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Article

Efficacy of Combined Oral Itraconazole and Griseofulvin Regimen in Treatment of Chronic and Recurrent Tinea Corporis and Tinea Cruris Infections

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Abstract: Dermatophytosis is still a major worldwide health problem, causing an estimated 20–25% of the world's population to suffer from infections caused by species of Trichophyton, Microsporum, or Epidermophyton, with the majority of cases involving tinea pedis and tinea corporis. A number of fungal strains have developed resistance to the drugs previously used to treat them, especially Trichophyton indotineae, which has made the epidemiology of the condition far more complex and made chronic, recurrent and drug-resistant infections more common. Standard oral antifungal monotherapy often results in sub-optimal clinical response, failure of treatment and high relapse rates, particularly given at standard doses for standard durations. This study was a comparative trial of oral itraconazole monotherapy with a combination regimen of griseofulvin to evaluate the efficacy of the two treatment regimens for eight weeks in the treatment of chronic and recurrent tinea corporis and tinea cruris. The clinical study was conducted from 1st of January 2024 to 1st of September 2024 at the Dermatology Outpatient Unit of Samarra General Hospital and private dermatology clinic in Samarra city, Salahaddin Governorate, Iraq, through a comparative study. 80 patients with chronic tinea corporis or tinea cruris or both (duration of the disease >3 months) were recruited and split equally into two groups. Group I (n = 40) was treated with a cyclic regimen of itraconazole 200 mg daily for 4 days followed by griseofulvin 500 mg (morning) and 250 mg (night) for 3 days then 4 days, and this cycle was repeated every week for 8 weeks. The group II (n = 40) was given itraconazole 200 mg twice a day for eight weeks. Both groups were also treated with topical clotrimazole cream twice a day and ketoconazole shampoo once a day. Patients received follow-up for 16 weeks once a month. Complete cure (negative microscopy and elimination of all clinical symptoms), marked cure, partial cure, and recurrence rate were outcome measures. Chi-square and Fisher's exact tests were used for statistical analysis in the SPSS software, version 22. A p-value < 0.05 was considered as significant. Groups were not different with respect to age, gender, residence, family history or type of infection at baseline. The complete cure rate for Group I (30%) was significantly greater than Group II (17.5%) at the 2nd visit (4 weeks) (p = 0.05). In Group I, the complete cure percentage was 77.5% at the third visit (8 weeks) while in Group II, it was 47.5% (p = 0.02). At the fourth visit (16 weeks), the relapse rate was 12.5% for Group I while it was 40% for Group II (p = 0.01). None of the serious adverse effects were reported during the study period. Oral itraconazole + griseofulvin had significantly greater efficacy than itraconazole alone in the treatment of chronic and recurrent tinea corporis and tinea cruris, resulting in higher complete cure rates and significantly lower relapse rates. This may be due to the fact that the two agents act in complementary ways; itraconazole inhibits ergosterol biosynthesis, and griseofulvin does so by inhibiting microtubule assembly. These results indicate the need for combination antifungal treatment in today's age of increasing antifungal resistance. Treatment strategies should incorporate antifungal susceptibility testing and molecular diagnostics such as SQLE mutation detection to enhance clinical response to therapy in individual patients moving forward.

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Keywords: Dermatophytosis, Tinea Corporis, Tinea Cruris, Itraconazole, Griseofulvin, Combination Therapy, Antifungal Resistance, Trichophyton Indotineae

1. Introduction

Dermatophytosis, particularly tinea corporis and tinea cruris, is a major public health problem, being one of the most common superficial fungal infections of the world [1]. T. species, M. species, and E. species are responsible for the infection of at least 20–25% of the world population [2, 4]. Keratinophilic fungi invade the skin, hair and nails causing erythema, scaling and itching. [3]. Dermatophytosis is now more chronic, recurrent and resistant to treatment, both in industrialized and in developing countries [1, 5].

In addition to its clinical manifestations, dermatophytosis also has a significant impact on the social, psychological and occupational functioning of the affected person [4]. Often, patients describe the itching, difficulty sleeping, and social embarrassment as being of severe magnitude, which may result in psychological distress and depression [6]. In many areas, such as Iraq, treatment of these infections is becoming more difficult. The standard treatment used by most clinicians would usually be a single drug, either fluconazole, itraconazole or griseofulvin, usually applied orally and sometimes with an antifungal on the skin as well. However, this regular treatment often fails to yield optimal clinical responses, treatment failures and high relapse rates, especially at the traditional dosage and treatment durations [2].

