Original Article

Comparative study of efficacy of Terbinafine 500mg vs Terbinafine 250mg and Itraconazole 200mg in the treatment of dermatophytosis.

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Abstract

Background: Now a days superficial fungal infections become endemic in a hot humid region/tropic region like Bangladesh. In outpatient department of dermatology most of the patients come with dermatophytic infection. Most of them are maltreated or inadequately treated. We, dermatologist, are facing difficulties in treating these patients.

Materials and Methods: In this study, we tried to find out the effective doses and duration of antifungal drugs Terbinafine and Itraconazole.

Result: Total 92 patients with dermatophytosis of either sex aged 22-60years without any significant systemic diseases were included in this study. The patients were randomly divided into two groups; Group A and Group B. Group A was treated with Terbinafine 500mg daily and Group B was treated with combination of Terbinafine 250 mg & Itraconazole 200mg daily. Duration of treatment was for 6weeks.Itraconazole and Terbinafine containing combined groups showed significantly higher cure rates than terbinafine only groups both at 4 and 8 weeks ($P < 0.001$).

Conclusion: combination of daily Terbinafine 250mg with Itraconazole 200mg was more efficacious than Terbinafine 500mg

Key words: Dermatophytosis, Terbinafine, Itraconazole
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Introduction:

Superficial fungal infections are a worldwide problem that affects more than 20%–25% of the population. [5] Among the various classes of cutaneous mycoses, dermatophytes are the most common causative agents. Certain parts of the body, namely intertriginous areas (axillae and groins) are more susceptible to the infections since they provide favorable media for the fungi to grow .[8] The traditional division of ringworm i.e.(Tinea capitis, Tinea faciei, tinea corporis, tinea cruris, t mannum, ,t unguium), according to the site of the body infected is used because it is of considerable merit in terms of diagnosis

and management.[6] True to its more common name, ringworm, this cutaneous fungal infection has a classical appearance of a central clearing that is surrounded by an active border of redness and scaling.[8].The clinical diagnosis of a dermatophyte infection can be confirmed by microscopic detection of fungal elements, by identification of the species through culture, or by histologic evidence of the presence of hyphae in the stratum corneum.[5] Multiple systemic and topical antifungal agents are available to treat dermatophytoses of skin, hair and nails .[5] Topical agents provide safe, cost-effective therapy for limited superficial fungal infections. When considering the use of an oral antifungal agent, factors include the type of infection, organism, spectrum, pharmacokinetic profile, safety, compliance, age, and cost.[4] Five main systemic agents for superficial dermatologic indications are available: (1) terbinafine, (2) itraconazole, (3) fluconazole, (4) griseofulvin, and (5) ketoconazole.[7]. The oral antifungals exert their effect by interfering with the enzymes involved in the manufacture of ergosterol, a crucial component of the fungal cell membrane.[7] Terbinafine is a fungicidal drug and acts by inhibiting the enzyme squalene epoxidase which converts squalene to lanosterol. Itraconazole is basically a fungistatic drug that acts through inhibition of the enzyme 14α-demethylase. Many dermatologists have started using higher doses and combination regimens of antifungals to treat fungal infection. However, such regimens have not been validated.[1,2] Hence, in this study we decided to evaluate the commonly used systemic antifungal drugs ; terbinafine and itraconazole.

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Materials and Methods

A Non experimental longitudinal comparative study was conducted in the

department of Dermatology and Venereology at ZH Sikder Women's Medical College Hospital, Dhaka from September 2020 to September 2021 among the patients suffering from Dermatophytosis. Patients were selected by taking complete history and diagnosed clinically and microscopically. It was a Judgmental sampling .Out of 100 patients 28 patients missed during the treatment period and follow up. Therefore only 92 patients was taken, out of which 46 patients was treated with double dose of Terbinafine 250 mg. and 46 patients was treated with oral Terbinafine 250 mg & Itraconazole 200 mg combined for 6 weeks. Follow up was done in every 2 weeks till 8weeks. After informed written consent, the patient's history ,clinical examination ,patients were evaluated on the basis of three parameters: Cutaneous Lesions, Pigmentation and Pruritis. Each parameter was graded on a 4-point scale (0=absent, 1=mild, 2=moderate and 3=severe). Each parameter was graded with a 10cm long visual analog scale (Figure 1) under direct supervision of the dermatologist (Score 0 on the visual analog scale=absent, scores 1-3=mild, 4-7=moderate and 8-10=severe.

