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Comparing Three Distinct Oral Terbinafine - Based Regimens in Recurrent Tinea Corporis and Cruris Infection in a Prospective, Randomized, Parallel Group, Open-Label Research

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Abstract

Background

Oral terbinafine 250 mg ODfor two weeks is the standard treatment for Tinea Corporis and Cruris infections. However, this regimen has a relatively high frequency of infection recurrence.

Materials and Methods

The study was conducted on 60 patients with recurrent tinea infection. The patients were randomly divided into three groups A, B, C and were given oral terbinafine 500mg OD for 2 weeks, 250 mg OD for 4 weeks, and 250 mg OD for 2 weeks respectively. The groups were compared by CRS scale for efficacy at 0, 2, 4 and 6 weeks. GCAS scale for clinical efficacy at the end of treatment and DLQI scale for quality of life at 0, 2, 4 and 6 weeks of study.

Results

Patients in group B showed significant improvement (95 %) by CRS as opposed to 40 % and 20 % in groups A and C, respectively. Similarly, by GCAS, 30% , 85%, and 5% were declared cured in groups A, B, and C, respectively. Quality of life was

also maximally improved in Group B patients.

Conclusion

Terbinafine, when administered for four weeks is more effective and improves quality of life in cases of recurrent tinea infection.

Keywords

Terbinafine; tinea corporis; tinea cruris; Clinical response scale (CRS); Global clinical assessment scale (GCAS); Dermatological quality of life index (DLQI)

Introduction

With high humidity and temperatures throughout the majority of the year, India's characteristic tropical environment provides ideal circumstances for the development of bacterial and fungal diseases [1]. The most prevalent fungal infection is tinea, which affects 4% of the world's population [2]. Incidences of recurrent tinea corporis and cruris (also known as jock's itch), which are defined as the reappearance of signs and symptoms together with KOH-mounted confirmation within 6 weeks of treatment, have dramatically increased over time [3,4]. Dermatologists have been forced to consider alternatives to the standard two-week oral terbinafine medication in a normal dose of 250 mg OD to combat the threat of tinea cruris and tinea corporis relapses. Most popular amongst them is using oral antifungal at larger dosages or prolonging the course of treatment at recommended dosages [5,6]. Although there is enough data to show the effectiveness of antifungal monotherapy in certain illness cases, there is less information on recurrence cases [7]. Patients suffering from frequent relapses also complain about significant impairment in quality of life [8]. Hence, this study was planned with the aim to compare three distinct oral Terbinafine-based regimens (500mg once a day for two weeks, 250 mg once a day for four weeks, and 250 mg once a day for two weeks) in patients with recurrent Tinea corporis and cruris infection.

Material and Methods

A prospective, randomized, parallel group, open-label comparative study was conducted in the Skin and VD Department of PGIMS, Rohtak between January 2019 and January 2020 to compare the three different terbinafine regimens in terms of efficacy and quality of life amongst the patients with recurrent tinea capitis and cruris infection. The study was initiated after the Institutional Ethical Committee's permission (letter No. IEC/18/pharma0l dated 19/12/2018). A convenient sampling technique was used where all the patients presenting in the department were screened as per the inclusion and exclusion criteria. The inclusion criteria included all patients between 18 and 60 years of age presenting with relapse of tinea infection (defined as recurrence of the disease within 6 weeks of stopping treatment), confirmed clinically as well as by KOH measurement, and willing to give informed consent. Those suffering from infections other than tinea corporis and cruris, intolerant to terbinafine, having any concomitant illness, hepatic or renal disease, and pregnant females were excluded from the study.

Sixty-seven eligible patients were randomized using a computer-assisted program into any of the following three groups by the principle investigator and primary treating clinician in Department of Skin and VD , PGIMS, Rohtak : Group A (Terbinafine 500mg OD for 2 weeks), Group B (Terbinafine 250mg OD for 4 weeks) and Group C (Terbinafine 250 mg OD for 2 weeks. All patients were blinded, out of them, sixty completed the study and only those

were included while computing the results. Five were lost to follow up and two required escape treatment with itraconazole. Study participants were evaluated at the end of 0, 2, 4 and 6 weeks for their response to treatment. The Clinical response scale (CRS) and Global clinical assessment scale (GCAS) scales were used to measure the efficacy of treatment and the Dermatology life quality index (DLQI) for noting the quality of life.

CRS has four grades based on the percentage of clinical improvement. Grade I indicate that the lesions have improved by more than 75% (clinically cured); Grade II indicate that the lesions have improved by 51% to 75% (good response). Grade III means improvement of between 26% and 50% (poor response), and Grade IV means improvement of 25% or less.

GCAS identifies clinical response to the treatment as either healed, mild residual, unchanged or deteriorated lesions. Healed patients were taken as cured.

