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ORIGINAL RESEARCH

Evaluation of efficacy and safety of oral terbinafine and itraconazole combination therapy in the management of superficial dermatophytosis- A Randomised Clinical Double blinded Trial

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ABSTRACT

Background: Common fungal infections like dermatophytosis are brought on by Trichophyton, Epidermophyton, and Microsporum species. All patients with dermatophytosis should get a combination of systemic and topical antifungal medication, with the exception of those who have localised naive tinea. Study participants took oral terbinafine and itraconazole to see how well they worked together against superficial dermatophytosis.

Materials and Methods: For this randomised clinical trial, 50 people with superficial dermatophytosis were divided into two groups. The study was conducted in the Department of Dermatology's Outpatient Department from December 2021 to May 2022. Treatment in Group I consisted of four weeks on Terbinafine 250 mg OD and 200 mg OD itraconazole, whereas in Group II, just Terbinafine 250 mg OD was given. As a result, the patients were seen every two weeks and given the necessary diagnostics. The statistical analysis was performed using SPSS version 16.0, the Statistical Package for the Social Sciences.

Results: Itraconazole containing group reported a better clinical cure rate than the griseofulvin containing group ($p<0.05$). Neither of the combination showed effectiveness against tinea infections pre-treated with topical steroid containing formulations.

Conclusion: When terbinafine and itraconazole are combined, a greater clinical cure rate is achieved than when terbinafine is used alone.

Keywords: Dermatophytosis,topical antifungal therapy, Tinea,Itraconazole, Topical steroids, Erythema.

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INTRODUCTION

There is a lot of concern for both patients and doctors when it comes to fungal infections, particularly those that manifest on the skin. Infestations of skin fungi, known as dermatophytosis or tinea, are a prevalent problem for people all over the world. An external fungus penetrates the keratinized tissue, where it thrives and causes the condition (skin, hair, nails). Between 20 and 25 percent of people everywhere suffer with tinnitus.[1] Dermatophytosis is often caused by three different types of fungi: Trichophyton, Microsporum, and Epidermophyton.[2] Recently, there has been a shift in the tinea pattern, with an increase in the prevalence of difficult-to-treat resistant, recurring, and chronic dermatophytosis.[3] Various factors such as global warming, hot and humid climate, migration of laborers, increased frequency of wearing tight and synthetic clothing, obesity, sedentary lifestyle, increasing prevalence. Terbinafine, the first-line systemic medicine for dermatophytosis therapy, works by blocking the enzyme squalene epoxidase, which is involved in the manufacture of ergosterol, which is required for the creation of the fungal cell membrane.[4] Itraconazole inhibits 14-demethylase, which produces fungistatic activity, while griseofulvin disrupts microtubule spindle formation, inhibiting fungal cell wall production.[5] The synergistic and cumulative effects of two or more treatments suggest that using a combination therapy of systemic antifungal medications with different mechanisms of action improves the cure rate and helps avoid drug resistance.[6] Systemic antifungal combination therapy with terbinafine and itraconazole for the treatment of dermatophytosis has been the subject of only a small number of research, most of which have focused on its effectiveness rather than its safety. This study was meant to investigate the efficacy of oral terbinafine in combination with either itraconazole and to assess the negative effects of this combination therapy.

MATERIALS & METHODS

50 people with superficial dermatophytosis were divided into two groups in this double-blind, randomised clinical research. The study was conducted in the Department of Dermatology's Outpatient Department from December 2021 to May 2022. Treatment in Group I consisted of four weeks on Terbinafine 250 mg OD and 200 mg OD itraconazole, whereas in Group II, just Terbinafine 250 mg OD was given. As a result, the patients were seen every two weeks and given the necessary diagnostics. The institution's ethics board gave its approval to the trial.

Epi-info programme determined that a sample size of 50 would be necessary to achieve a 95% confidence level, 80% power, and 79% remission rate. Researchers used a random-number generator to split their subjects in half. The patients were assigned at random using a random number table and a basic random sampling method.

Inclusion criteria:

Those over the age of 18 who were diagnosed with Tinea corporis, Tinea cruris, or Tinea faciei and had lesions covering at least half of their body's surface area was included in the research.

Exclusion criteria:

Patients under the age of 18, women who were pregnant or nursing, those who were allergic to terbinafine, itraconazole, or griseofulvin, those who had not taken oral antifungals in the previous month, those with cardiac, renal, or hepatic disease, those with abnormal complete

hemograms, and those with abnormal renal function tests and liver function tests were all excluded from this study.

Methodology:

Patients were randomly split into two groups of 25 by random selection using a random number table; Group I got oral terbinafine 250 mg OD with oral itraconazole 200 mg OD PO for four weeks, whereas Group II received oral terbinafine 250 mg OD for four weeks. Patients were graded on the severity of clinical parameters, namely erythema, using a four-point scale: 0=none, 1=mild, 2=moderate, and 3=severe.[7]

Complete blood count, liver function test, and electrocardiography (ECG) were repeated at the beginning, middle, and end of therapy for the terbinafine with itraconazole group, and for the terbinafine group only at the beginning and middle of treatment. No antifungal creams were used to any group. Each group received antihistamines that did not put people to sleep as well as liquid paraffin as part of the palliative care they received. Patients were asked about any unintended consequences of treatment. Patients were followed every two weeks for a maximum of eight weeks (four weeks after therapy or cure, whichever occurred earlier). They were followed up on during treatment and for an additional four weeks thereafter. It was decided to use the "Rule of 9" to calculate body surface area (BSA).

