REVISTA
ESPAÑOLA DE PODOLOGÍA

Publicación Oficial del Consejo General de Colegios Oficiales de Podólogos

ORIGINAL
Bilingual article English/Spanish

Rev Esp Podol. 2024;35(2):80-84
DOI: http://dx.doi.org/10.20986/revesppod.2024.1695/2024

Evaluation of the improvement of onychomycosis after 6 months of treatment with ciclopirox 8 % and different vehicle solutions. A retrospective observational pilot study

Evaluación de la mejoría de la onicomicosis tras 6 meses de tratamiento con ciclopirox al 8 % y distintas soluciones vehículo. Un estudio piloto observacional retrospectivo

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Keywords:

Onychomycosis, topical antifungal, severity index, treatment.

Abstract

Introduction: Onychomycosis is a condition with a prevalence of around 5.5 % of the population. Within the antifungal treatments we find topical and oral treatments. Recently, new topical treatments have been developed, such as ciclopirox P-3051, which is the reference water-soluble lacquer. Two lacquers are marketed in Spain with this active ingredient and different vehicle solutions in their composition: hydroxypropyl chitosan (HPCH) and Ciclotech®. The aim of this study was to compare the evolution of onychomycosis after 6 months of treatment with Ciclopirox P-3051 and its different vehicle solutions.

Patients and methods: the sample consisted of 18 patients with onychomycosis from the University Podiatry Clinic of the Complutense University of Madrid treated between January 2022 and December 2023. Each onychomycosis was assessed by photographic follow-up and the Onychomycosis Severity Index (OSI) with an image at the start of treatment and another at 6 months.

Results: After evaluation of the results, there was a statistically significant improvement (p = 0.012) in the baseline and final OSI in all patients, regardless of the treatment received. A comparison of the mean OSI scores at baseline and at the end of treatment between the two groups showed no statistically significant differences (p = 0.074).

Conclusions: With topical ciclopirox 8 % there is an improvement in OSI after six months of antifungal treatment regardless of the vehicle used. No statistically significant differences were found in the efficacy of topical treatment of onychomycosis using ciclopirox 8 % with the different vehicles.

Palabras clave:

Onicomicosis, antifúngico tópico, índice de severidad, tratamiento.

Resumen

Introducción: La onicomicosis se trata de una afección con una prevalencia entorno al 5.5 % de la población. Dentro de los tratamientos antifúngicos nos encontramos con tratamientos a nivel tópico y oral. Recientemente se han desarrollado nuevos tratamientos tópicos, como el ciclopirox P-3051, siendo la laca hidrosoluble de referencia. En España se encuentran comercializadas dos lacas con este principio activo y distintas soluciones vehículo en su composición: hidroxipropil-quitosano (HPCH) y Ciclotech®. El objetivo de este estudio fue comparar la evolución de las onicomicosis tras 6 meses de tratamiento con ciclopirox P-3051 y sus diferentes soluciones vehículo.

Pacientes y métodos: La muestra se compuso de 18 pacientes con onicomicosis de la Clínica Universitaria de Podología de la Universidad Complutense de Madrid tratados entre enero de 2022 y diciembre de 2023. Se valoró cada onicomicosis mediante seguimiento fotográfico y el índice de severidad de onicomicosis (OSI) con una imagen al inicio de tratamiento y otra a los 6 meses.

Resultados: Tras la evaluación de los resultados, hubo una mejoría estadísticamente significativa (*p* = 0.012) del OSI inicial y final en el total de los pacientes, independientemente del tratamiento recibido. Al realizar una comparación de las puntuaciones medias del OSI al inicio y al final del tratamiento entre los dos grupos no se encontraron diferencias estadísticamente significativas (*p* = 0.074).

Conclusiones: Con el ciclopirox tópico al 8 % existe una mejoría del OSI a los seis meses de tratamiento antifúngico independientemente del vehículo que se use. No se han encontrado diferencias estadísticamente significativas en la eficacia del tratamiento tópico de la onicomicosis al usar ciclopirox 8 % con los distintos vehículos.

Received: 28-04-2024
Accepted: 20-06-2024

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Introduction

Onychomycosis is a fungal infection of the nails, which constitutes half of all nail disorders and affects approximately 5.5 % of the global population[1,2]. Dermatophytes such as *Epidermophyton*, *Microsporum*, and *Trichophyton* are the most frequently found microorganisms in onychomycosis (90 % of onychomycosis cases), followed by non-dermatophyte molds and yeasts[1-3].

The most common clinical signs include changes in nail coloration and thickening of the nail plate, onycholysis, and the appearance of subungual hyperkeratosis[2,4,5]. There are several diagnostic methods to confirm the presence of fungal infection, and recent studies indicate that the combination of microbiological culture and polymerase chain reaction (PCR) is the reference test, as it improves onychomycosis detection rates and may help reduce false-negative results[2,4,6,7].

