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Original Research Article

Evaluation of efficacy and safety of terbinafine and itraconazole in superficial mycoses: a prospective, randomized, controlled and cost-effective analysis study

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ABSTRACT

Background: Superficial mycoses are common worldwide. Dermatophytic infections can greatly affect quality of life. Several newer antimycotic agents, have been reported effective and safe. Hence this study was planned to analyse effectiveness as well as cost effectiveness of these treatments.

Methods: It were a prospective, randomized, parallel, open label, comparative study. Fifty patients were included in the study and divided into 2 groups. They were randomized to receive either oral terbinafine 250 mg or itraconazole 100 mg once daily for 4 weeks. Scaling, erythema and pruritus were rated as clinical score 0 to 3: 0 - absent, 1 - mild, 2 - moderate, and 3 - severe for the above three target symptoms. Total symptom score was assessed. Pruritus was also graded on visual analogue scale (VAS). Mycological cure was assessed by skin scraping with KOH mounts and fungal culture. Clinical efficacy scoring and VAS were assessed before the study and at each follow up visit at 2 and 4 weeks. Patients were followed up for another 4 weeks after completion of the treatment.

Results: There was highly significant decrease $p < 0.001$ in the mean total symptoms scores in both the study groups from baseline. No significant difference in the mean total symptoms score was observed when compared between groups. ADRs were more in terbinafine group.

Conclusions: Both terbinafine and itraconazole are effective and safe against superficial mycoses, but adverse effects are more with terbinafine. Itraconazole was found to be cost effective compared to terbinafine.

Keywords: Superficial mycoses, Terbinafine, Itraconazole, Cost-effectiveness

INTRODUCTION

Superficial mycoses are common worldwide. They are believed to affect 20-25% of world's population and the incidence continues to increase. They are predominantly caused by dermatophytes and the causative species vary with geographic region. Dermatophytic infections do not result in significant mortality, but they can greatly affect quality of life. Dermatophytes constitutes a group of about 40 fungal species that are members of

trichophyton, microsporium and epidermophyton genera and because superficial infection called dermatophytosis, ring worm, tinea respectively.¹ Topical therapy is recommended for a localized infection because dermatophytes rarely invade living tissues. Topical therapy should be applied to the lesion and at least 2 cm beyond this area once or twice a day for at least 2 weeks, depending on which agent is used.² Topical therapies for treatment of superficial dermatoses include terbinafine, butenafine, econazole, miconazole, ketoconazole, clotri-

mazole, and ciclopirox. Topical formulations may eradicate smaller areas of infection, but oral therapy may be required where larger areas are involved or where infection is chronic or recurrent.³ Several newer anti mycotic agents, including sertaconazole, eberconazole, Luliconazole, Amorolfine, itraconazole, terbinafine, and fluconazole, have been reported as effective and safe.¹ A review found that these agents may be similar to griseofulvin for treatment in children with tinea capitis caused by *Trichophyton* species and have the advantage of shorter treatment durations; however, they may be more expensive.⁴

Common systemic antifungal agents used are oral griseofulvin, terbinafine, fluconazole and itraconazole. These agents inhibit the synthesis of ergosterol, a major fungal cell membrane sterol.⁵ Systemic therapy may be indicated for superficial dermatoses that includes extensive skin infection, immune suppression, resistance to topical antifungal therapy, and co morbidities of tinea capitis or tinea unguium. Use of oral agents may lead to adverse effects and requires monitoring.

Terbinafine is an allylamine. It is a synthetic antifungal agent. The drug is well tolerated with low incidence of gastrointestinal distress, head ache and rash. Very rarely fatal hepatotoxicity, severe neutropenia, Stevens-Johnson syndrome or toxic epidermal necrolysis may occur. Fluconazole and itraconazole are synthetic triazole derivative antifungal agents. Itraconazole is the drug of choice in infections due to blastomyces dermatitis, histoplasma capsulatum, coccidioides immitis, paracoccidioides braziliensis and invasive Aspergillosis outside CNS. Itraconazole solution is approved for use in oropharyngeal and oesophageal candidiasis. Anorexia, abdominal cramps, diarrhoea and rash are common with itraconazole. Intravenous itraconazole may lead to congestive heart failure in patients with impaired ventricular function. With higher doses (≥ 600 mg/day) of Itraconazole profound hypokalaemia, adrenal insufficiencies, hypertension, Stevens-Johnson syndrome are observed.⁶

We want to evaluate the efficacy and safety of terbinafine and itraconazole. Treatment of fungal infections is a costly affair. Hence this study is planned to analyse the cost of each treatment and to establish cost effectiveness of these treatments.

