

## Original Research Article

# Effectiveness and safety of ciclopirox olamine in patients with dermatophytosis: a retrospective cohort analysis

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## ABSTRACT

**Background:** The current scenario of dermatophytosis is alarming, despite the availability of multiple antifungal agents the management of dermatophytosis is still challenging. Hence there is a need for a different antifungal with a novel mechanism of action for the management of dermatophytosis.

**Methods:** It was retrospective cohort study where in record of patients with dermatophytosis who were candidates for topical therapy only were analysed. All the patients were treated with Ciclopirox olamine 1% twice daily for 6 weeks. The efficacy end points were complete cure rate, mycological cure rate and clinical cure rate.

**Results:** 613 patients were included in the final analysis. At the end of study period the complete, mycological and clinical cure rates were 73.89%, 75.37% and 77.65% respectively. Out of 613 patients included 528 patients showed treatment failure to previous topical antifungal agents while 84 patients were treatment naïve. In treatment failure patients the complete, mycological and clinical cure rates were 72.15%, 73.48, and 75.56% respectively. In treatment naïve patients the complete, mycological and clinical cure rates were 84.70%, 87.05% and 90.58% respectively. 5.70% reported adverse events. The most common adverse event was pruritus followed erythema, dryness and rash.

**Conclusions:** Results of this study proves that ciclopirox is efficacious and safe in the management of dermatophytosis. This study also proves that ciclopirox is useful in those patients who failed to respond to other topical antifungal agents.

**Keywords:** Ciclopirox olamine, Dermatophytosis, Effectiveness, Safety

## INTRODUCTION

Dermatophytoses are among the commonest of dermatological infections occurring in India owing to the warm and humid climate, crowded living conditions and other socioeconomic factors. Even though dermatophytoses are not life-threatening, the consequences on DLQI cannot be overlooked. Within the past five years, there has been a dramatic yet unexplained surge in dermatophytoses in India. This is paralleled by the paucity of relevant literature on the same. Not only are we encountering unusual morphologies like pseudoimbricate and erythrodermic forms, the treatment aspect is also

becoming a therapeutic menace. This changed face of dermatophytosis has resulted in prolonged duration of antifungal therapy, partial treatment response, and many times, treatment failure.<sup>1-3</sup>

Despite the availability of multiple antifungal agents, the management of dermatophytosis is still challenging.<sup>4</sup> Currently in India, topical imidazole's and allylamines are the most commonly used antifungal drugs for the management of dermatophytosis.<sup>5</sup> However, because of widespread use, the fungistatic nature of imidazole's, and concomitant use with topical corticosteroids, a rise in minimum inhibitory concentration (MIC) values and

reduced response to these drugs have been reported.<sup>3</sup> Hence there is a need for a different antifungal with a novel mechanism of action for the management of dermatophytosis.

Ciclopirox Olamine (CPO) is a hydroxypyridone derivative that differs in structure and mechanism of action from the other known antifungal agents.<sup>6</sup> It acts through the chelation of polyvalent metal cations, such as ferric ( $\text{Fe}^{3+}$ ) and aluminum ( $\text{Al}^{3+}$ ), 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 membranes. It also alters membrane permeability causing blockage of intracellular transport of precursors.<sup>6</sup>

Multiple clinical trials have shown the efficacy and safety of Ciclopirox Olamine in the management of dermatophytosis with overall cure rates ranging from 60-90%.<sup>7,8</sup> However, there are no studies comparing the effectiveness and safety of Ciclopirox to other antifungal agents, especially in the Indian setup.

Keeping this scenario in mind we conducted this retrospective study of use of topical ciclopirox in management of dermatophytosis in real world setting in India.

### **Objective**

The objective of the study was to evaluate the real-world effectiveness and safety of Ciclopirox olamine in management of patients with naïve dermatophytosis as well as in those patients with dermatophytosis who have failed to achieve disease clearance with previous topical antifungal agent.

## **METHODS**

The present study was retrospective cohort study, wherein review of medical records of patients of dermatophytosis was conducted from various centers across India. The study duration was May 2019 to October 2019. Data were collected in a structured manner which was specific for the management of dermatophytosis.

### **Ethical considerations**

This research was undertaken in compliance with the ICH harmonized tripartite guidelines for good clinical practice (GCP) adherence to the Helsinki declaration of ethical standards. The research was initiated after approval by the institutional ethics committee "Suraksha - Ethics Committee".

### **Inclusion criteria**

Data of following patients was included in the study.

Both male and female patients >18 years of age, patients with tinea infection confirmed by KOH microscopy, patients with dermatophytosis who are candidate for topical monotherapy alone, patients with naïve localized tinea infection (Naïve infection is defined as the patient who is not previously exposed to dermatophytes and is presenting with disease for the first time and have not used any topical antifungal agent.; localized infection is defined as the presence of large solitary lesion or few small lesions confined to single area of the body), patients with localized tinea infection who failed to respond to previous topical monotherapy. (treatment failure was defined as lack of response after 2-3 weeks of therapy with topical antifungal drugs).