The following were the outcome measurements:

- Cured (complete clinical resolution of all lesions).
- Partially cured (improvement of more than 50% in the affected total BSA) and
- Failure (increase in severity of the lesions or no change in the lesions after four weeks after initiating antifungal drugs or improvement of less than 50% in the involved total BSA).

Statistical Analysis:

The information was aggregated in an Excel file and sent to SPSS (Version 22.0). Descriptive analyses were performed to compare the baseline characteristics of the study participants in the two groups. To compare the mean values of the quantitative variables, the student t-test was used. The categorical variables were analysed using the chi-square test. Statistical significance was defined as a p-value of 0.05.

RESULTS

Table 1: Baseline details of Group I and Group II (n=50)

Characteristics	Group I (n=25)	Group II (n=25)	Total (n=50)	p-value
Age in years* (mean±SD)	35.32±10.45	37.16±10.71	36.47±11.03	0.70
Age group (18-40years) n(%)	28(56)	22(44)	50 (100)	0.71
Male n(%)	9(31)	11(39.3)	20(40)	0.59
Female n(%)	20(69)	10(60.7)	30 (60)	
Disease duration less than six months, n(%)	22(88)	21(87)	43(86)	0.48
Topical application prior to the visit to OPD, n(%)	22(88)	19(76)	41(83)	0.83
Topical steroid application prior to the visit to OPD, n(%)	13(52)	11(44)	25(50)	0.31
Systemic therapy, n(%)	5 (20)	7(25)	12(48)	0.37
Co-morbities, n(%)	5 (20)	3 (10)	8(16)	0.11
Family h/o of dermatophytosisn (%)	18(72.1)	13(52)	31(62)	0.53

As per [Table 1] a total of 50 participants were enrolled in the study with tinea infections which mainly affected the trunk, groin, and face. Participants' average ages were determined to be 36.47± 11.03 years. According to statistics, 66.9% of the study's participants were between the ages of 18 and 40, with 64.4% of them being female overall. 75.8% of the patients had an illness duration of less than or equal to six months, it was observed. The majority of individuals (72.9%) had previously used topical medications, and 43.2% had done so before their first visit to the OPD. Meanwhile, it was discovered that 20.1% of patients had used systemic medicines prior to their first visit to our OPD. The research also revealed that 54.1% of current patients had a history of related symptoms.

Table 2: Comparison between the erythema score and scaling score of baselines at 4th and 8th weeks in each group.

Groups	**Erythema score (mean±SD)**			**Scaling score (mean±SD)**		
	At 1stvisit	**4weeks**	**8weeks**	**At 1stvisit**	**4weeks**	**8weeks**
*Group I (n=29)	2.14± 0.57	0.83±0.71 (p<0.001)	0.77±0.94 (p<0.001)	2.55± 0.57	0.85±0.78 (p<0.001)	0.79±0.90 (p<0.001)
*Group II(n=28)	2.29± 0.63	1.39±0.786 (p<0.001)	1.21±0.78 (p<0.001)	2.50± 0.60	1.37±0.951 (p<0.001)	1.35±0.91 (p<0.001)
Total (n=57)	2.26± 0.58	1.15±0.78 (p<0.001)	1.36±0.91 (p<0.001)	2.53± 0.60	1.15±0.90 (p<0.001)	1.17±0.96 (p<0.001)
+Group I vs II (p-value)	0.73	0.06*	0.03*	0.74	0.03*	0.02*

As per [Table 2] shows that at four and eight weeks, erythema and scaling score were significantly improved as compared to the baseline values in both the groups, slightly higher improvement noted in the Group I. This finding suggests, in an indirect manner, that the medication administered improved the clinical characteristics of the patients at the end of the fourth and eighth weeks in both groups. After eight weeks, there was no significant difference in the mean erythema score between the two groups. However, there was a substantial improvement in the mean scaling score for Group I compared to Group II.

Table 3: Comparison of association between the disease duration and topical steroid application with the treatment outcome in group I and group

Variables	**Parameters**	**Group I(n=25)**		**Group II(n=25)**		**p-value**
		(n)	**(%)**	**(n)**	**(%)**	
At the end of fourth weeks	Complete cure	5	20	5	20	0.01
	Partial cure	17	68.2	5	20	
	Failure	3	12	15	60	
At the end of eight weeks	Complete cure	10	40	6	24	0.01
	Partial cure	13	52	6	24	
	Failure	2	8	13	52	

[Table 3] shows that after four weeks, five (31%) members of group I and five (17.9%) members of Group II had fully recovered. Eight weeks later, 10 (48.6%) patients in Group I and 6 (21.2%) patients in Group II had fully recovered. The itraconazole-containing group exhibited greater clinical cure rates than the non-statistically significant group at 4 and 8 weeks. At the conclusion of four weeks, there were 58.2% and 17.2%, respectively, of group I and Group II patients who were only partly healed. At the conclusion of eight weeks, group

I had a partial cure rate of 44.2%, whereas Group II had a partial cure rate of 21.8%. The rates of failure for the combined treatments in Groups I and II after eight weeks were 6.6% and 57.4%, respectively.