In addition to diagnostic confirmation through laboratory tests, there are numerical classifications that allow for the assessment and quantification of the severity and response to treatment of onychomycosis[8-11]. The Onychomycosis Severity Index (OSI), introduced and validated by Carney et al.[8], is the only validated scoring classification system (from 0 up to 35 points) available that allows for an effective assessment of the severity of onychomycosis. The OSI classification is based on specific clinical characteristics, such as the affected area, the proximity of the lesion, and the presence of dermatophyte infection or hyperkeratosis > 2 mm, which are used to categorize onychomycosis as mild (1-5 points), moderate (6-15 points), or severe (≥ 16 points)[10]. A recent study published by Navarro-Pérez et al.[10] also reported that the OSI is a test with high agreement among professionals with varying clinical experience, showing a higher incidence of severe onychomycosis vs visual classification, which helps guide treatment.

There are multiple treatments, including topical antifungals, oral antifungals, and adjunctive therapies such as laser and photodynamic therapy[2,3,12,13]. All of these have very heterogeneous clinical and mycological cure rates across different published studies, with complete cure rates ranging from 6% up to 9% with the most widely used topical treatment (ciclopirox), 22% up to 46% with oral treatments (terbinafine and itraconazole), and 11 % with laser treatment[2,3,12,13].

Recently, new topical treatments in the form of water-soluble lacquers, such as ciclopirox P-3051, have emerged as the current reference topical treatment[14,15]. Currently, in Spain, 2 lacquers with this active ingredient (ciclopirox 8%) are marketed with different vehicle solutions in their composition: hydroxypropyl chitosan (HPCH) and Ciclotech® (sodium lauryl sulfate, hydroxypropyl-beta-cyclodextrin, and poloxamer-407)[15-18].

A recent clinical trial compared the efficacy results between both solutions through mycological and total cure without finding statistically significant differences between the 2 vehicle solutions[16]. As far as we know, as these lacquers are recently introduced, there is no study that compares the improvement with both products in an objective and quantified manner using the OSI scale. Therefore, conducting a pilot study comparing both treatments would assist professionals in making therapeutic decisions in the routine clinical practice. Therefore, the primary aim of this study is to compare the progression of onychomycosis using the OSI after 6 months on ciclopirox 8 % and different vehicle solutions.

Patients and methods

A retrospective study was conducted by collecting all health records from patients with onychomycosis from January 2022 through December 2023 treated at the Podiatry Service of the University Podiatry Clinic of Universidad Complutense de Madrid (Madrid, Spain).

The study inclusion criteria were patients older than 18 years, who had undergone an, at least, 6-months follow-up on treatment with 1 of the topical antifungals included in this study (ciclopirox 8 % with different vehicle solutions), and patients with a positive mycological culture/PCR result for onychomycosis. The study exclusion criteria were comorbidities of the immune system such as diabetes mellitus, rheumatoid arthritis, and HIV, patients with poor adherence to topical antifungal treatment, and patients who did not attend monthly follow-ups.

The products included in the study are as follows: ciclopirox 80 mg/g + HPCH (Onytec®, Laboratorio Almirall S.A); ciclopirox 80 mg/g + Ciclotech® (Dexulac®, Laboratorio Reig Jofre S.A). The treatment was carried out according to the protocol established for the treatment of onychomycosis at the University Podiatry Clinic of Universidad Complutense de Madrid, where the topical antifungal treatment is applied daily by the patient at home and they attend monthly for review and mechanical debridement through thorough cutting and milling of the affected nail plate. As this was a retrospective study, the choice of treatment was made prior to the study and was left to the professional's criteria.

The demographic variables collected from the patients' health records were sex, date of birth, age, health record No., causative organism of onychomycosis, and type of treatment used. The progression of onychomycosis was analyzed through photographic follow-up using the OSI classification as described by Carney et al. before the start of antifungal treatment and first mechanical debridement, and after 6 months of treatment, as this is the minimum treatment time indicated in the technical data sheets of both treatments[8,17,18].

Statistical analysis was performed using SPSS® for Windows, version 22.0 (SPSS Inc. Chicago, IL, United States), using non-parametric tests, as the Shapiro-Wilk test showed that the sample did not have a normal distribution ($p < 0.01$). For statistical analysis of qualitative variables, the Pearson chi-square test was used; to compare a qualitative variable and a quantitative variable, the Wilcoxon Mann-Whitney test was used; and to compare 2 quantitative variables, the Spearman test was used. Significant differences were established at alpha values of 5%, i.e., $p < 0.05$ for a 95 % confidence interval and beta values establishing a study statistical power of 80%. The study was conducted based on principles originating from the Declaration of Helsinki and the current national legislation regulating research involving patients as subjects of research[19].