### **Exclusion criteria**

Data from following patients was excluded from the study.

Patients with history of multisite or multi lesional tinea infection, patients with use of systemic antifungal agents or who are candidate for systemic antifungal therapy, patients with negative 10% KOH microscopy at baseline, pregnant or nursing females, patients with known hypersensitivity to the study drugs, patients with history of other dermatological conditions which may impact the outcome of the study.

### **Visits and follow-ups**

Each patient was treated with topical Ciclopirox Olamine 1% applied twice daily for 6 weeks. All the patients in this study followed up with dermatologist every 2 weeks. During each visit patients were examined for their improvement of symptoms. KOH examination was performed at initial visit and after 6 weeks.

### **Effectiveness assessment**

#### **Primary effectiveness end point**

Primary effectiveness endpoint was percentage of patients achieving complete cure at the end of the treatment period from baseline. Complete cure was defined as the patients achieving both clinical cure and mycological cure at the end of treatment.

#### **Secondary effectiveness end point**

Secondary effectiveness end points were: percentage of patients achieving clinical cure at the end of treatment period. Clinical cure was defined as clear or almost clear symptoms at the end of treatment.

Percentage of patients achieving mycological cure at the end of treatment period. Mycological cure was defined as negative microscopy under potassium hydroxide (KOH) examination at the end of therapy.

Improvement in total symptom score from baseline in each visit. (total symptom score was calculated by taking average of scores of each symptom i.e., erythema, scaling, itching and incrustation)

For effectiveness assessment each patient was evaluated for clinical and mycological improvement. Clinical improvement was assessed by evaluating the improvement in common symptoms of dermatophytosis (scaling, erythema, itching and incrustation) on five-point scale (0-4) with 0 being the complete resolution of symptom while 4 being the severe symptom. Mycological improvement was assessed by examining 10% KOH mount of skin scraping under microscope before and after treatment.

#### Safety assessment

Safety assessment was done by analyzing all the AEs reported by the patients during treatment.

#### Data analysis

Descriptive statistics were used to summarize effectiveness and safety endpoints using GraphPad Prism version 8 (San Diego, California: GraphPad Software Inc., 20057).  $P \leq 0.05$  were considered statistically significant.

## RESULTS

Data of a total of 1500 patients with dermatophytosis who visited for dermatological consultation during the study period was screened. Of the 1500 patients screened, 670 patients fulfilled the inclusion criteria and were included in the study. Of these 670 patients, 613 patients were considered for final analysis. 44 patients were lost to follow up while 13 patients developed worsening of their symptoms and discontinued Ciclopirox therapy. The baseline demographic characteristics of patients are described in Table 1.

The average age of patients in our study was  $37.06 \pm 12.34$  years. Out of 613 patients, 58.89% ( $n=361$ ) patients were males while 41.10% ( $n=252$ ) patients were females. Tinea corporis was most common condition reported in our study followed by tinea cruris. Out of 613 patients, 86.13% ( $n=528$ ) patients were using various topical antifungal agents with luliconazole being the most common followed by Sertaconazole. 13.87% ( $n=85$ ) patients were treatment naïve with no history of use of previous topical antifungal agent.

#### Effectiveness analysis

##### Complete cure

Out of 613 patients analyzed, 73.89% ( $n=453$ ) patients achieved complete cure at the end of treatment period. In patients with treatment failure to previous topical antifungal therapy ( $n=528$ ) the complete cure rate was

72.15% ( $n=381$ ) while in treatment naïve patients ( $n=85$ ) the complete cure rate was 84.70% ( $n=72$ ).

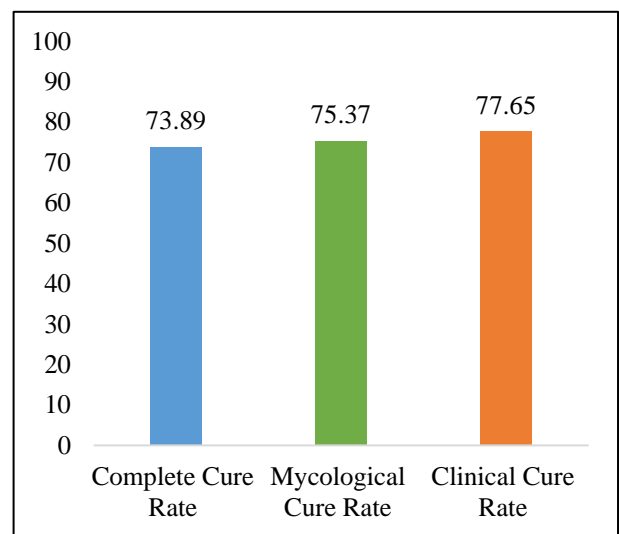
##### Mycological cure

At the end of treatment period of 6 weeks, 75.37% ( $n=462$ ) patients achieved mycological cure i.e., negative microscopy at the end of treatment period.

