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Comparison of the Efficacy of Terbinafine versus and Co-Administration of Terbinafine and Fluconazole in Patients of Tinea Corporis

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Abstract **Original Research Article**

Background: Dermatophytosis management is difficult in Bangladesh, and there have been reports of systemic antifungals being used at greater doses. However, there have been numerous reports of increased treatment failures with terbinafine at standard dosage, consequently we performed this study to compare the efficacy and safety of terbinafine at high dose with terbinafine fluconazole at 150mg weekly dose. In both arms, topical ciclopirox olamine was used. ***Objectives:*** The aim of the study was to compare of the efficacy of terbinafine versus and co-administration of terbinafine and fluconazole in patients of tinea corporis. ***Methods:*** This was randomized, open label, comparative study where 80 patients with tinea corporis et cruris infection were included. Patients were either prescribed terbinafine 250mg twice a day or Terbinafine 250mg daily and Fluconazole 150mg weekly. Efficacy was assessed based on complete, clinical and mycological cure rate. Safety was assessed by evaluating adverse events and monitoring liver function of patients***. Results:*** Total 80 patients completed the study with 40 in each group. 81.5% patients achieved complete cure in Terbinafine and Fluconazole group compared to 73.9% patients in Terbinafine group. At the end of 6 weeks, there was a statistically significant improvement (p value<0.05) in the total symptom score (erythema, scaling, and pruritus) in Terbinafine as well as in terbinafine and fluconazole compared to baseline. None of the patients showed any significant side effect in both groups. No changes in liver function were observed in both the groups. ***Conclusion:*** This study shows that the high dose of terbinafine and Co-administration of standard dose of terbinafine fluconazole along with CPO is effective and safe in management of tinea corporis et cruris.

Keywords: Terbinafine, fluconazole, Tinea Corporis.

INTRODUCTION

Trichophyton, Microsporum, and Epidermophyton-induced dermatophytosis is the most common fungal infection, affecting 20%–25% of the global population with different geographic distribution [1, 2]. In recent years, there has been a rapid increase in occurrences of dermatophytosis and unusual presentation due to Bangladesh's hot and humid climate [3, 4]. Furthermore, the suggested treatment of regularly prescribed antifungal medications does not appear to be applicable in the current circumstance, resulting in treatment failures and relapses when administered in normal doses and for standard time [5]. As a result, in order to overcome these problems, dermatophytosis care is becoming increasingly subjective [6, 7]. Furthermore, various criteria such as concurrent involvement of a

large body area, hair follicles, and a history of treatment failures, recurrences, and relapses influence the choice of therapy. Combination treatment is a well-established concept that involves combining the synergistic and additive effects of two or more medications in order to improve therapeutic efficacy and overcome drug resistance. [8] Murlidhar *et al*. [10] and Sahoo *et al*. [9]. In their extensive evaluations, the authors suggested using a combination of topical and systemic antifungals to treat individuals with big lesions or resistant tinea infections. The authors also stated that when employing combination therapy, medications from two different classes should be utilized to provide broader coverage, synergistic or additive activity, and to limit the possibility of resistance. Terbinafine is regarded a first-line medication for the treatment of dermatophytosis due to its favorable mycological and pharmacokinetic profile [11]. It works by blocking the enzyme squalene epoxidase, which prevents ergosterol formation [12]. Till recent years, the drug was consistently effective with cure rates of >90% achieved at doses of 250 mg once a day for two weeks [11, 12]. But recently, due to the overuse of the drug, there has been an increase in the incidence of terbinafine resistance resulting in increasing numbers of clinical failures and relapses [13, 14]. Hence it is advisable to use higher dose of terbinafine as seen in an article by Murlidhar *et al*. [10]. In a recent study, Terbinafine was reported to be efficacious and safe in the management of dermatophytosis at higher doses of 500 mg/day [15]. Fluconazole is another antifungal drug which acts by inhibiting ergosterol synthesis. It has shown good results in the treatment of dermatophytosis at doses of 100 mg once a day for two weeks and with 200 mg once a day for seven days [16, 17]. But due to frequent relapses at short intervals, some physicians in Bangladesh have used it in doses of 200 mg once a day for prolonged periods [7, 18]. High dose of fluconazole may not be beneficial due to non-linear pharmacokinetic property.10 Ciclopirox Olamine (CPO), a hydroxypyridone derivative has been recently approved in Bangladesh. It differs in structure and mechanism of action from the other known antifungal agents [19]. It acts through the chelation of polyvalent metal cations, such as ferric (Fe3+) and aluminium (Al3+), thereby causing inhibition of metal-dependent enzymes (cytochromes, catalase, and peroxidase) leading to the disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membrane [20]. It also alters membrane permeability causing blockage of intracellular transport of precursors. Due to widespread resistance to various antifungal agents and a high relapse rate when used in conventional doses, there is a need to find an effective first-line therapy for the management of dermatophytosis to achieve the maximum results with fewer relapses. Some recent trials compared the efficacy of terbinafine and fluconazole but in standard doses and duration [16, 21]. A combination of fluconazole and terbinafine has recently been studied [22], indicating the requirement for either a high dose or a combined dose of multiple systemic antifungals in contemporary conditions in Bangladesh. However, no studies have been conducted to compare high doses of terbinafine to conventional doses of fluconazole. As a result, the current study was designed to examine the efficacy and safety of a high dose of oral terbinafine and CPO vs a conventional dose of fluconazole and terbinafine along with CPO in the treatment of tinea corporis et cruris.