Results

A total of 18 patients were included in the study, 14 of whom were women (77.8 %) and 4, men (22.2 %). The mean age of all patients was 70.22 ± 8.948. Regarding the pathogen, dermatophytes were the most prevalent, found in 16 cases (88.9 %), while 2 cases were caused by candida (11.1 %).

Of the total patients, 9 had received a 6-month regimen of ciclopirox 8 % + HPCH, and the remaining[9], ciclopirox 8 % + ciclotech®.

The results of the initial and final OSI for all patients can be seen in Table I. There was a statistically significant improvement (p value = 0.012) in the initial and final OSI for all patients, regardless of the treatment received (Figure 1). Additionally, there was an increase in the frequency of mild classification and a decrease in moderate cases, while severe cases remained constant.

Table II shows the frequency and percentage of mild, moderate, and severe cases before the start and after 6 months of treatment by groups.

The mean OSI scores before the start of each treatment and the mean OSI scores after 6 months of each treatment can be seen in Table III. Comparing the mean scores at the start and end of treatment between the 2 groups, no statistically significant differences were found (p value = 0.074).

Table II. OSI Classification before the start and after 6 months of treatment by treatment subgroups.

Ciclopirox 8 % + Hydroxypropyl chitosan (Ony-Tec®)			
	Mild	**Moderate**	**Severe**
Initial OSI	4 (44.4 %)	2 (22.2 %)	3 (33.3 %)
OSI at 6 Months	3 (33.3 %)	2 (22.2 %)	4 (44.4 %)
Ciclopirox 8 % + Ciclotech® (Dexulac®)			
	Mild	**Moderate**	**Severe**
Initial OSI	2 (22.2 %)	6 (66.7 %)	1 (11.1 %)
OSI at 6 Months	7 (77.8 %)	2 (22.2 %)	0 (0.0 %)

Discussion

In this pilot study conducted on a sample of 18 patients undergoing treatment for onychomycosis, we observed an improvement

Tabla I. OSI classification before the start and after 6 months of treatment for all patients.

	Mild	**Moderate**	**Severe**
Initial OSI	6 (33.3 %)	8 (44.4 %)	4 (22.2 %)
OSI at 6 months	10 (55.6 %)	4 (22.2 %)	4 (22.2 %)

Table III. OSI scores at baseline and at 6 months in each treatment.

		Ony-Tec®	**Dexulac®**
Initial (SD)	**Mean (SD)**	11.22 (9.54)	7.67 (5.57)
	Median (Range)	9 (1-25)	6 (4-22)
6 months	**Mean (SD)**	12.78 (11.14)	3.67 (2.59)
	Median (Range)	6 (1-30)	4 (1-9)

SD: standard deviation.