The DLQI Questionnaire by Finlay and Khan [10] was used to assess the quality of life of patients at the beginning and end of treatment in all the groups. The DLQI has ten questions related to the effect of skin problems on six aspects of life-labelled individual domains: symptoms and feelings (two questions), daily activities (two questions), leisure (two questions), work and school performance (one question), personal relationships (two questions), and treatment (one question). Each question is scored from 0 (not at all) to 3 (very much), indicating the intensity of its impact on individual aspects of life. The total domain score varies from 0 to 3 in domains with one question and from 0 to 6 in domains with two questions. The DLQI is calculated by summing the scores of each question, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The composite score of QOL was recorded in all the patients before drug administration (baseline) and at the ends of 2 weeks (Group A and C) and 4 weeks (Group B).

The results obtained were analyzed statistically using the software SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program

Results and Interpretation

The demographic details of the patients in three groups are summarized in Table 1.The three groups were comparable in terms of age, gender, marital status, literacy, and residential characteristics. It also shows that the recurrence was common in literate, married, male, urban residents above 30 years of age.

Table 1: Demographics of patients suffering from recurrent tinea corporis and cruris in different treatment groups

Variables	Terbinafine (500mg OD * 2 wk) Group A (n=20)	Terbinafine (250mg OD * 4 wk) Group B (n=20)	Terbinafine (250mg OD* 2 wk) Group C (n=20)	*p-value*
Age (Years)	36.4±3.18	36.75±3.10	31.8±1.70	0.371#
Gender				
Male	8 (40%)	13 (65%)	11 (55%)	0.280*
Female	12 (60%)	7 (35%)	9 (45%)	
Marital Status				
Married				
Unmarried	13(65%)	15(75%)	14(70%)	0.788*
	7(35%)	5(25%)	6(30%)	
Education				
Illiterate	7(35%)	5(25%)	3(15%)	0.731*
Literate	13(65%)	15(75%)	17(85%)	
Resident				
Rural	4(20%)	6(30%)	4(20%)	0.716*
Urban	16(80%)	14(70%)	16(80%)	
Co-morbid illness	-	-	-	-

- Age expressed as Mean ± SEM
- #One way ANOVA was applied to calculate p-value
- *Chi-square test is applied

The response in three groups as per the clinical response scale (CRS) is shown in Table 2. It was observedthat group B patients showed maximum efficacy of 90% at 4 weeks of treatment which was also maintained (95%) at 6 weeks of treatment i.e., after 2 weeks of discontinuing the terbinafine treatment. These values are much higher than the response shown by the patients of group A (25% and 40%) and C (30% and 20%) at 4 and 6 weeks respectively. The difference in clinical response was statistically significant at 2, 4 and 6 weeks (p value<0.05).

Table 2: Assessment by clinical response scale in different treatment groups

Evaluation	Terbinafine (500mg OD * 2 wk) Group A (n=20)	Terbinafine (250mg OD * 4 wk) Group B (n=20)	Terbinafine (250mg OD * 2 wk) Group c (n=20)	*p- value** (interGroup)
• **Healed**	6 (30%)	17 (85%)	1 (5%)	**<0.001**
• **Mild residual disease**	8 (40%)	3 (15%)	8 (40%)	0.146
• **Considerable residual disease**	3 (15%)	0	9 (45%)	**0.001**
• **No change**	2 (10%)	0	2 (10%)	0.343
• **Deteriorated**	1 (5%)	0	0	0.362

*Chi-square test

Patients with assessment in the top two categories, that is, healed and mild residual disease, were considered as responders and the same patients were considered cured if they had negative KOH smear. This scale was applied at the end of the treatment in all groups

The number of patients with no relief in signs and symptoms were given escape treatment which was Itraconazole 200mg once daily for 2 weeks. Patients in Group B and Group C did not require escape treatment while 2 patients in Group A required escape treatment. Patients recovered after that.

The Composite DLQI score to assess quality of life in recurrent tinea infection is shown in Table 4. Group A reported 43.70% improvement in composite quality of life score at the end of 2 weeks whereas, improvement in Group B was 91.41 % at end of 4 week and those in Group C was 46.4% at 2 weeks compared to their baseline values.

On intergroup analysis, there was statistically significant improvement in quality of life at the end of 2 and 4 weeks compared to baseline values in Group A, B and C.

On intragroup analysis statistically significant ($p < 0.05$) improvement was seen in all groups. However, there was significant réduction in Group B.