DISCUSSION

Although the percentage of clinical cure rates in both groups was lower than in previous similar studies, the clinical cure rate was greater in this experiment when terbinafine and itraconazole were combined than when terbinafine alone was administered. This shows that a recent combination of systemic medications has reduced the fungal organism's susceptibility. When compared to terbinafine, the research group that included itraconazole and terbinafine had a higher cure rate. Indication for systemic therapy in dermatophytosis are extensive tinea corporis, involvement of multiple sites, recurrent or chronic dermatophytosis, immunocompromised patients, non-responsive to topical antifungals, tinea involving scalp, palms and soles.[8,9] Patients with chronic or recalcitrant cases and tinea infections pre-treated with topical steroid containing formulations need treatment for a longer duration than the naïve tinea.[10,11] Treatment options for tinea include the use of systemic antifungals such terbinafine, griseofulvin, itraconazole, and fluconazole. Out of these, the commonly prescribed drugs are itraconazole and terbinafine as the other two require a longer duration. Terbinafine is the only fungicidal drug among these. In another study, by Singh SK et al., reported predominance of male patients.[12] This shows an increasing trend about the concern regarding cosmetologically impact in dermatological diseases among women. It may also be due to the unbearable symptoms.

The illness duration was shorter than or equivalent to six months in 75.4% of the cases. The similar period was reported by Sharma P et al.[7] In our investigation, the clinical cure rate of terbinafine with griseofulvin was just 21.4%. Singh S et al., reported a clinical cure rate of 28.8% which is almost comparable to our study.[13]

CONCLUSION

When terbinafine and itraconazole are used together, the clinical cure rate is higher than when either drug is used alone, but the percentage of patients who experience a cure is less. When applied to tinea infections that had already received topical steroid-containing formulations, neither combination was successful. The improper use of topical steroid-antifungal medicines must be made known to general practitioners. Public education on general tinea prevention techniques and how to treat family members may also help to reduce the infection load.

REFERENCES

1. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. Mycose. 2008;51:02-15.
2. Rajabian A, Hosseinzadeh H. Dermatological effects of nigella sativa and its constituent, thymoquinone. In: Preedy VR, Watson RR, editors. Nuts and Seeds in Health and Disease Prevention. San Diego, CA: Elsevier; 2020. Pp. 329–55.
3. Dogra S, Uprety S. The menace of chronic and recurrent dermatophytosis [4] in India: Is the problem deeper than we perceive? Indian Dermatol Online J. 2016;7(2):73-76
4. Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. J Am Acad Dermatol. 2019;80(4):853-67
5. Gupta AK, Mays RR, Versteeg SG, Piraccini BM, Shear NH, Piguet V, et al. Tinea [9] capitis in children: A systematic review of management. J Eur Acad Dermatol Venereol. 2018;32(12):2264-74.
6. Johnson MD, MacDougall C, Ostrosky-Zeichner L, Perfect JR, Rex JH. [10] Combination antifungal therapy. Antimicrob Agents Chemother. 2004;48:693-715.

7. Sharma P, Bhalla M, Thami GP, Chander J. Evaluation of efficacy and safety of oral terbinafine and itraconazole combination therapy in the management of dermatophytosis. J Dermatolog Treat. 2020;31(7):749-53.
8. Gupta AK, Chaudhry M, Elewski B. Tinea corporis, tinea cruris, tinea nigra, and [12] piedra. Dermatol Clin. 2003;21:395 400.
9. Ellis D, Watson A. Systemic antifungal agents for cutaneous fungal infections. [13] Aust Prescr. 1996;19:72-75.
10. Janaki VR. Therapeutic options in mycoses. In: Sentamilselvi G, Janaki VR, [14] Janaki C, editors. The Hand book of Dermatomycology & Colour Atlas. 1st ed.. India: Sentamilselvi; 2006. Pp. 61-82
11. Thursky KA, Playford EG, Seymour JF, Sorrel TC, Ellis DH, Guy SD, et al. [15] Recommendations for the treatment of established fungal infections. Intern Med J. 2008;38:496-520.
12. Singh SK, Subba N, Tilak R. Efficacy of terbinafine and itraconazole in different [16] doses and in combination in the treatment of tinea infection: A randomized controlled parallel group open labeled trial with clinico mycological correlation. Indian J Dermatol. 2020;65:284-89
13. Singh S, Anchan VN, Raheja R. Futility of combining griseofulvin and terbinafine in current epidemic of altered dermatophytosis in India: Results of a randomized pragmatic trial [Internet]. medRxiv. 2019.Pp. 19007617.