In treatment naïve patients ( $n=85$ ) the mycological cure rate was 87.05% ( $n=74$ ) while in patients with treatment failure to previous topical antifungal therapy ( $n=528$ ) the mycological cure rate was 73.48% ( $n=388$ ).

**Table 1: Baseline demographic characteristics of study population.**

Characteristics	Values
<b>Age (Mean, SD) (year)</b>	$37.06 \pm 12.34$
<b>Sex No. (%)</b>	
Male	361 (58.89)
Female	252 (41.10)
<b>Type of infection (%)</b>	
Tinea corporis	270 (44.04)
Tinea cruris	162 (26.42)
Tinea pedis	86 (14.02)
Tinea facie	61 (9.95)
Others	34 (5.54)
<b>Previous therapy (%)</b>	
Treatment naïve	85 (13.86)
Luliconazole 1% twice daily	233 (38.09)
Sertaconazole 2% twice daily	80 (13.05)
Clotrimazole 2% twice daily	62 (10.11)
Amorolfine 0.25% twice daily	44 (7.17)
Ketoconazole 2% twice daily	44 (7.17)
Others	65 (10.60)

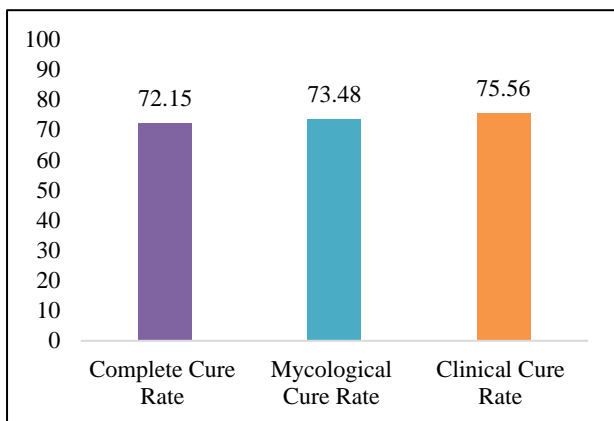


**Figure 1: Treatment response in all the patients (n=613).**

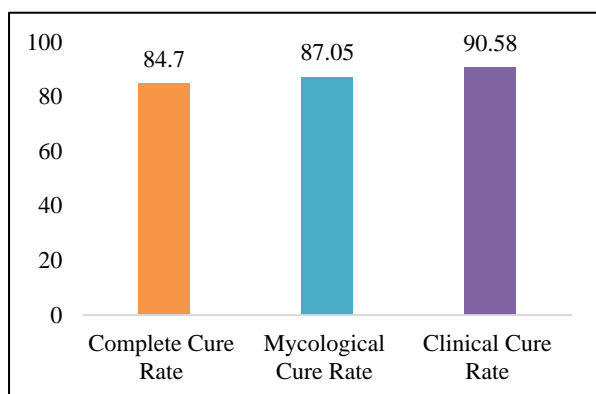
### Clinical cure

After 6 weeks of antifungal therapy, 77.65% (n=476) patients showed complete resolution of their symptoms of erythema, scaling, pruritus and incrustation thus achieving clinical cure.

The clinical cure rate in treatment naïve patients (n=85) was 90.58% (n=77) while the clinical cure rate in patients with treatment failure to previous antifungal therapy (n=528) was 75.56% (n=399).



**Figure 2: Treatment response in patients who failed previous topical antifungal therapy (n=528).**



**Figure 3: Treatment response in naïve patients.**

### Total symptom score

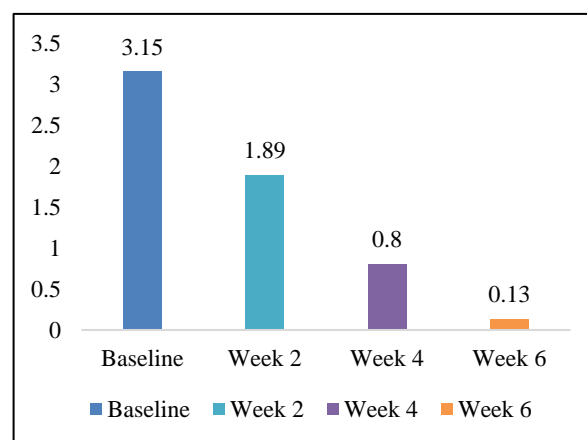
Total symptom score at baseline was  $3.15 \pm 0.68$  which significantly reduced at every visit. On day 14, 28 and 42, TSS was  $1.89 \pm 0.7$ ,  $0.8 \pm 0.6$  and  $0.13 \pm 0.33$  respectively.