Figure 1: Visual analog scale.

Results

This clinical trial was conducted in the Department of Dermatology and Venereology, Zainul Haque Sikder Women's Medical College & Hospital at Rayerbazar, Dhaka between the periods of September 2020 to September 2021 for duration of 12 months. The study was conducted to find out the comparison of efficacy Terbinafine vs Terbinafine & Itraconazole in the treatment of Dermatophytosis .Total of 92 patients of dermatophytosis of age group 16-67 years were analyzed. Patients were diagnosed clinically by physical examination and fungal microscopic examination which was positive on baseline visit and became negative on subsequent visits. They were randomized into two groups, Group-A (n=46) and Group-B (n=46). Group A was treated by Terbinafine 500mg and group B was treated by combination of Terbinafine 250mg & Itraconazole 200mg . All patients completed 8 weeks study period were reviewed after 2nd , 4th , 6th and 8th week.

Table-1: Distribution of patients according to sex:

Sex	Group-A (n=46)	Group-B (n=46)	p value
Male	20 (43.5%)	25 (54.3%)	0.404
Female	26 (56.5%)	21 (45.7%)	
Total	46 (100.0)	46 (100.0)	

Chi-square test was done to measure the level of significance, ns= not significant

Figure within parentheses indicated in percentage

Table-1 shows the distribution of patients according to sex. In Group-A female was predominant than male which was 26 (56.5%) cases and 20 (43.5%) cases respectively. In Group-B male was predominant than female which was 25 (54.3%) cases and 21 (45.7%) cases respectively. The difference between these two group was not statistically significant. (p value >0.05)

Table-2: Distribution of patients according to age group

Age (in years)	Group-A (n=46)	Group-B (n=46)	p value
16 – 22	05 (10.9%)	04 (8.7%)	
23 – 32	13 (28.3%)	12 (26.1%)	
33 – 42	12 (26.1%)	15 (32.6%)	0.968
43 – 52	08 (17.4%)	07(15.2%)	
>52	08 (17.4%)	08 (17.4%)	
Total	46 (100.0%)	46 (100.0%)	
Mean ± SD	38.85 ± 13.95	38.50 ± 12.47	

Chi-square test was done to measure the level of significance, ns= not significant

Figure within parentheses indicated in percentage

Table-2 shows the distribution of patients according to age Group-A majority of the patients were in the age group of 23-32 years which as 13 (28.3%) cases followed by 16-22 years were 05 (10.9%) cases, 33-42 years were 12 (26.1%) cases, 43-52 years were 08 (17.4%) cases and >52 years were 08 (17.4%) cases respectively. In Group-B majority of the patients are in the age group 33-42 years 15(32.6%) followed by 16-22 years 04 (8.7%), 23-32 years 12 (26.1%),43-52years 07 (15.2%) and >52 years 08 (17.4%) cases respectively. The difference between the ages of the two groups was not significant. (p value >0.05)

Table-03: Frequency of the scores at baseline visit.

Scores	Cutaneous lesions		Pigmentation		Pruritus	
	Group-A	Group-B	Group-A	Group-B	Group-A	Group-B
0(absent)	0	0	0	2	0	0
1 (mild)	0	0	12	11	1	0
2 (moderate)	18	10	34	26	22	9
3 (severe)	28	36	0	7	23	37

Table-4: Frequency of the scores in the 8th week.