MATERIALS AND METHODS

It was a prospective, observational study conducted in the dermatology outpatient of Shahid Syed Nazrul Islam Medical College, Kishorganj, Bangladesh. Clinically confirmed cases of tinea corporis et cruris were recruited for the study and followed up for 8 weeks, till the completion of their treatment. All consenting patients, in the age group of 14-69 years, who were diagnosed by the dermatologist as suffering from tinea corporis et cruris were included in the study, irrespective of the presence and extent of dermatophytosis in other regions of the body. Patients who were pregnant, lactating, non-consensual, as well as those who had a history of anti-mycotic treatment within 2 weeks prior to baseline visit were excluded from the study. The patients were randomly allocated either to Terbinafine 250 mg twice a day or Terbinafine 250 mg once a day and fluconazole 150mg weekly for four weeks. Both the groups received additional topical Ciclopirox Olamine cream for six weeks along with antihistamines.

RESULTS

A total of 80 patients were randomly assigned treatment and included in the study. Forty patients were treated with Terbinafine and 40 with terbinafine and fluconazole. The demographic profile of patients, the diagnosis and the skin scraping for fangus (SSF) reports in both the groups. The average age of the patients was 38.28 and 33.25 years, respectively, in Terbinafine and Terbinafine and fluconazole. There were 14 males (35.0%) and 26 females (65.0%) in Terbinafine, while Terbinafine and fluconazole had 13 males (32.5%) and 27 females (67.5%). All the patients were co- prescribed CPO and anti-histamines. At the end of four weeks, there was a statistically significant improvement (p value<0.05) in the total symptom score (erythema, scaling, and pruritus) in terbinafine as well as in terbinafine and fluconazole compared to baseline [Figure 1]. The significant improvement started from 0-2 weeks and then persisted till the end of the treatment in both the groups. On comparing the groups, there was a significant improvement in the total symptom score at the end of four weeks (p value<0.05) but no statistically significant change was observed at the end of 6 weeks (p value>0.05) complete cure was achieved in 73.9% and 81.5% in Terbinafine and terbinafine and fluconazole respectively at the end of four weeks (Figure 2). At the end of four weeks, the clinical cure rate was significantly better in the combination group as compared to the terbinafine group. But no statistical difference was

observed at the end of six weeks. Tolerability and None of the patients showed any significant side effect in both Combination and Terbinafine groups. No significant change in LFTs was also observed in both the groups during the study period.

Table-1: Demography, diagnosis and culture report in both the groups

Age Distribution	Terbinafine		Terbinafine and Fluconazole	
	n=40	%	n=40	%
14-30	18	45.0	19	47.5
31-40	10	25	9	22.5
41-50	6	15	7	17.5
51-60	4	10	3	7.5
61-70	2	5	2	5
Sex Distribution				
Male	14	35.0	13	32.5
Female	26	65.0	27	67.5
Marital Status				
Married	30	75.0	29	72.5
Unmarried	10	25.0	11	27.5
Occupation				
Service	5	12.5	4	10.0
Business	4	10.0	5	12.5
Housewife	18	45.0	17	42.5
Student	10	25.0	10	25.5
Farmer	3	7.5	4	10.0