The problem has been exacerbated by the development of antifungal resistance, especially with resistance to Trichophyton indotineae. Despite the overall advantage of its pharmacokinetic property and affinity for keratinized tissues, itraconazole is still far from being the only option for systemic therapy as the incidence of resistant disease has increased, thus requiring more effective and stronger therapeutic options [7]. This is why clinical management has started to use individual experiences more and more, to resolve therapeutic challenges [2].

To address these challenges, clinicians are again interested in the efficacy and potential for reducing risk of relapse with combination antifungal therapy. The mechanism of action of griseofulvin is different from itraconazole, which blocks ergosterol synthesis by inhibiting the enzyme lanosterol 14-alpha-demethylase (CYP51) that belongs to the cytochrome P450 family [8]. These two agents could have a synergistic effect or add-on effect, which would make them more effective against drug resistance than either agent used alone. In this background, it is crucial to understand whether griseofulvin added to itraconazole offers better clinical efficacy. Itraconazole plus griseofulvin was compared with itraconazole alone in this trial in order to evaluate the therapeutic effectiveness and superiority of the combination therapy over itraconazole alone in treating tinea corporis and tinea cruris over an 8-week period.

2. Materials and Methods

This comparative study was conducted for patients with chronic tinea at the dermatology outpatient's unit, Samarra General Hospital, and the private dermatology clinic, Samarra city\Salahaddin governorate\Iraq, during the period between 1st of January 2024 to 1st ofSeptember 2024**.**

Patients gave informed written permission after considering the clinical research material and its risks and benefits.

Chronic tinea corporis, tinea cruris, or both were required for men and females over 18. Chronic cases are individuals with the condition for more than 3 months, with or without treatment [9].

Hypersensitivity to itraconazole or griseofulvin, immunocompromised status, pregnancy or lactation, cardiac disease, diabetes, Cushing's syndrome, and abnormal

complete blood counts, renal function tests, or liver function tests. The dermatologist clinically diagnosed tinea infections and supported them with a potassium hydroxide examination.

This study was conducted to compare the efficacy and safety of 200mgitraconazole 200 mg once daily on four subsequent days, followed by 3 subsequent days on500 mg griseofulvin tab at the morning and 250mg at night for 40 eligible patients in group I patients, and 200mg itraconazole alone daily in 2 divided doses for same number of cases in group II patients. Both groups of patients also used topical clotrimazole cream twice daily and ketoconazole shampoo once daily, and all of them were treated for 8 wks duration.

Follow-up occurred monthly for 16 weeks. All patients reported their age, sex, residence, and family history at baseline. The dermatologist described lesion kind and shape.

Patients who had aberrant laboratory findings throughout the follow-up period had additional blood samples drawn after the second month of treatment, in addition to the two-weekly samples collected before therapy began. Alkaline phosphatase (ALP), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, blood urea, total bilirubin (TBL), prothrombin time (PT), and the International Normalization Ratio (INR) were among the investigations conducted. To determine whether the therapy was effective, we looked at both mycological and clinical cure rates at the conclusion of the course of treatment. In mycology, a negative microscopy is the treatment of choice. When tinea's pruritus, redness, desquamation, and hyperpigmentation go away, we say that the condition has cured clinically.Here are the grades for mycological and clinical cures as a result of treatment [10], [11]:

- Complete cure: microscopically negative results and complete resolution of all clinical manifestations.
- Marked cure: just hyperpigmentation, no pruritus, erythema, or desquamation, and negative microscopic examination.
- Incomplete cure: Under a microscope, hyperpigmentation, absence of itching, redness, and scaling.
- Not changed: confirmation by microscopy and the existence of all clinical manifestations.
- Worsen.

Two months (16 weeks) after treatment ended, participants were back for another round of assessments to see if relapse had occurred. During the follow-up phase, relapse might occur if new lesions or even the old ones show up [9]. When determining safety, we looked at the potential for major side effects.

Statistical Analysis

For the statistical analysis, we used SPSS, version 22, and for the categorical variables, we used chi-square or fissures exact tests, both of which required a significance threshold of 0.05 or below.

3. Results

This study enrolled 80 patients with Tinea Corporis and Cruris infection; 40 patients treated with combination of Itraconazole and Griseovulvin therapy (Group I) and 40 patients treated with Itraconazole alone (Group II). Concerning demographic variables including age, gender, place of residence, family history, and infection type, there were no statistically significant differences between the two groups, see Table 1.

Table 1. Basic features in regard to study groups.

