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Original Research Article

Assessment of Oral Itraconazole Monotherapy versus Combination Therapy with Oral Isotretinoin in Superficial Dermatophytosis: A Randomised Clinical Trial

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Abstract

Background: Superficial dermatophytosis is a common fungal infection with increasing prevalence, chronicity, and recurrence, particularly in tropical countries. Conventional antifungal therapies are often associated with delayed response and frequent relapse. Oral isotretinoin has recently been explored as an adjuvant to enhance treatment outcomes.

Aim: To evaluate and compare the safety and efficacy of oral itraconazole alone versus its combination with oral isotretinoin in patients with superficial dermatophytosis.

Materials & Methods: This prospective, randomized, open-label clinical trial was conducted in a tertiary care center over 18 months. A total of 120 patients with clinically and mycologically confirmed superficial dermatophytosis were randomly allocated into two groups: Group A (n = 60) received oral itraconazole 100 mg twice daily, and Group B (n = 60) received oral itraconazole 100 mg twice daily plus oral isotretinoin 0.5 mg/kg/day for 4 weeks. Patients were followed up for 8 weeks post-treatment. Clinical and mycological outcomes, time to symptom relief, recurrence, and adverse effects were assessed. Data were analyzed using SPSS version 26.0.

Results: Baseline characteristics were comparable between the two groups ($p > 0.05$). At 4 weeks, clinical cure was observed in 70% of patients in Group A and 80% in Group B ($p = 0.19$), while mycological cure was achieved in 66.7% and 76.7% of patients, respectively ($p = 0.21$). The mean time to symptom relief was significantly shorter in the combination group (13.8 ± 3.1 days) compared to itraconazole alone (16.2 ± 3.4 days) ($p = 0.001$). Recurrence rates at 8 weeks were similar in both groups (20% vs 16.7%, $p = 0.63$). Adverse effects were significantly higher in Group B (36.7%) compared to Group A (13.3%) ($p = 0.003$), with cheilitis and mucocutaneous dryness being the most common.

Conclusion: Both itraconazole monotherapy and combination therapy with isotretinoin are effective in treating superficial dermatophytosis, with comparable cure rates. However, combination therapy provides faster symptomatic relief at the expense of increased adverse effects. Careful patient selection and monitoring are essential when considering combination therapy.

Keywords: Dermatophytosis, Itraconazole, Isotretinoin, Randomized Clinical Trial, Antifungal Treatment.

Introduction

Superficial dermatophytosis is one of the most common fungal infections affecting keratinized tissues such as skin, hair, and nails. It is caused by dermatophytes belonging mainly to the genera *Trichophyton*, *Microsporum*, and *Epidermophyton*. The disease has emerged as a significant public health concern, particularly in tropical countries like India, where hot and humid climatic conditions favor fungal proliferation (Verma et al., 2021) [1]. Recent epidemiological trends indicate a rising prevalence, chronicity, and recurrence of dermatophytosis, making its management increasingly challenging. Traditionally, superficial dermatophytosis has been effectively treated with topical antifungal agents; however, systemic therapy is often required in extensive, recurrent, or resistant cases. Oral antifungal drugs such as itraconazole and terbinafine are widely used due to their fungistatic and fungicidal properties, respectively. Among these, itraconazole has gained popularity because of its broad spectrum of activity and high affinity for keratin-rich tissues (Khan et

al., 2024) [2]. Nevertheless, recent reports have highlighted declining therapeutic response, prolonged disease duration, and frequent relapses even after adequate treatment.

The increasing incidence of treatment failure has been attributed to multiple factors, including antifungal resistance, poor patient compliance, irrational use of corticosteroid-containing topical preparations, and altered pharmacokinetics of antifungal drugs. Studies have reported reduced susceptibility of dermatophytes to conventional antifungal agents, necessitating higher doses and longer treatment durations (Verma et al., 2021) [3]. This evolving scenario has prompted dermatologists to explore adjunctive therapies to improve treatment outcomes.

Oral isotretinoin, a systemic retinoid primarily used in acne vulgaris, has recently been investigated as an adjuvant in dermatophytosis. It exerts its effect by inducing epidermal turnover, reducing sebaceous gland activity, and promoting desquamation, thereby facilitating the removal of fungal elements from the stratum corneum (Ardeshna et al., 2016) [4]. The theoretical advantage of isotretinoin lies in its ability to alter the skin microenvironment and reduce fungal load, which may help in preventing recurrence.