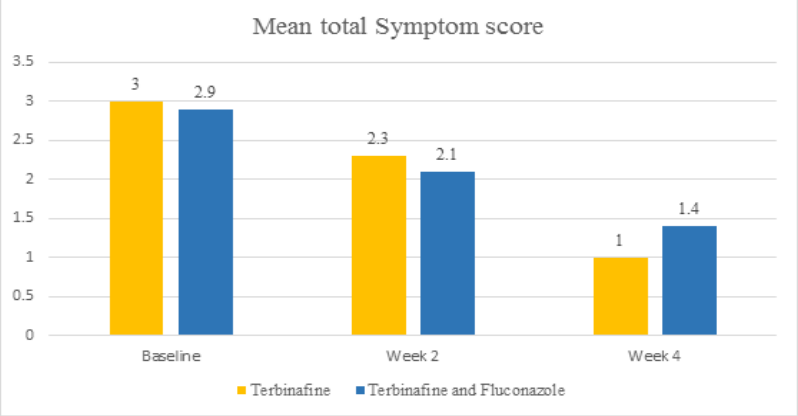

Fig-I: Total symptom score comparison

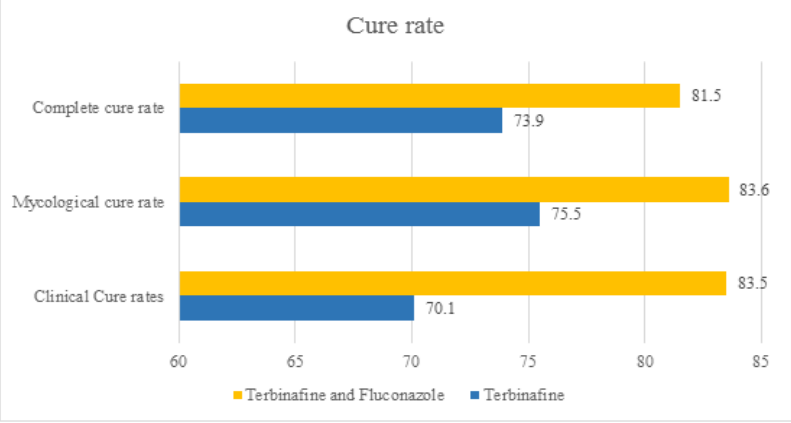

Fig-II: Cure rates

DISCUSSION

In recent years, the medical fraternity in Bangladesh has been observing an increase in the prevalence of dermatophytosis and resistance to conventional dosage of anti-fungal drugs. This change in the clinical scenario with increasing frequency of treatment failures has given rise to the search for an effective first-line treatment strategy that brings about rapid and complete clearance of dermatophytosis. Based on initial studies and recommendations, topical antifungals are the first line drugs in the management of dermatophytosis. However, in the current clinical scenario in Bangladesh, patients with large lesions or multisite dermatophytosis, only topical therapy fails to clear the lesions, leading to treatment failures and relapses. In such patients, systemic therapy is often recommended. Recently, Sahoo *et al*. [9] and Murlidhar *et al.* [10] in their comprehensive reviews recommended the use of a combination of topical and systemic antifungals in the management of patients with large lesions or recalcitrant tinea infections. Authors commented that while using combination therapy, drugs from two different classes should be used for wider coverage, synergistic or additive action and to reduce the chance of resistance. Ciclopirox Olamine (CPO) is a hydroxypyridone derivative that differs in structure and mechanism of action from the other known antifungal agents.19 It acts through the chelation of polyvalent metal cations, such as ferric (Fe3+) and aluminium (Al3+), thereby causing inhibition of metal-dependent enzymes (cytochromes, catalase, and peroxidase) leading to a disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membranes.20 It also alters membrane permeability causing a blockage of the intracellular transport of precursors. CPO is widely available in nail lacquer formulation but has been recently approved in Bangladesh in cream formulation. Systemic anti-fungal agents such as griseofulvin, terbinafine, fluconazole, and combination have been known to be active against dermatophytes, terbinafine being the only fungicidal drug [23, 24]. Among these, combination and terbinafine are more often prescribed compared to griseofulvin and fluconazole, probably because the latter require a longer duration of treatment [25]. In the past, Terbinafine, in the dosage of 250 mg/day, has shown consistent efficacy against dermatophytosis, achieving more than 90% cure rates at a dose of 250 mg/day when administered for two weeks [11, 12]. However, recently, an increase in the incidence of terbinafine resistance has resulted in treatment failure [14]. Although resistance to terbinafine in dermatophytosis is not common in clinical practice, it has been reported in clinical isolates by a few Authors [26, 27]. It has been seen that ineffective drug concentration in skin tissues may lead to anti-fungal resistance [28]. Hence, a higher concentration of terbinafine 500 mg/day has seen found to be more effective in some clinical studies [15, 29, 30]. Combination is a triazole antifungal drug which is also increasingly being used as a first-line drug for dermatophytosis, but it is being given for longer periods as compared to before [6, 18]. Though combination therapy is widely practised in Bangladesh, no much of the literature is available regarding the effectiveness of the combination therapy. Only one study is available indicating efficacy of combination therapy [31]. As per that study, terbinafine with sertaconazole achieved better efficacy than combination and sertaconazole combination though results are not statistically significant. Secondly, there is still the question on the right combination of systemic and topical anti-fungal agents. In our study, both the combination therapy options were efficacious in the management of dermatophytosis. Although the patients in Terbinafine and fluconazole achieved clinical cure much faster as compared to Terbinafine, there is no statistical difference in the complete cure at the end of six weeks.