Scores	Cutaneous lesions		Pigmentation		Pruritus	
	Group-A	Group-B	Group-A	Group-B	Group-A	Group-B
0(absent)	24	41	2	7	37	39
1 (mild)	19	2	36	38	8	6
2 (moderate)	3	3	8	1	1	1
3 (severe)	0	0	0	0	0	0

During baseline visits, majority of patients in Group-A suffered from severe Cutaneous lesions and Pruritus but moderate Pigmentation was more frequently seen. Similar findings were evident for Group-B as well. Group-B saw highest frequency of severe scores in two parameters. During the 8th visit, Group-B showed higher improvement rates as compared to Group-A. Group-B had higher frequency of score 0 in all three parameters

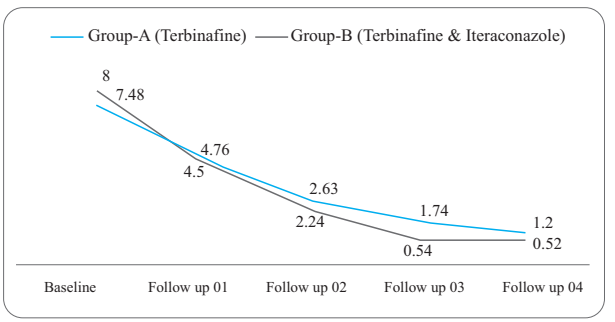


Figure 1: Comparison of Cutaneous lesions scores for the two medications.

The mean Cutaneous lesions scores of the two drugs were nearly equal for the first two visits but during the final visits (8th week), Cutaneous lesions score for Group-A (Terbinafine) was 1.2 while that of Group-B (Terbinafine & itraconazole) was 0.52. Overall, differences at 8th week from the baseline scores for Group-A and B were 6.28 and 7.48 respectively (Figure 2).

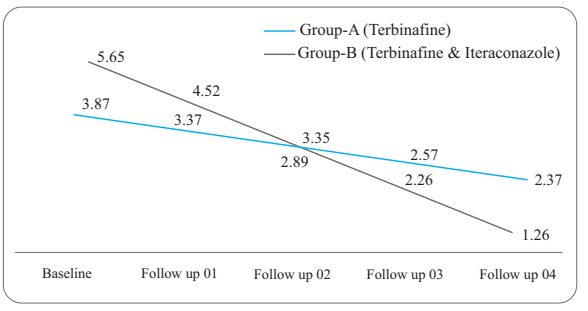


Figure 2: Comparison of Pigmentation scores for the two medications.

Initially, the mean Pigmentation score for Group-A (Terbinafin) was 3.87 and Group-B (Terbinafin & itraconazole) was 5.65. The score for Group-A decreased dramatically during the 4th week (with a difference of 0.98) where as Group-B showed a difference of 2.3 in that week. The scores decreased progressively for the two drugs for the next two weeks and finally at week 8, the scores for Group-A and B were 2.37 and 1.26 respectively. Group-B showed an overall difference of 4.39 while Group-A showed only a difference of 1.5 from the baseline visit (Figure 3).

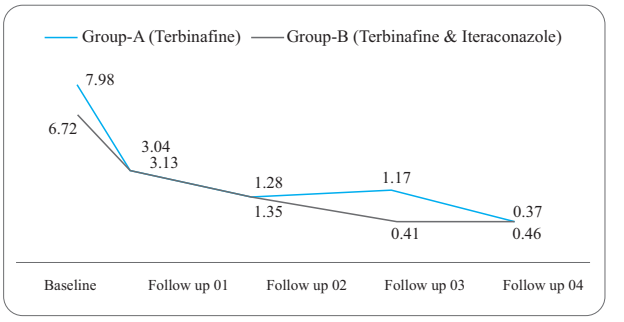


Figure 3: Comparison of Pruritus scores for the two medications.