METHODS

The study was conducted in the Department of Clinical Pharmacology and Therapeutics, in collaboration with Department of Dermatology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India between July 2017 to July 2019. It was a prospective, randomized, parallel, open label, and comparative study. Study was started after Institutional ethics committee approval. Initially the participants were screened for eligibility into the study. Fifty patients were included in the study after

obtaining written informed consent. Inclusion criteria were Patients of either gender aged between 18-60 years and patients freshly diagnosed of superficial fungal infections. Exclusion criteria were patients hypersensitive to study drugs, pregnant and lactating women, patients having pre-existing renal, liver and cardiac illness and patients already on treatment with topical antifungal agents.

Methodology

All the participants were screened for eligibility into the study. As a part of screening, medical history of the patient was taken, physical examination, clinical examination and routine laboratory tests were conducted. Subjects fulfilling the inclusion and exclusion criteria were recruited into the study. The selected patients were divided into two groups of 25 each and were randomized to receive either oral terbinafine 250 mg daily or oral itraconazole 100 mg once daily. All the study drugs were given for a period of 4 weeks.

The clinical signs and symptoms assessed were scaling, erythema, and pruritus. The signs and symptoms were rated as clinical score 0 to 3: 0 - absent, 1 - mild, 2 - moderate, 3 - severe for the above three target symptoms.¹ Pruritus was graded depending on visual analog scale (VAS) marked by the patient.⁷ Mycological cure was assessed by skin scraping with KOH mounts and fungal culture. Basic investigations (hemogram, renal function tests and liver function tests), skin scraping with KOH mounts and fungal culture were done before and after the study. Patients were asked to come for study visits at 2 and 4 weeks of treatment. Clinical efficacy scoring and VAS were assessed before the study and at each visit. Patients were followed up for another 4 weeks after completion of the treatment. Patients were enquired for any side effects at each visit. Compliance was checked for at each visit. 80% of pill intake was considered compliant. Cost was assessed for each treatment.

Statistical analysis

Data was expressed as mean \pm SD and categorical data in percentage. P value of <0.05 was considered as statistically significant. The differences within groups before and after treatment were assessed using student's paired t-test. The difference between the groups was assessed using unpaired t-test. Power of the study was kept at 80%. Categorical data was analysed using chi square test.

RESULTS

In the present study, total 60 patients were screened. Six patients were screen failures and 54 patients were enrolled into the study. Out of 54 patients, 2 patients were lost to follow up, 2 patients withdrew from the study. A total of 50 patients were included in the final analysis, 25

patients in terbinafine group and 25 patients in itraconazole group. Male patients were 34 and females were 16. Mean age of patients in terbinafine group was 32.16±9.5 and in itraconazole group was 33.4±9.7 years (Table 1).

Table 1: Demographic characteristic.

Parameter	Terbinafine group (n=25)	Itraconazole group (n=25)
Age in years (mean±SD)	32.16±9.5	33.4±9.7
Males	16	18
Females	9	7

In terbinafine group the mean total symptoms score (sum of scores of scaling, erythema and pruritus) before and after study was 6.84±2.1 and 0.80±1.2 respectively (Table 2). In itraconazole group the mean total symptoms score (sum of scores of scaling, erythema and pruritus) before and after study was 6.24±2.37 and 0.80±1.12 respectively (Table 2). There was highly significant decrease (p<000.1) in the mean total symptoms scores in both the study groups.

Table 2: Efficacy parameters before and after the study.

Parameter	Terbinafine group (n=25)		Itraconazole group (n=25)	
	Before	After	Before	After
The mean symptoms score	6.84±2.1	0.80±1.2 [§]	6.24±2.37	0.80±1.12 [§]
VAS score	66±18.9	6.4±5.3 [§]	61.2±28.5	6.4±7.8 [§]
KOH mount and fungal culture +ve	25	5 (80%)	25	8 (68%)

§ - p<0.0001.

There was no significant difference in the mean total symptoms score when compared between groups. The mean percentage (%) improvement in total symptoms score was 78.36±9.07 in terbinafine group and was 79.04±9.22 in Itraconazole group at the end of study (p=0.79).

There was highly significant (p<0.0001) decrease in itching on VAS scale in terbinafine group from the baseline to end of the study. In itraconazole group also highly significant (p<0.0001) decrease in itching on VAS scale was observed compared to baseline (Table 2). The mean itching score on VAS was not significant, when compared between the two study groups.

In itraconazole group, 8 subjects showed positive KOH mounts and fungal cultures at the end of 4 weeks.

Mycological cure rate with itraconazole was 68% where as in terbinafine group 5 subjects showed positive KOH mounts and fungal cultures at the end of 4 weeks. Mycological cure rate with terbinafine was 80% (Table 2).

