type I error probability as 5%, power of the study as 80%, two-sided testing and attrition rate as 10%, we estimated a recruitment target of 105 patients in each group. The calculation was done using nMaster 2.0 (Department of Biostatistics, Christian Medical College, Vellore) software.

Consenting adult patients (18–65 years age) of either sex presenting with localized tinea lesions, without nail or scalp involvement, and without any secondary bacterial infection over the lesions were recruited who provided that they had not applied any topical or taken any oral antifungal drug before the baseline visit. Diabetic, immunocompromised, pregnant, and lactating patients were excluded from the study.

During screening, if recruitment was an option, the protocol was explained in vernacular to the patient. If the patient provided written informed consent, scrapings were taken from the lesion and subjected to potassium hydroxide (KOH) was explained in vernacular to the patient. If the patient applied any topical or taken any oral antifungal drug before enrollment, the patient was excluded from the study. If recruitment was not an option, the protocol was explained in vernacular to the patient. If the patient applied any topical or taken any oral antifungal drug before enrollment, the patient was excluded from the study.

During the follow-up visit at 2 weeks, the lesions were clinically reexamined by the dermatologist. Based on previous studies, “complete clinical cure” was defined as the complete absence of erythema, scaling, and pruritus and the dermatologist’s impression of a “cleared” lesion. This was the primary end point and clinically cured patients were regarded as “treatment completed” [Figure 1a and b]. If a patient showed only partial improvement after the first 2 weeks, the assessment parameters were graded once more and a fresh supply of the ongoing medication was provided in a separate, opaque, sealed envelope bearing only the code “A” or “B” on its face. These patients were to report after another 2 weeks.

Any patient presenting with persistence of existing signs and symptoms and persistence of fungal hyphae in skin scrapings at the first follow-up visit was regarded as “clinical failure” [Figure 2a and b]. In such an instance, topical therapy was terminated and the concerned patient was switched over to an oral antifungal drug at the discretion of the dermatologist.

The decoding was done only after the completion of data collection. Data from individual CRFs were entered into a Microsoft Excel spreadsheet and then analyzed by GraphPad Prism version 5 (GraphPad software Inc., San Diego; 2007) software. Numerical variables that satisfied the normality assumption were compared between subgroups by Student’s independent samples t-test while categorical variables were compared by Fisher’s exact test or Chi-square test as appropriate. Changes in symptom score from baseline were assessed for statistical significance by Wilcoxon’s matched pairs signed-rank test. \(P < 0.05\) was considered statistically significant. The 95% confidence interval (CI) values have been presented where deemed relevant.
Results

A total of 384 patients were screened over a period of 12 months and 203 were finally recruited. Figure 3 depicts the flow of study participants. As per the software-generated random allocation sequence, 101 cases received sertaconazole 2% cream (medication “A”) and 102 cases received terbinafine 1% cream (medication “B”). A total of 24 cases were lost to follow-up– 13 on “A” and 11 on “B” – without appearing for even one follow-up visit. Since the modified intention-to-treat strategy was to include patients who appeared for at least one postbaseline visit, this data set essentially were equal in numbers to the per protocol dataset. Thus, 88 recipients of sertaconazole and 91 of terbinafine were finally analyzed.

As seen from Table 1, the two groups did not differ significantly in age and gender distribution. The inguinal region and abdomen were the two most common sites where lesions were detected, with involvement in 43% and 27%, respectively. The two groups were also comparable with regard to the varieties of tinea infections encountered.

The clinical performance of the study medication at 2 weeks is summarized in Table 2. After the first 2 weeks of topical therapy, the clinical cure rates of sertaconazole (77.27%; 95% CI 68.52%–86.03%) and terbinafine (73.63%; 95% CI 64.57%–82.68%) did not differ significantly between groups (P = 0.606). A total of 6 recipients of sertaconazole and 10 recipients of terbinafine were diagnosed as “clinical failure” and switched to oral antifungal drugs. The clinical performance distribution overall was comparable between groups (P = 0.620 by Chi-square test).

In each group, 14 patients showed partial improvement after the first 2 weeks. Within each group, the total and individual scores of erythema, scaling, and pruritus of these 14 patients at 2 weeks were compared with their baseline scores. Both

Table 1: Comparison of basic demographic and clinical profile of the study groups

| Variable | Sertaconazole (n=88) | Terbinafine (n=91) | P   |
|----------|----------------------|--------------------|-----|
| Age (years) | 39.3±13.76          | 37.8±13.58        | 0.625 |
| Sex distribution | Male:female 62:26   | 52:39              | 0.087 |
| Lesion type | Tinea corporis 49    | 53                 | 0.858 |
|            | Tinea cruris 36      | 34                 |      |
|            | Both 3               | 4                  |      |

Age is summarized as mean±SD. P value in the last group is from intergroup comparison by Student's independent samples t-test for age, Fisher's exact test for sex distribution, and Chi-square test for lesion profile. SD=Standard deviation