Variable	Study groups				P
	Group I		Group II		
	No.	%	No.	%	
Age					
<30 years	6	15.0	5	12.5	0.89 NS
30-39 years	22	55.0	24	60.0	
≥40 years	12	30.0	11	27.5	
Gender					0.64 NS
Male	27	67.5	24	60.0	
Female	13	32.5	16	40.0	
Residence					0.82 NS
Urban	17	42.5	19	47.5	
Rural	23	57.5	21	52.5	
Family history					0.8 NS
Positive	25	62.5	23	57.5	
Negative	15	37.5	17	42.5	
Type of infection					
Tinea corporis	16	40.0	15	37.5	0.4 NS
Tinea cruris	12	30.0	17	42.5	
Both	12	30.0	8	20.0	

NS= Not significant.

Complete cure rate for group I at 2nd visit of (30%) was significantly higher than complete cure rate of (17.5%) for group II (p=0.05). Complete cure rate for group I at 3rd visit of (77.5%) was significantly higher than complete cure rate of (47.5%) for group II (p=0.02). The disease relapse rate for group I at 4th visit was (12.5%) which significantly lower than disease relapse rate of (40%) for group II (p=0.01). (**Table 2 and Figures 1-3**)

Table 2. Post-treatment outcomes in regard to study groups.

Variable	Study groups				P
	Group I		Group II		
	No.	%	No.	%	
Response to treatment at 2nd visit (4 weeks)					**0.05** S
Complete cure	12	30.0	7	17.5	
Marked cure	20	50.0	15	37.5	
Incomplete cure	8	20.0	18	45.0	
Response to treatment at 3rd visit (8 weeks)					**0.02** S
Complete cure	31	77.5	19	47.5	
Marked cure	5	12.5	11	27.5	
Incomplete cure	4	10.0	10	25.0	
Relapse of disease at 4th visit (16 weeks)					**0.01** S
Present	5	12.5	16	40.0	
Absent	35	87.5	24	60.0	

S=Significant, NS=Not significant.

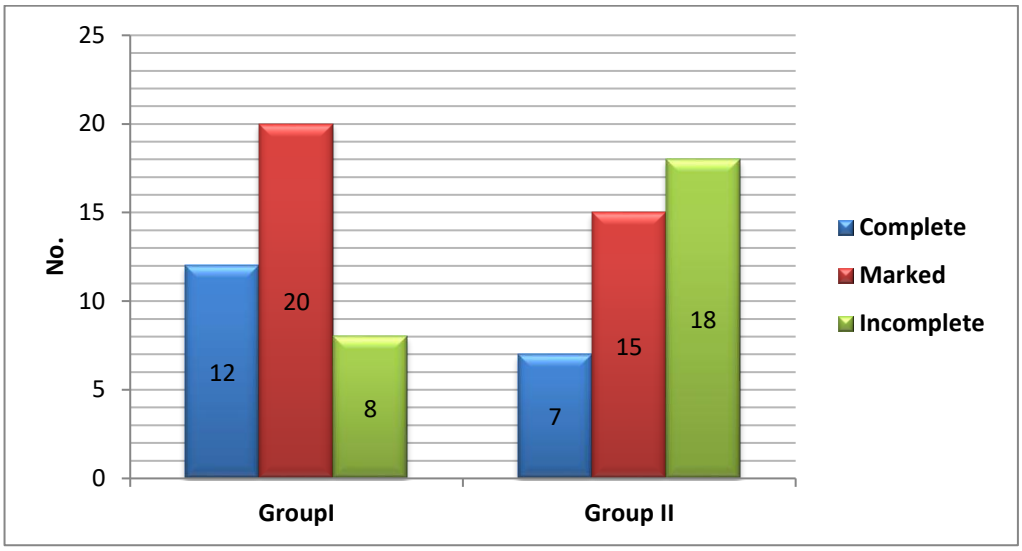


Figure 1. Response to treatment at 2nd visit in regard to study groups.