Table 4: Assessment of composite DLQI score in different treatment groups

	Terbinafine (500mg OD * 2 wk) Group A (n=20)		Terbinafine (250mg OD * 4 wk) Group B (n=20)		Terbinafine (250mg OD * 2 wk) Group c (n=20)		*P-value*
	Mean±SEM	% reduction from baseline	Mean±SEM	% reduction from baseline	Mean±SEM	% reduction from baseline	
Baseline	12.70±1.30	-	13.40±1.05	-	15.50±1.39	-	0.270#
Week 2	7.15±1.49	-5.55 (-43.70%)	-	-	8.30±1.01	7.2 (46.4%)	0.528*
Week 4	-	-	1.15±0.46	-12.25 (-91.41%)	-	-	-

- #ANOVA test applied, *Independent t-test

Discussion

The mean age of the patients showing relapse of tinea corporis and cruris in the present study was 34.9 years. This finding is in accordance with a study done by Ahmad S M, et al. who reported patients above 30 years of age comprised more than 75% of total relapse cases [11]. This could be because of increased environmental exposure to the fungus and decreased immunity with age.

Males showed slightly more predominance for the disease than females (53:47) in our study. These results are consistent with the study findings of G. Sentamilselvi et al., on chronic dermatophytosis in India and., Ahmad S M et al., on relapses of cutaneous fungal infection, who had 77.1% and 67.5% of male patients in their respective studies [12,11]. Long working hours outside, tight clothing, and the

anatomy of the scrotum in males might be the reasons for male predominance as compared to females, as described by the researchers.

In the present study, literate people were affected more than illiterate ones. This observation was in agreement with the study by Arishta B et al [13]. We also found more patients from urban areas like the researchers in the study by Ahmed S. M. et al., who reported that patients living in urban areas (56%) were more likely to have a relapse than those living in rural areas [11]. Numerous factors might be contributing to the relapsing fungal infections in urban areas, which include poor housing conditions due to overcrowding causing person-to-person spread and reinfection despite adequate initial control. However, in contrast to our finding, Fatima A et al.'sstudy observed that tinea infections were more common in rural areas (66.6%) as compared to people living in urban areas [14]. The reasons given were that rural areas are inhabited by families living with animal husbandry, which is a source of tinea infections, and these infections are easy to spread in such areas where healthy accommodations are limited as compared to urban areas. Married people were more frequently affected by recurrent tinea corporis and cruris as compared to unmarried people in the present study. Factors that could contribute to the relapse in married couples may include reinfection after the initial cure that occurs in the family due to sharing of infected footwear, towels, clothing, and bedding. The scales shed from the skin contain fungal spores which survive for a much longer period of time in the immediate environment of the patients. Fatima A et al. also reported a higher prevalence of dermatophyte infection in married people (71.5%) than in single people [14].

The present study comparing the efficacy of different oral terbinafine regimens in Group A (500mg once a day for 2 weeks), Group B (250 mg once a day for 4 weeks) and Group C (250 mg once a day for 2 weeks) on the Clinical Response Scale found that Grade I response, considered as clinical cure on more than 75% of improvement in the lesions of recurrent tinea corporis and cruris, was comparable at 2 weeks of treatment. However, it was maximally achieved by the longer-duration treatment groups, i.e., Group B, at the ends of 4 and 6 weeks, and the difference was statistically significant. These findings are consistent with a survey in which Babu PR et al who found that 500 mg once daily terbinafine was effective after 2, 4, and 6 weeks of treatment at 87%, 92%, and 80% on the clinical response scale, respectively [5].

The comparison of efficacy between the groups on the basis of GCAS in the present study revealed that at the end of the treatment period, there were 70%, 100%, and 45% of responders in groups A, B, and C respectively. The number of healed patients was significantly higher with longer-duration of treatment. A study by Majid I et al. found incomplete mycological cure as well as relapseafter standard (2-week) terbinafine therapy in ~~our~~ patients with tinea cruris/corporis irrespective of the body surface area involvement or the causative organism involved between the cured, persisted, or relapse groups[15]. Only 43% of patients had complete clinical and mycological cure after 2 weeks of therapy. A Bhatia et al. who compared terbinafine with itraconazole reported that global clinical response and mycological cure was significantly better in the itraconazole group than the terbinafine group [6].

All groups in the present study showed improvement in quality of life from baseline; however, no statistically significant difference was seen between the groups. Although the group with longer duration of terbinafine treatment showed significant improvement in all 6 aspects of the questionnaire as compared to the groups with increased dose or the standard treatment. A similar study by Sirohi S, et al. compared the safety, efficacy, and QoL of oral terbinafine with Amphoterecin B gel and Sertaconazole cream for the treatment of tinea corporis. It found that the results were comparable and that the difference was statistically insignificant[16].

Limitations

It was a single-center study done on a limited number of patients.

Conclusion

Terbinafine is significantly more efficacious and substantially improves quality of life in recurrent tinea infection cases when given for four weeks instead of two weeks at the same dose of 250 mg once a day as in standard treatment. Therefore, due to the lack of any consensus on treatment of recurrent tinea corporis and cruris, a longer duration of treatment with terbinafine should be considered.

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