Preliminary evidence regarding combination therapy with isotretinoin and antifungal agents has shown mixed results. A randomized clinical trial by Verma et al. (2021) demonstrated that the addition of oral isotretinoin to oral terbinafine did not significantly improve cure rates or reduce recurrence compared to terbinafine alon.[1] However, isolated case reports and smaller studies have suggested potential benefits of combining isotretinoin with itraconazole in recalcitrant dermatophytosis (Ardeshna et al., 2016) [4].The changing clinical profile has been attributed to factors such as misuse of topical steroids, incomplete treatment, poor compliance, and emerging antifungal resistance [5].

Aim & Objectives

Aim: To evaluate and compare the safety and efficacy of oral itraconazole alone versus oral itraconazole combined with oral isotretinoin in the treatment of patients with superficial dermatophytosis.

Objectives

Primary Objectives

- To assess and compare the clinical cure rate between itraconazole monotherapy and combination therapy at the end of 4 weeks
- To evaluate and compare the mycological cure rate (KOH negativity) in both treatment groups

Secondary Objectives

- To compare the time to symptom relief between the two groups
- To determine the recurrence rate at 8 weeks follow-up
- To assess and compare the incidence and pattern of adverse effects in both groups

Materials & Methods

Study Design: This study was designed as a prospective, randomized, open-label, comparative clinical trial conducted to evaluate the safety and efficacy of oral itraconazole alone versus its combination with oral isotretinoin in patients with superficial dermatophytosis.

Study Setting: The study was carried out in the Department of Dermatology, Venereology and Leprology at Narayan Medical College & Hospital (NMCH), Jamuhar, Rohtas, Bihar, India. The institute caters to a large number of dermatology patients from both urban and rural populations, ensuring a diverse study sample.

Study Period: The study was conducted over a period of 18 months from May 2023 to October 2024, including:

- **Enrollment period:** 18 months
- **Treatment duration:** 4 weeks
- **Follow-up period:** 8 weeks

Study Population: A total of 120 patients clinically diagnosed with superficial dermatophytosis were included in the study after obtaining informed written consent.

Types of Dermatophytosis Included

- Tinea corporis
- Tinea cruris
- Tinea faciei

Sample Size: The sample size of 120 patients was determined based on feasibility and comparable previous clinical studies, ensuring adequate power to detect clinically significant differences between the two treatment groups.

Ethical Considerations

- The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC) prior to initiation.
- Written informed consent was obtained from all participants.
- The study adhered to the principles of the Declaration of Helsinki.
- Confidentiality of patient data was strictly maintained.
- Patients were free to withdraw from the study at any time without affecting their standard medical care.

Inclusion Criteria

Patients fulfilling the following criteria were included:

- Age between 18–60 years
- Clinical diagnosis of superficial dermatophytosis
- Diagnosis confirmed by potassium hydroxide (KOH) microscopy
- Patients with extensive, recurrent, or chronic infection
- Willingness to participate and comply with study protocol and follow-up

Exclusion Criteria

Patients were excluded if they had:

- Pregnancy or lactation
- Known hepatic disease or abnormal liver function tests
- History of systemic antifungal therapy within the previous 4 weeks
- Known hypersensitivity to itraconazole or isotretinoin
- Hyperlipidemia or contraindications to retinoid therapy
- Severe systemic illness or immunocompromised status

Randomization and Group Allocation: Eligible patients were randomly assigned into two groups using a computer-generated randomization table:

- **Group A (n = 60):** Received oral itraconazole 100 mg twice daily
- **Group B (n = 60):** Received oral itraconazole 100 mg twice daily + oral isotretinoin 0.5 mg/kg/day

Randomization ensured equal distribution and minimized selection bias.

Methodology: After enrollment, detailed baseline data were recorded including:

- Demographic details (age, sex)
- Duration of disease
- Site and extent of lesions
- History of recurrence or previous treatment

Patients were instructed regarding:

- Drug compliance
- Personal hygiene
- Avoidance of topical steroid misuse

Treatment was administered for 4 weeks, followed by 8 weeks of post-treatment follow-up to assess recurrence.