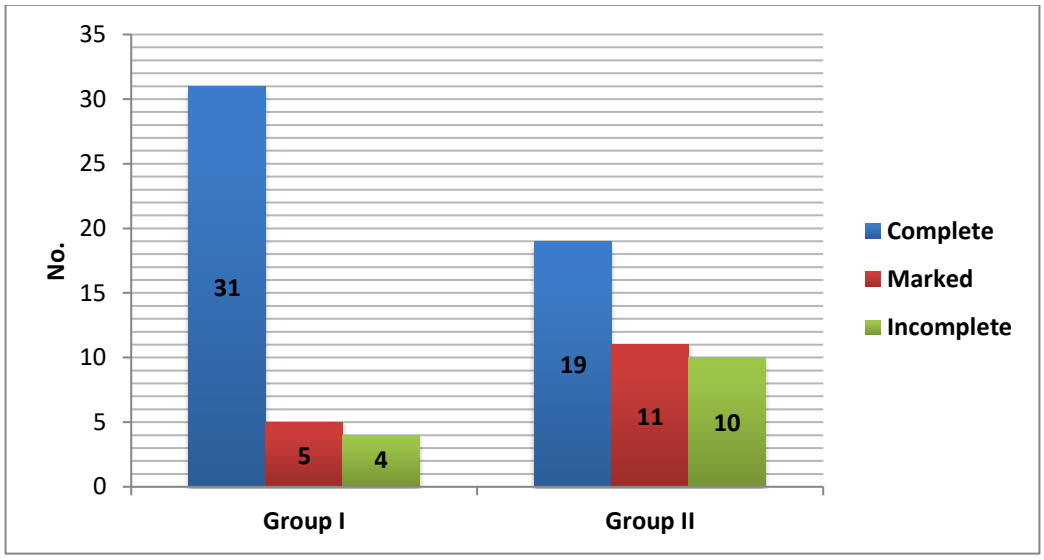


Figure 2. Response to treatment at 3rd visit in regard to study groups.

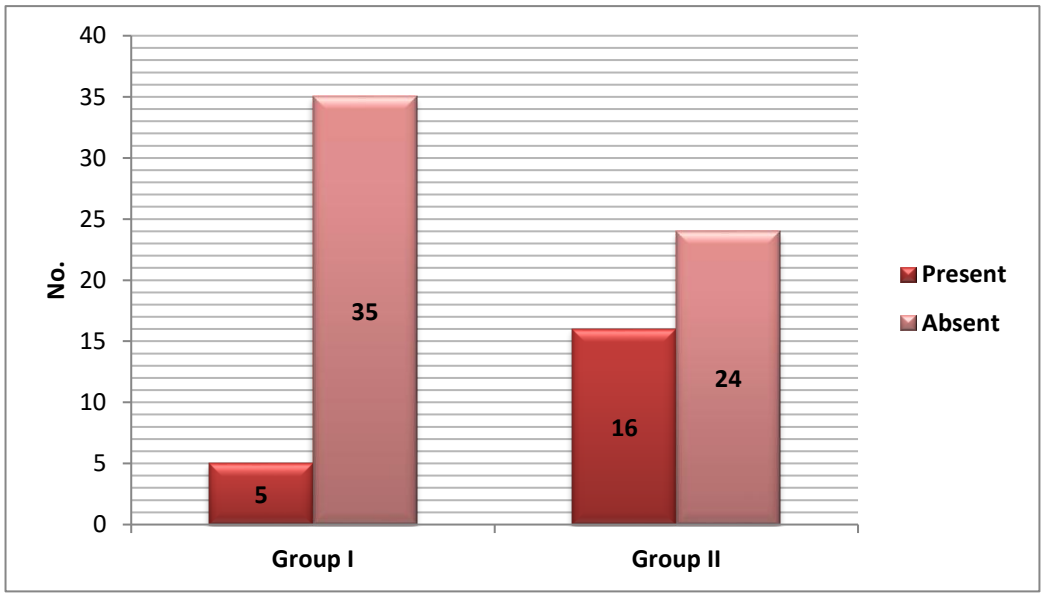


Figure 3. Disease relapse at 4th visit in regard to study groups.

As shown in Figure 4, no statistically significant differences in infection types in regard to gender of patients (p=0.67).