Table 2: Clinical performance of the study medication at 2 weeks

| Variable | Sertaconazole, n=88 (%) | Terbinafine, n=91 (%) | P   |
|----------|-------------------------|-----------------------|-----|
| Complete cure | 68 (77.27) | 67 (73.63) | 0.606 |
| Clinical failure (topical drug withdrawn) | 6 (6.82) | 10 (10.99) | 0.434 |
| Some improvement (topical drug continued) | 14 (15.91) | 14 (15.38) | 1.000 |
| Erythema Grade 1 (mild) as opposed to other grades | 9 | 7 | 0.704 |
| Scaling Grade 0 (absent) as opposed to other grades | 9 | 9 | 1.000 |
| Pruritus Grade 1 (mild) as opposed to other grades | 10 | 5 | 0.128 |

Values are summarized as counts with percentage within respective group in parentheses. P value in the last group is from intergroup comparison by Fisher's exact test. The composite P value for clinical performance at 2 weeks is 0.620 by Chi-square test.
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**Discussion**

In the present study, majority of the patients receiving either of the study drugs achieved complete clearing of tinea lesions within the first 2 weeks of topical treatment. Even those who needed treatment beyond 2 weeks achieved significant improvement in erythema, scaling, and pruritus within 2 weeks. Overall, around 93% of sertaconazole recipients and 89% of terbinafine recipients achieved complete clinical cure within 4 weeks of treatment while the rest had to be switched to systemic antifungal therapy. Cure rates were slightly higher with sertaconazole but did not differ significantly from that of terbinafine. These results suggest that though topical terbinafine has proven superior to topical azoles in several studies, the cure rates of the relatively newazole antifungal, sertaconazole did not differ significantly from that of terbinafine. The absence of significant differences between the two is possibly due to the unique fungicidal action of sertaconazole which includes direct fungal cell membrane damage and subsequent leakage of intracellular contents.\[20,21\]

The absence of significant differences between the cure rates of these two drugs has also been reported by Choudhary \[20\] in a study conducted in the Western part of India. The differences from the present study were that no “failures” were reported and the sample size was 15 per group. We speculate that a difference in the sample size as well as recent emergence of antifungal-resistant strains among dermatophytes may have accounted for this difference.

Thaker \[21\] compared the cure rates of topical sertaconazole and topical butenafine in localized epidermal tinea infections and reported a significant reduction of sign and symptom scores at the first follow-up visit. Choudhary \[20\] also reported that after the first 2 weeks, there was hardly any scale left over in either sertaconazole or terbinafine recipients.

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**Figure 3:** Scheme depicting flow of study participants
to perform KOH microscopy. A nearly identical scenario was encountered in the present study among those patients who needed topical therapy beyond 2 weeks.

In another comparative study between sertaconazole and terbinafine, Jerajani et al. detected that the antipruritic efficacy of sertaconazole was significantly superior to that of terbinafine. In the present study, the antipruritic effect suggested a possible trend in favor of sertaconazole though the numbers were too small to yield statistical significance. Furthermore, this study was on localized tinea lesions without marked inflammatory features such as pustules, vesicles, or crust formation. Thus, a difference, even if it exists, was not discernable. A similar explanation was given by Vidhya Lakshmi et al. who compared the efficacies of topical terbinafine and topical luliconazole, another newer azole. A significant improvement in the baseline scores of disease parameters was reported after the first 2 weeks in case of both the drugs.

The present study detected a failure rate of approximately 11% among terbinafine and 7% among sertaconazole recipients. Mukherjee et al. have reported resistance to terbinafine. Six isolates of *T. rubrum* were obtained sequentially from an onychomycosis patient who failed to respond to oral terbinafine (250 mg daily for 24 weeks). All the isolates were resistant to terbinafine but sensitive to itraconazole, fluconazole, and griseofulvin. A target-specific mechanism of resistance was suggested. Resistance to sertaconazole has been documented by Croxall et al. who detected 4% resistance among 250 clinical isolates of dermatophytes. This resistance, though small in quantum at present, remains a worrying feature for clinicians.

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Azoles usually need twice-daily application. An interesting aspect of the present study was that sertaconazole showed comparable results with terbinafine even with once-daily application. This could be attributed to its prolonged retention in the stratum corneum on account of the lipophilicity of its benzothiophene ring.

The tolerability of the two drugs was excellent in this study. A similar view is shared by authors of earlier studies. Jerajani et al. reported that in their study, only a single sertaconazole recipient withdrew because of contact dermatitis. The present study has its share of limitations. Due to logistic constraints, blinding was not possible. Hence, only an observer-blind procedure was implemented. Fungal culture, species identification, and determination of resistance patterns among dermatophytes could not be done. Furthermore, the effectiveness of the two topical drugs was not compared in other variants of tinea beyond localized uncomplicated infections on the trunk, limbs, or groin.

Nonetheless, we can still conclude that the performance of the azole sertaconazole does not differ significantly from the established fugalid agent terbinafine in localized epidermal dermatophytosis. Further studies are required to compare their effectiveness in other variants of tinea and in patients with comorbidities or immunocompromised status.

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Conflicts of Interest
There are no conflicts of interest.

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