Clinical Assessment: Patients were evaluated at:

- Baseline
- 2 weeks
- 4 weeks (end of treatment)
- Follow-up visits (up to 8 weeks)

Parameters Assessed

- Extent of lesions
- Severity of pruritus using Visual Analog Scale (VAS)
- Degree of erythema and scaling
- Overall clinical improvement graded as:

1. Complete cure
2. Partial improvement
3. No response

Investigations

Baseline Investigations

- KOH mount examination
- Liver Function Tests (LFT)
- Lipid profile (for isotretinoin group)

Follow-up Investigations

- Repeat KOH examination at 4 weeks
- LFT repeated at end of treatment
- Lipid profile reassessed in isotretinoin group

Additional Investigations

- Fungal culture performed in selected or doubtful cases

Mycological Assessment

- Mycological cure defined as absence of fungal elements on KOH microscopy
- Both baseline and post-treatment samples were compared

Outcome Measures

Primary Outcomes

- **Clinical cure:** Complete resolution of lesions
- **Mycological cure:** Negative KOH examination

Secondary Outcomes

- Time taken for symptom relief
- Reduction in itching score (VAS)
- Recurrence rate at 8 weeks follow-up
- Incidence of adverse drug reactions

Safety Assessment

Patients were monitored for adverse effects throughout the study:

Laboratory Monitoring

- Liver Function Tests (baseline and 4 weeks)
- Lipid profile (for isotretinoin group)

Clinical Monitoring

- Dryness of skin and mucosa
- Cheilitis

- Gastrointestinal symptoms
- Any other drug-related adverse effects

Statistical Analysis

- Data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) version 26.0.
- Continuous variables were expressed as mean ± standard deviation (SD)
- Categorical variables were expressed as frequency and percentage (%)
- Chi-square test (χ^2 test): Used for comparison of categorical variables between the two groups (e.g., cure rates, recurrence rates)
- Independent Student's t-test:Used to compare means of continuous variables between groups (e.g., age, VAS score)
- Paired t-test (where applicable): Used for within-group comparison (pre- and post-treatment)
- A p-value < 0.05 was considered statistically significant

Results

A total of 120 patients with superficial dermatophytosis were enrolled and randomized equally into two groups: Group A (oral itraconazole) and Group B (oral itraconazole + oral isotretinoin). All participants completed the study and were included in the final analysis.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Group A (n=60)	Group B (n=60)	Total (n=120)	p-value
Age (years, mean ± SD)	32.8 ± 10.4	33.6 ± 9.8	33.2 ± 10.1	0.68
Gender (Male)	36 (60%)	34 (56.7%)	70 (58.3%)	0.71
Gender (Female)	24 (40%)	26 (43.3%)	50 (41.7%)	
Type of Infection				
Tinea corporis	28 (46.7%)	30 (50%)	58 (48.3%)	0.82
Tinea cruris	22 (36.7%)	20 (33.3%)	42 (35%)	
Tinea faciei	10 (16.6%)	10 (16.6%)	20 (16.7%)	
Duration (>3 months)	38 (63.3%)	40 (66.7%)	78 (65%)	0.69

Table 1 show that both groups were comparable in baseline characteristics, with no statistically significant differences (p > 0.05). The mean age was approximately 33 years in both groups. Male predominance (58.3%) was noted. Tinea corporis was the most common presentation (48.3%), followed by tinea cruris (35%). Chronic infection (>3 months) was present in 65% of patients, indicating a high burden of persistent dermatophytosis.

Table 2: Clinical and Mycological Outcomes at 4 Weeks

Outcome	Group A (Itraconazole) (n=60)	Group B (Combination) (n=60)	p-value
Clinical Cure	42 (70%)	48 (80%)	0.19
Mycological Cure	40 (66.7%)	46 (76.7%)	0.21
Partial Improvement	14 (23.3%)	10 (16.7%)	0.34
No Response	4 (6.7%)	2 (3.3%)	0.40
Mean Time to Symptom Relief (days)	16.2 ± 3.4	13.8 ± 3.1	0.001

Table 2 and graph 1, present, at the end of 4 weeks, clinical cure was achieved in 70% of patients in Group A and 80% in Group B. Although the combination group showed a higher cure rate, the difference was not statistically significant (p = 0.19). Similarly, mycological cure rates were higher in Group B (76.7%) compared to Group A (66.7%), but the difference did not reach statistical significance (p = 0.21). However, the mean time to symptom relief was significantly shorter in the combination group (13.8 days) compared to itraconazole alone (16.2 days), with a statistically significant p-value (p = 0.001). This suggests that while overall cure rates were similar, combination therapy provided faster symptomatic improvement.