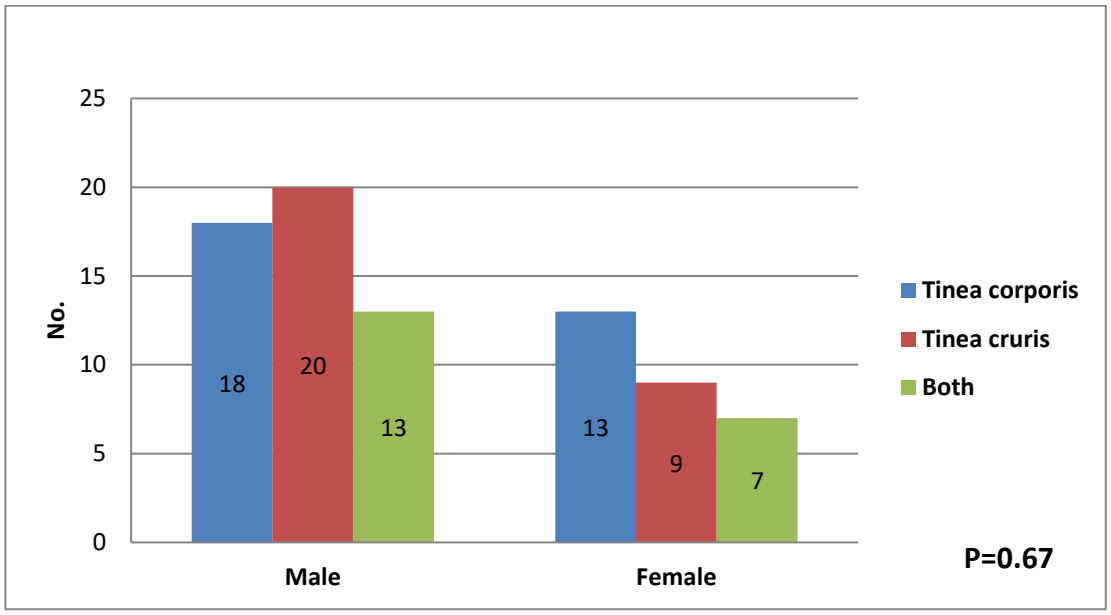


Figure 4. Infection types in relation to gender of patients.

4. Discussion

The therapeutic scenario of dermatophytosis has significantly changed, with an increasing proportion of chronic, relapsing and treatment resistant infections [1, 2]. This is especially true for Iraq where the clinical picture that was once easily manageable often appears as chronic epidemics [2]. Our study was designed to overcome this problem and to assess the efficacy of combination therapy of Itraconazole and Griseofulvin as compared with Itraconazole alone in a group of 80 patients suffering from Tinea corporis and Tinea cruris.

Increased resistance has been attributed to the emergence of Trichophyton indotineae which belongs to the T. mentagrophytes complex as one of the main factors [12, 13]. In the past, the most common pathogen was T. rubrum, but recent studies indicate that the more recent strains are more inflammatory and resistant such as T. indotineae [14, 15]. Typically, these pathogens show reduced response to standard azole monotherapies, including fluconazole and itraconazole, which may lead to the need for alternative treatment options [7, 9].

Itraconazole and Griseofulvin are given together because of the complementary mechanisms of action. Itraconazole is a sterol 14-alpha-demethylase inhibitor that disrupts ergosterol biosynthesis and Griseofulvin targets microtubule assembly and the formation of the mitotic spindle [16-18]. Two synergistic antifungal growth pathways are targeted to achieve the goal of a higher mycological and clinical cure rate, and prevent the emergence of single-agent resistance [19, 20].

Our study showed that combination group (Group I) had significantly better results than the monotherapy group (Group II). The curing rate was observed in Group I as 77.5% at 8th week (3rd visit) as compared to 47.5% in Group II ($p = 0.02$). Additionally, there was a significant difference between the relapse rates of the combination group (12.5%) and the monotherapy group (40%) ($p = 0.01$). These findings confirm that dual agent therapy is effective in providing long-term clearance of large areas of dermatophytosis.

Several important trends can be observed when we compare our results to the earlier research done. The cure rate for our combination is 77.5%, which is quite similar to general superiority of combination (87.5%), but less than the one reported by Saleh et al. (2024)

(92.8%) and Vanapalli et al. (2022) (93.1%) [12, 13]. Likewise, our cure rate with monotherapy (47.5%) is significantly lower than those figures (69% and 71.4%, respectively) reported in these studies as well as by Singh et al. (2019) [9, 12, 13]. This disparity could signify that the local pathogen population is more resistant to antifungal drugs, or that the severity of the infections seen in our practice is less than that seen elsewhere.

The dramatic failure of monotherapy in our study (cure rates < 50%) is congruent with those reported from recent pragmatic trials in India including those that have reported cure rates in the single digits for some resistant cases [9, 18]. We are pleased with the marked difference in relapse rates (12.5% vs 40%) that we obtained with our combination regimen, indicating not only that we were able to clear active lesions better, but that we also were able to lower the levels of subclinical fungal load that cause relapses.

5. Conclusion

To sum up, our results add to the existing literature that combination therapy is an indispensable treatment for resistant dermatophytosis. The absolute cure rates in our group were inferior to some previous trials (possibly indicating continuing development of drug resistance) but the relative superiority of the Itraconazole-Griseofulvin combination was still highly significant. Integration of antifungal susceptibility testing and molecular diagnostics in future protocols are needed to optimize these combination regimens in individual patients.

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