The baseline scores for Pruritus scores were 6.72 for Group-A (Terbinafin) and 7.98 for Group-B (Terbinafin & itraconazole). At the end of the 8th week, the differences in the scores were 6.26 for Group-A and 7.61 for Group-B (Figure 4).

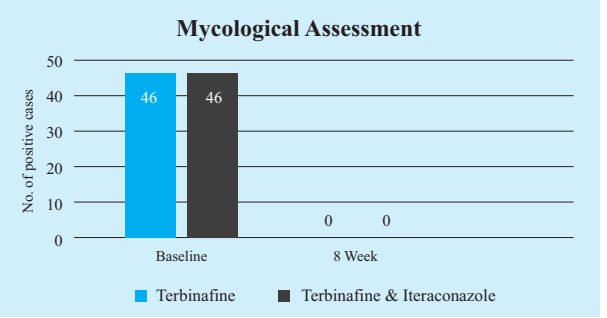
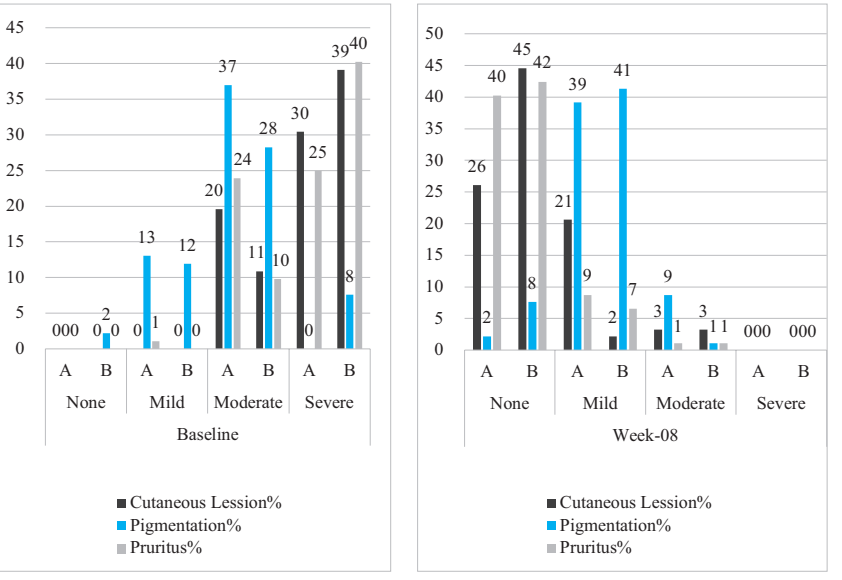


Figure 4: Comparison of Mycological cure in both the groups

Mycological assessment at baseline, all the patients were KOH positive (hyphae seen), and at the completion of therapy, both the groups showed 100% KOH negative (hyphae not seen), as depicted in Figure 5.

In Cutaneous Lesion clinical response rate of Group-B at 8th week was 45%, whereas, of Group-A was 26% patients were none Cutaneous Lesion. There is slight more increase in clinical response rate in Group-B than of Group-A. In Pigmentation clinical response rate of Group-B at 8th week was 41%, whereas, of Group-A was 39% patients were mild Pigmentation. There is slight more increase in clinical response rate in Group-B than of Group-A and In Pruritus clinical response rate of Group-B at 8th week was 42%, whereas, of Group-A was 40% patients were none Pruritus. There is slight more increase in clinical response rate in Group-B than of Group-A. Finally there was a significant decrease in the clinical score beginning from baseline to 8th week in both the groups. If we compare the clinical score of both the groups after 8th week, there is slight more reduction of clinical score in Group-B than Group-A.



Discussion

Dermatophytosis, are the most common fungal infection worldwide. Transmission is mostly by direct contact with infected animals, humans or contact with fomites.