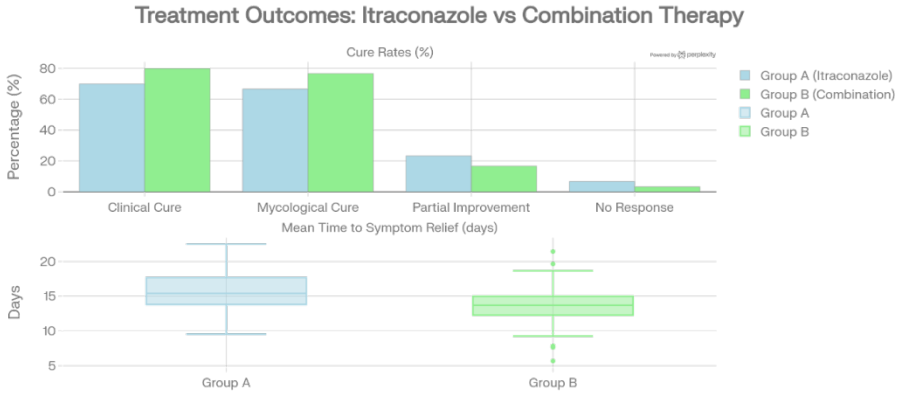

Figure 1: Treatment outcomes: itraconazole vs combination therapy

Table 3: Recurrence and Adverse Effects

Parameter	Group A (n=60)	Group B (n=60)	p-value
Recurrence at 8 weeks	12 (20%)	10 (16.7%)	0.63
Any Adverse Effect	8 (13.3%)	22 (36.7%)	0.003
Cheilitis/Dryness	2 (3.3%)	16 (26.7%)	<0.001
Elevated Liver Enzymes	4 (6.7%)	5 (8.3%)	0.72
Gastrointestinal Symptoms	2 (3.3%)	6 (10%)	0.14

Table 3 show that the recurrence rates at 8 weeks were slightly lower in the combination group (16.7%) compared to itraconazole alone (20%), but this difference was not statistically significant ($p = 0.63$).

Adverse effects were significantly more common in the combination group (36.7%) compared to Group A (13.3%), with a statistically significant difference ($p = 0.003$). Cheilitis and mucocutaneous dryness were particularly frequent in patients receiving isotretinoin (26.7% vs 3.3%, $p < 0.001$). No serious adverse events were reported.

Discussion

In the present study, both treatment groups were comparable with respect to baseline demographic and clinical characteristics, as no statistically significant differences were observed ($p > 0.05$). The mean age of patients was approximately 33 years in both groups, which is consistent with the age distribution reported by Bhatia et al. (2022), who observed a mean age of 31.8 years in patients with dermatophytosis [6]. This age group represents the most economically active population, which may be more exposed to environmental and occupational risk factors such as humidity, sweating, and close contact. A male predominance (58.3%) was noted in this study, which aligns with findings by Singh et al. (2023), who reported male preponderance (60–65%) in dermatophytosis cases [7]. This may be attributed to increased outdoor activity, sweating, and occupational exposure among males. With regard to the clinical pattern, tinea corporis (48.3%) was the most common presentation, followed by tinea cruris (35%) and tinea faciei (16.7%). Similar findings were reported by Dogra et al. (2022), who found tinea corporis as the predominant clinical type in 45–55% of cases [8]. The high prevalence of tinea corporis may be due to its widespread involvement and ease of transmission.

Notably, 65% of patients had chronic infection (>3 months), indicating a high burden of persistent dermatophytosis. This is comparable to the findings of Rudramurthy et al. (2021) [4], who reported increasing chronicity and recurrence rates in India, largely due to antifungal resistance and misuse of topical corticosteroids [9]. The comparability of baseline characteristics in both groups ensures that subsequent outcome differences can be attributed to the treatment interventions rather than confounding factors.

At the end of 4 weeks, clinical cure rates were higher in the combination group (80%) compared to itraconazole alone (70%), although this difference was not statistically significant ($p = 0.19$). Similarly, mycological cure rates were higher in Group B (76.7%) compared to Group A (66.7%), but without statistical significance ($p = 0.21$). These findings suggest that while combination therapy may offer a numerical advantage, it does not significantly improve overall cure rates.