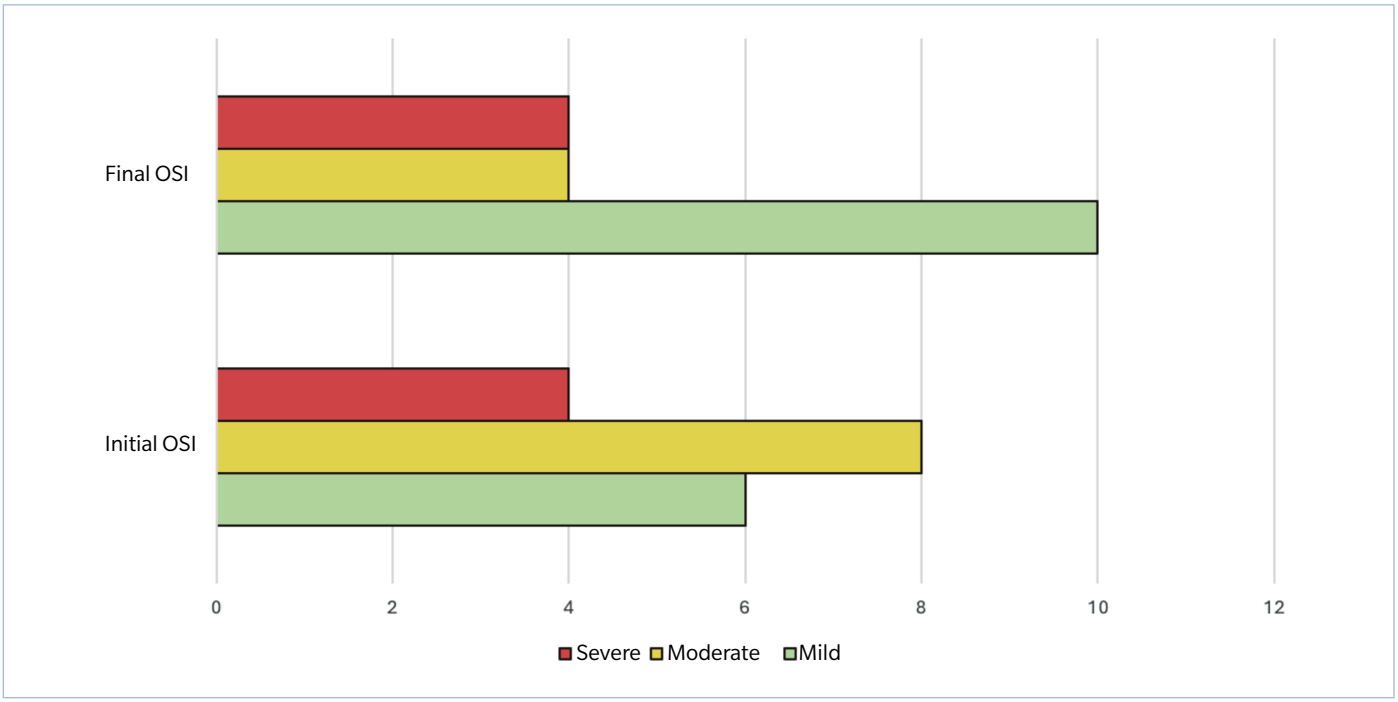

Figure 1. OSI classification before the start and after 6 months of treatment in the total patients included in the study.

in the OSI classification after 6 months of treatment with ciclopirox 8 % + HPCH and ciclopirox 8 % + ciclotech® (p = 0.012). Former studies have validated the OSI as a classification with high interobserver agreement (ICC, 0.899) regardless of the clinician's clinical experience, ruling out the possibility of measurement bias in the study10. In a clinical trial conducted on a sample of 381 patients, Zalacaín et al.[16] studied the efficacy of these treatments through complete cure rates, mycological cure, and improvement (mycological cure and reduction of clinical signs of onychomycosis ≥ 20 %), and did not observe statistically significant differences between the 2 groups (p = 0.839) in complete cure rates at 52 weeks of treatment, which were 10.48 % in the group treated with ciclopirox 80 mg/g + ciclotech® (p = 0.012), and 11.1 % in the group treated with ciclopirox 80 mg/g + HPCH. They also found no significant differences between the 2 groups in terms of mycological cure (cure rate of 32 % with ciclopirox 8 % + ciclotech® and 27 % with ciclopirox 80 mg/g + HPCH) and improvement (27.2 % in the group treated with ciclopirox 8 % + ciclotech® and 20.6 % in the group treated with ciclopirox 80 mg/g + HPCH)[16].

Moreover, regardless of the treatment group, there was an increase in the frequency of mild classification and a decrease in moderate cases, while severe cases remained constant. This suggests that both treatments are effective and suitable for mild and moderate onychomycosis, but for severe cases, other treatments such as systemic antifungals should be considered. In the Zalacaín et al.[16] study, only cases of distal onychomycosis from mild to moderate (with ≥ 20 % to ≤ 60 % involvement of the nail plate attached to the distal bed without affecting the lunula) due to dermatophytes were included. In a recent review on the treatment of onychomycosis with ciclopirox 8 % + HPCH, the authors stated that this product is indicated for cases of mild-to-moderate onychomycosis caused by fungi sensitive to ciclopirox without involvement of the matrix[15].

As far as we know, this is the first study reporting mean scores and changes in OSI classification at the start and after 6 months of treatment with these 2 products, without finding statistical differences between treatments. The results regarding the frequency and percentage of mild, moderate, and severe cases before the start and after 6 months of treatment by groups (Table II) may suggest that improvements were greater in the group treated with ciclopirox 8 % + ciclotech®, with a higher number of mild cases and a greater reduction in moderate and severe cases by the end of the study vs the other treatment group (0.061), which we believe might be due to initially including more severe cases treated with ciclopirox 8 % + HPCH, possibly introducing a bias in the results.

The limitations of this study are the small sample size, which is justified as it is a pilot study. Additionally, it is a single-center study at a specialized onychomycosis treatment center, and different results might be obtained in other types of centers. Lastly, the follow-up period was limited to 6 months, whereas treatments are indicated for a minimum of 9 months[17,18].

As a pilot study, it would be interesting for future studies to increase the sample size and follow-up time to obtain more consistent results.

In conclusion, the present study has shown that there is an improvement in OSI after 6 months of antifungal treatment with topical ciclopirox 8 %, regardless of the vehicle used. We did not find statistically significant differences in the efficacy of the topical treatment of onychomycosis using ciclopirox 8% with the different vehicles.

Conflicts of interest

None declared.

Funding

None declared.

Authors' contributions

Conception and study design: DLH, SGO.
Data collection: MVC, VOF.
Result analysis and interpretation: DLH, SGO.
Creation, drafting, and preparation of the initial draft of the paper: DLH, SGO.
Review and final acceptance: DLH, SGO, FJAA, JLLM.

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