### Safety analysis

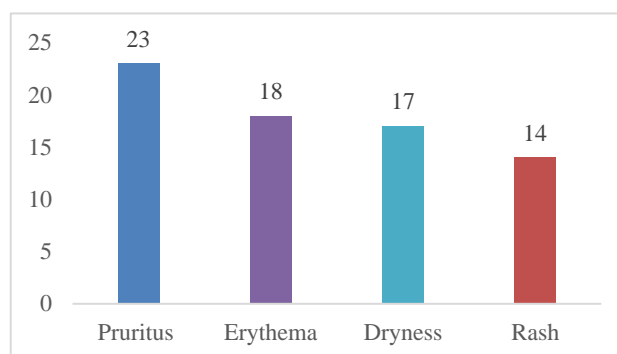
Out of 613 patients, 5.70% (n=35) reported 1 or more drug related AE. All the adverse events were of mild to moderate severity. None of the patient discontinued therapy because of AEs. The most common adverse event was pruritus (3.75%, n=23) followed erythema (2.95%, n=18); dryness (2.77%, n=7); and rash (2.28%, n=14).

## DISCUSSION

Dermatophytic infections are one of the commonest skin infections in India, with an increase in the incidence of difficult-to-treat cases.<sup>1-3</sup> Despite the availability of multiple antifungal agents, increasing MIC values to commonly used antifungal agents, and the misuse of topical steroids has led to distressing relapses in patients in recent times.<sup>4</sup> With a lack of recent studies on the efficacy of antifungals in the current scenario, dermatologists are using hit-and-trial methods, since the results of studies of antifungal effectiveness conducted many years ago cannot be extrapolated to the current scenario.<sup>1-4</sup> We evaluated the efficacy and safety of the recently launched novel antifungal Ciclopirox Olamine 1% in management of patients with localized tinea infection in real world setting in India.



**Figure 4: Change in total symptom score from baseline at each follow up period.**



**Figure 5: Adverse events reported during study period.**

In our study the complete cure rate was reported by 73.89% of patients while mycological and clinical cure rate was achieved by 75.37% and 77.65% patients respectively. These results are in accordance with previous studies conducted by various authors. Earlier studies by Bagatell, Kligman, Cullen and Corte et al have shown variable but appreciable complete cure rates for dermatophytosis in the range of 60-90% following

Ciclopirox therapy.<sup>9-12</sup> Similarly the mycological and clinical cure rates reported by these authors were in the range of 70-90%.

Majority of patients in our study were having treatment failure to previous topical antifungal therapy. This increasing rate of treatment failures can be attributed to multiple factors like inappropriate use of topical steroid containing medications, self-medication by patients with steroid containing creams, inappropriate and inadequate use of topical antifungal agents, wide spread use of azole antifungal agents which are usually fungistatic in nature. All these factors are associated with increase in chronic and treatment resistance dermatophytosis.<sup>1,3,4,13,14</sup>

In our study the complete cure rate, mycological cure rate and clinical cure rate was better in treatment naïve patients compared to those patients who failed to respond to previous topical antifungal therapy. In treatment naïve patients complete cure rate was 84.7% while the mycological and clinical cure rates were 87.05% and 90.58% respectively. Similarly, in patients who failed previous topical antifungal therapy, the clinical cure, mycological cure and complete cure was achieved by 75.56%, 73.48 and 72.15% patients respectively. This difference in cure between two group of patients can be attributed to the changing clinical patterns of dermatophytosis in India because of various factors as described earlier leading to chronic and treatment resistant tinea infection.<sup>1,3,4,13,14</sup>

The results of our study also justify that the effectiveness of ciclopirox in patients who have not responded to other antifungal drugs. This could be attributed to the novel mechanism of action of ciclopirox, its broad spectrum of antifungal activity including activity against azole resistant fungi, potent anti-inflammatory activity and low potentiation for development of resistance.<sup>13-16</sup>

With regard to safety, only 5.7% patients reported one or more AE in our study. All the adverse effects were of mild to moderate severity and none of the patients required discontinuation of the therapy. These results are in accordance with the safety profiles of ciclopirox reported in earlier studies.<sup>9-12</sup> Adherence to treatment was excellent in all the patients.

The limitations of study include retrospective nature of study which may lead to observer bias. The fungal culture and sensitivity could not be done due to non-feasibility.

## CONCLUSION

To conclude the results of this study proves that ciclopirox is efficacious and safe in the management of dermatophytosis. This study also proves that ciclopirox is useful in those patients who failed to respond to other topical antifungal agents thus justifying uniqueness of ciclopirox which can be instrumental in the management of dermatophytosis in the current scenario in India.

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