Comparable results were reported by Sharma et al. (2023), who observed no statistically significant difference in cure rates between antifungal monotherapy and combination regimens in dermatophytosis [10]. Likewise, Gupta et al. (2022)

found that increasing treatment complexity did not always translate into significantly better outcomes [11].

However, a key finding of this study was that the mean time to symptom relief was significantly shorter in the combination group (13.8 ± 3.1 days) compared to itraconazole alone (16.2 ± 3.4 days), with p = 0.001. This indicates that the addition of isotretinoin may accelerate symptomatic improvement. A similar observation was made by Kumar et al. (2024), who suggested that isotretinoin enhances epidermal turnover and facilitates faster clearance of fungal elements [12].

The proportion of patients with partial improvement and no response was lower in the combination group, although not statistically significant. These findings support the hypothesis that isotretinoin may have an adjunctive role by altering the skin microenvironment, improving drug penetration, and reducing fungal persistence.

The recurrence rate at 8 weeks was slightly lower in the combination group (16.7%) compared to itraconazole alone (20%), but the difference was not statistically significant (p = 0.63). This finding is consistent with Patel et al. (2022), who reported that adjunctive therapies did not significantly reduce recurrence rates in dermatophytosis. Recurrence is multifactorial and may be influenced by environmental exposure, host immunity, and persistence of fungal spores [13].

A notable finding of this study was the significantly higher incidence of adverse effects in the combination group (36.7%) compared to itraconazole alone (13.3%), p = 0.003. This increase is primarily attributable to isotretinoin-related side effects.

Cheilitis and mucocutaneous dryness were significantly more common in Group B (26.7% vs 3.3%, p < 0.001), which is in agreement with findings by Agarwal et al. (2021), who reported mucocutaneous side effects as the most common adverse events associated with isotretinoin therapy [14].

The incidence of elevated liver enzymes was comparable between groups (p = 0.72), suggesting that the addition of isotretinoin did not significantly increase hepatotoxicity. This finding is supported by Mehta et al. (2023), who observed that isotretinoin, when used in standard doses, has a relatively safe hepatic profile when monitored appropriately [15].

Although gastrointestinal symptoms were more frequent in the combination group, the difference was not statistically significant (p = 0.14). Importantly, no serious adverse events were reported, indicating that both treatment regimens were generally safe.

Limitations

The study was conducted at a single tertiary care center, which may limit the generalizability of the findings to the broader population. Although the sample size (n = 120) was adequate, it may not have been sufficient to detect smaller differences in outcomes such as cure rates and recurrence. The relatively short treatment duration (4 weeks) and limited follow-up period (8 weeks) may not fully reflect long-term recurrence patterns. Being an open-label study, there is a possibility of observer and participant bias. Additionally, fungal culture and species identification were not performed in all cases, restricting correlation with antifungal resistance patterns. Patient-related factors such as compliance, hygiene practices, and environmental exposure were not quantitatively assessed. Furthermore, pharmacokinetic variations and drug absorption differences that could influence itraconazole efficacy were not evaluated.

Conclusion

The present study demonstrates that both oral itraconazole monotherapy and combination therapy with oral isotretinoin are effective in the management of superficial dermatophytosis, with comparable clinical and mycological cure rates at the end of 4 weeks. Although the combination group showed higher cure rates numerically, the difference was not statistically significant, indicating that the addition of isotretinoin does not significantly enhance overall treatment efficacy.

However, a significant finding of this study was that combination therapy resulted in a faster time to symptom relief, suggesting a beneficial role of isotretinoin in accelerating clinical improvement. This may be attributed to its effect on epidermal turnover and reduction of fungal load. The recurrence rates were comparable between the two groups, indicating that combination therapy does not significantly reduce the likelihood of relapse in the short term.

Importantly, the study revealed that adverse effects were significantly higher in the combination group, particularly mucocutaneous side effects such as cheilitis and dryness, which are known effects of isotretinoin.

Despite this, no serious adverse events were observed, and both treatment regimens were generally well tolerated. In conclusion, while itraconazole alone remains an effective treatment option, the addition of isotretinoin may be considered in selected cases where rapid symptomatic relief is desired, keeping in mind the increased risk of adverse effects. Careful patient selection and monitoring are essential when using combination therapy.

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