Ninety-two patients diagnosed of dermatophytosis on history and examination was recruited as per inclusion criteria. They were divided by using random number table into group A and group B. Oral Terbinafine was given to group A in oral Terbinafine 250 mg two tablets daily. Group B were given oral combination Terbinafine 250 mg & Oral Itraconazole 200 mg for 6 weeks. Patients were followed up on 2nd , 4th,6th and 8th week and assessed for the efficacy . A detailed analysis revealed that the disease was common in males and females both, the male to female ratio being 0.95:1, i.e., 48.9% were males and 51.1% were females (Group-A: 0.76:1, Group-B: 1.19:1).Which is not supported by previous study.[3] The mean age of the sample was 38.67±13.16 years (Group-A: 38.85±13.95 years and Group-B: 38.50±12.47 years). which is similar to that of the previous studies.[2] Mahajan *et al.* also reported mixed tinea corporis and cruris infection as the commonest form.[8] Microscopic examination conducted only skin. Hyphae was present on Microscopy at only baseline and later follow up weeks hyphae was absent.

In our study we have found combination of Terbinafine 250 mg with Itraconazole 200mg is more efficacious then double dose of Terbinafine 250mg. Terbinafine and other allylamines inhibit squalene epoxidase, leading to accumulation of squalene and a subsequent deficiency of ergosterol. This deficiency of ergosterol leads to the fungistatic action that is associated with terbinafine use.[8] Itraconazole inhibits the CYP-dependent enzyme

lanosterol 14α demethlyase, with resultant inhibition of the conversion of lanosterol to ergosterol.Because of this mechanism of inhibition these drugs are associated with a fungistatic action.[8]The mean clinical cutaneous lesions score at baseline was 7.74±1.13 (Group-A: 7.48±1.30 and Group-B: 8.00±0.80) and 8th week was 0.86±1.57 (Group-A:1.20±1.5 and Group-B: 0.52±1.5). There was significant decrease in the clinical score beginning from baseline to 8th week in both the groups. If we compare the clinical score of both the groups after 8th week there is slight more reduction of clinical score in Group-B than of Group-A. There were statistically significant at 8th week with p value being less than 0.05. The mean pruritus score at baseline was 7.35±1.63 (Group-A: 6.72±1.82 and Group-B: 7.98±1.13)and 8th week was 0.39±1.05 (Group-A: 0.46±1.1 and Group-B: 0.37±1.1). There was significant decrease in the clinical score beginning from baseline to 8th week in both the groups. If we compare the clinical score of both the groups after 8th week there is slight more reduction of clinical score in Group-B than of Group-A and statistically insignificant at 8th week with p value being greater than 0.05. The mean clinical pigmentation score at baseline was 4.76±2.09 (Group-A: 3.87±1.12 and Group-B: 5.65±2.40) and 8th week was 1.82±1.15 (Group-A: 2.37±1.1 and Group-B: 1.26±0.9). There was significant decrease in the clinical score beginning from baseline to 8th week in both the groups. If we compare the clinical score of both the groups after 8th week there is slight more reduction of clinical score in Group-B than of Group-A. There were statistically significant at 8th week with p value being less than 0.05.Our study outcome is consistent with many study and sometimes is not compatible with other study. There is compelling evidence that itraconazole is the preferred agent for Terbinafine resistant *Trichophyton* infections.[12,13,14] Majid *et al.* reported a cure rate of 65% with terbinafine 250 mg daily after 2 weeks.[9] Satyendra et al. found Itraconazole is more effective than terbinafine.[3] Babu *et al.*, 80% of patients showed more than 75% improvement with terbinafine 500 mg daily.[10]

Hence,the facts of this study stand in the vicinity to the outcome of other previous studies with minor deviation to some of them.

Conclusion

Our study demonstrated that combination of daily Terbinafine 250mg with Itraconazole 200mg was more efficacious than Terbinafine 500mg daily. Our study had some limitations as its small sample size and short duration of follow-ups, and use of same doses among all patients although variation in the weights of the patients. Follow up for longer duration to evaluate any relapse couldn't be done due to financial and social constrain

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