Two patients developed diarrhoea, 1 patient developed rash and 2 patients developed gastrointestinal disturbance in terbinafine group. In itraconazole group, 1 patient developed rash. But no patient discontinued because of side effects.

The treatment cost in terbinafine group was Rs 660/- per patient per month. Total treatment cost of adverse effects in terbinafine group was Rs. 190. The treatment cost in Itraconazole group was Rs. 600/- per patient per month. Total treatment cost of adverse effects in Itraconazole group was Rs 20. Total treatment cost in terbinafine group was Rs 16, 690 where as in itraconazole group was Rs. 15,020. Hence itraconazole was cost effective compared to terbinafine.

DISCUSSION

Currently topical azoles and allylamines are used for the treatment of cutaneous mycoses. The disadvantage with these drugs is long duration of therapy which leads to poor compliance and a high relapse rate. Some of the newer agents require once daily application and shorter courses of treatment and are associated with lower relapse rate. In the present study, we compared terbinafine with itraconazole in dermatophytosis. There was highly significant decrease (p<000.1) in the mean total symptoms scores in both the study groups from baseline to the end of 4 weeks. In our study, mycological cure rate with terbinafine it was 80% and with itraconazole was 68%. Our results are consistent with the previous studies.⁸⁻¹¹ Bourlond et al compared itraconazole 100 mg/day with ultra-micronized griseofulvin 500 mg/day for tinea corporis or tinea cruris.⁸ He showed that significantly better clinical and mycological outcome with itraconazole after 2 weeks of therapy. In another study terbinafine was compared with griseofulvin (both 500 mg daily for 6 weeks).⁹ They found that mycological cure rate was 87% for terbinafine and 73% for griseofulvin. A double-blind study between itraconazole 100 mg/day and griseofulvin 500 mg/day found itraconazole to be superior to griseofulvin in providing mycological cure.¹⁰

In our study 5 patients in terbinafine group and 1 patient in itraconazole group developed adverse drug reactions. All were mild reactions and did not need discontinuation of therapy. In our study, we had attempted to estimate the cost of treatment with terbinafine and itraconazole as there were no studies on cost effectiveness of each treatment in superficial mycoses. We found that treatment cost was more with terbinafine compared to itraconazole.

CONCLUSION

In conclusion, both terbinafine and itraconazole are effective and safe against superficial mycoses, but adverse effects are more with terbinafine, which add to the cost of the treatment. In our study itraconazole was found to be cost effective compared to terbinafine. But further studies are to be conducted with a greater number of patients.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Chandana T, Saritha C, Sankaraiah P. Comparison of safety and efficacy of luliconazole and other antifungal agents. *Int J Pharma Sci Res (IJPSR)*. 2014;5(1):1-9.
2. Weinstein A, Berman B. Topical treatment of common superficial tinea infections. *Am Fam Physician*. 2002;65(10):2095-102.
3. Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra and piedra. *Dermatol Clin*. 2003;21:395-400.
4. Gonzalez U, Seaton T, Bergus G, Jacobson J, Monzon MC. Systemic antifungal therapy for tinea capitis in children. *Cochrane Database Syst Rev*. 2007:CD004685.
5. Tsunemi Y. Oral Antifungal Drugs in the Treatment of Dermatocycosis. *Med Mycol J*. 2016;57(2):71-5.
6. Brunton LL, Goodman and Gilman's the pharmacological basis of Therapeutics 12th edition, 2011: 1579-1586.
7. Reich A, Heisig M, Phan NQ, Taneda K, Takamori K, Takeuchi S, et al. Visual analog scale: Evaluation of instrument for the assessment of pruritus. *Acta Derm Venereol*. 2012;92:497-501.
8. Boulrond A, Lachapelle JM, Aussems J, Boyden B, Campaert H, Coninex S, et al. Double-blind comparison of itraconazole with griseofulvin in the treatment of tinea corporis and tinea cruris. *Int J Dermatol*. 1989;28:410-2.
9. Cole GW, Strickline G. A comparison of a new oral antifungal, terbinafine with griseofulvin as therapy for tinea corporis. *Arch Dermatol*. 1989;125:1537-39.
10. Panagiotidou D, Kousidou T, Chaidemenos G, Karakatsanis G, Kalogeropoulou A, Teknetzis A, et al. A comparison of itraconazole and griseofulvin in the treatment of tinea corporis and tinea cruris: a double-blind study. *J Int Med Res*. 1992;20:392-400.
11. Sahoo AK, Mahajan R. Management of tinea corporis, tinea cruris and tinea pedis: a comprehensive review. *Indian Dermatol Online J*. 2016;7:77-86.

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