A recent study by Majid *et al*. [14] could achieve only 43% cure rate after two weeks of daily 250mg terbinafine oral treatment in dermatophytosis. This recent decrease in the clinical efficacy is well corroborated by an upsurge in the cases encountered by dermatologists in daily clinical practice along with a failure to respond to the standard oral terbinafine therapy. Another study showed the mycological cure rate of terbinafine as 74%21 and 71% [16]. In another study, three-week therapy of terbinafine 250 mg/day showed a 35% cure rate, which was even lower as compared to other studies [22]. In all these studies, terbinafine 250 mg/day was used. But in our study, we have used terbinafine in the dose of 500 mg/day, which was well supported by some recent studies. In a recent study, three-week treatment with combination 200 mg/day showed a cure rate of 50%22 which was lower as compared to previous studies showing variable cure rates of 80-92% [16,21]. These variable results of clinical efficacy of combination are well evidenced in some of the literature. In our study, the mycological cure rates in Terbinafine and Terbinafine and fluconazole were 82% and 84% respectively. Though the mycological cure rate is similar to recently done studies in the combination group, in the terbinafine group, it is better than previous studies. This clearly indicates the need of using a higher dose of terbinafine along with a topical anti-fungal agent. Though many studies showed resistance or no clinical response to terbinafine, our study showed reverse results. Similarly, the clinical cure rate in the terbinafine group was much better than the combination group at week four. This could be due to the fungicidal property of terbinafine and its ability to persist in stratum corneum for several months after stopping the treatment [32], In the standard dosage, terbinafine and combination have been used extensively for the treatment of dermatophytosis and have been found to be safe and well tolerated [6, 33]. In the present study, the duration of the combination therapy was only four weeks but all the patients continued with topical for another two weeks. At the end of four weeks, patients in the terbinafine

group showed good clinical resolution but in the combination group, there was partial clinical response. But at the end of six weeks, patients in both the groups showed marked improvement indicating beneficial extended use of topical therapy. This indicates the need of monotherapy with topical for an extended duration in order to achieve higher cure rates in the treatment of dermatophytosis as suggested by Verma *et al*. [3]. In the present study, none of the patients in either group reported any adverse events. The conventional systemic terbinafine and combination monotherapy regimens at standard doses for two weeks duration have shown high treatment failure and recurrence rate in the present scenario. Though better results can be achieved by extending the dose and duration of systemic anti-fungal agents up to four weeks, a comparable cure can be achieved by combining with topical of different classes of anti-fungal agents with extended use. This combination can thus limit the duration of the treatment. In the present scenario, antifungal combination therapy appears to have a promising future in the prompt management of dermatophytosis.

Limitations of the study

Limitations of our study include its small sample size and short duration of follow-ups. Due to short duration of the follow-ups, we could not evaluate patients' relapse rates. Additionally, this study was conducted at a single centre and hence these findings cannot be generalized. For this purpose, further multicentre studies with larger sample size are required.

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