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Article

Effects of the Topical OLEOZON®, Ketoconazole and Terbinafine on Skin Lesions and Dermatophytes in Patients with Epidermophitosis

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Abstract

Dermatophytoses are fungal infections that are frequently diagnose all over the world. Dermatophytes are keratinophilic filamentous fungi that damage nails, skin, and hair. Treatment for dermatophytosis can be topical (creams, lotions, or ointments, such as ketoconazole and terbinafine) or systemic. Topical OLEOZON® (ozonated sunflower oil) is registered in Cuba for the treatment of Epidermophytosis. The aims of this post-hoc analysis was to evaluate and compare, for the first time, the effects of topical OLEOZON® versus ketoconazole and terbinafine on skin lesions and dermatophyte clearance in cuban patients with Epidermophytosis. The present analysis was obtained from the data of patients included in a previous Phase III comparative study. Efficacy variables include significant reduction in skin lesions and presence of dermatophytes. Statistical analysis was performed using the intention-to-treat approach. Three hundred patients of both sexes with a diagnosis of Epidermophytosis, were randomly assigned to receive topical OLEOZON®, or ketoconazole, or terbinafine. At the six weeks, all treatments significantly reduced all skin lesions and the presence of dermatophytes. However, there were no significant differences between groups in the comparisons made. The treatments were safe and well tolerated. It is concluded that topical OLEOZON® showed comparable effects to ketoconazole and terbinafine in reducing all skin lesions and the presence of dermatophytes in Cuban patients with Epidermophytosis, with a favorable impact on the clinical and mycological cure rate of these patients. These findings support the potential utility of OLEOZON® as an affordable, well-tolerated alternative in settings where conventional antifungal options may be limited or contraindicated.

Keyword

Skin lesions, Dermatophytes, Epidermophytosis, Topical Oleozon®, Ketoconazole, Terbinafine

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1. Introduction

Dermatophytosis, caused by dermatophytes, affects up to 25% of the world's population, with higher rates in Africa and Asia. Dermatophytes are keratinophilic filamentous fungi of the genera *Trichophyton, Microsporum, Epidermophyton*, and *Nannizzia* that damage nails, skin, and hair. They are sometimes difficult to treat and can develop a chronic course [1-3].

Anthropophilic, zoophilic, and geophilic sources are known for various dermatophytes. These types of fungi grow best in warm, humid environments and are most common in tropical and subtropical regions. The incidence and isolation of the different species of dermatophytes varies greatly from one region to another in the world and is influenced by multiple factors such as age, sex, ethnic group, hydration, humidity, pathogenic power, host resistance, source of infection, etc., and according to their habitat [4].

For the effective management, treatment and prevention of dermatophytes, it is crucial to identify the etiological agents. The treatment of dermatophytosis can be topical or systemic. Topical treatment uses several drugs in cream, lotion or ointment form, including ketoconazole and terbinafine [5,6].

The growing emergence of resistance mechanisms and side effects associated with antifungal agents highlight the need for alternative therapies. Topical OLEOZON® (ozonated sunflower oil) is registered for the treatment of Epidermophytosis [7]. It has demonstrated antifungal and antibacterial activity in preclinical studies and no toxicity related to its use has been found [8-16].

The mechanism of action of ozonized sunflower oils has not been fully elucidated so far, but their effects on microorganisms could respond to: 1) direct oxidation (the release of ozone, trioxolanes and lipoperoxides could directly destroy microorganisms through their oxidation); 2) cytotoxicity (compounds such as trizolanes, lipoperoxides and aldehydes are cytotoxic for microorganisms and can inactivate key enzymatic pathways for their survival); 3) release of growth factors (various components of ozonated oils can release growth factors such as PDGF, TGF-β and VEGF that must influence tissue remodeling); and 4) oxidative pre-conditioning (local oxidation of tissues by components of ozonated oils can stimulate endogenous antioxidant mechanisms and promote tissue repair) [17].

The clinical studies carried out with topical OLEOZON® have investigated its effects in the treatment of various dermatological diseases and it has been found to be safe and well tolerated [18-23].

Taking into account the above background, the objective of this post-hoc analysis was to evaluate and compare, for the first time, the effects of topical OLEOZON® versus ketoconazole and terbinafine on skin lesions and dermatophyte clearance in cuban patients with Epidermophytosis.

2. Materials and Methods

2.1 Study Design and Participants

The data used in the present post-hoc analysis was obtained from the results of all patients included in a previous comparative study [24], which include three hundred patients treated with topical OLEOZON®, or ketoconazole, or terbinafine, for six weeks after randomization.

This phase III study had an open-label, multicenter, randomized design, with comparable efficacy between topical OLEOZON®, ketoconazole and terbinafine applied twice daily for six weeks. The doses administered in this study for topical OLEOZON®, ketoconazole and terbinafine were the same as those usually recommended in Cuba for the treatment of these patients and the proposed treatment time of six weeks corresponded a period in which the effects of these treatments on Epidermophytosis have been observed.

This study was conducted in accordance with the principles of the Declaration of Helsinki, the recommendations of the World Health Organization, and Cuban standards for Good Clinical Practice. The study protocol was approved by the Ministry of Public Health and the Clinical Research Ethics Committee of the Manuel Fajardo Hospital (IRB 9-2019) and Carlos Juan Finlay Hospitals (IRB 2-2020), as well as by the Cuban State Center for Drug Control. The original study was included in the Cuban Public Registry of Clinical Trials (RPCEC-00000289).

The study outline consisted of five consultations: one for a recruitment in which the initial history was taken, and the tests to be performed were indicated (Consultation 1), an inclusion one in which the treatments were delivered to the patients who met the selection criteria (Consultation 2) and three follow-up visits at 2, 4 and 6 weeks of treatment (Consultations 3-5). In each visit, a physical examination was performed, and in visits 3-5, adherence to treatment was monitored and adverse events were questioned. The clinical and microbiological laboratory tests were carry out prior to Consultation 2 and at the end of the treatment.

As a multicenter study, it consisted of volunteer patients from the common population who attended the Dermatology Consultations of the ¨Manuel Fajardo¨ Hospital and the ¨Carlos Juan Finlay¨ Hospital with *Tinea pedis* or Epidermophytosis.

2.2 Diagnostic Criteria (Recruitment)

Patients with Epidermophytosis were recruited. It was considered that a patient is diagnosed with Epidermophytosis of the lower limbs when it meets the clinical criteria and is confirm microbiologically.

Clinical: Skin lesions characteristic of these conditions such as scales, macerated areas, vesicles and erythema.

Microbiological: Through direct microscopic observation of the clinical material and culture of the sample in an appropriate mycological medium. These microbiological studies demonstrated the presence of dermatophytes.

2.3 Inclusion Criteria

Patients ≥ 18 years of age, both sexes, with a clinical and microbiological diagnosis confirming Epidermophytosis, without any other superimposed infection and without prior treatment, were included after signing their informed consent.

2.4 Exclusion Criteria

Patients with diagnosed neoplasms, severe septic states, history of liver failure, history of kidney failure, decompensated chronic non-communicable diseases, alcoholism, pregnancy, concomitant use of corticosteroids, cytostatics, or immunosuppressants, or antibiotics, and usual clinical history of drug allergies were excluded.

2.5 Treatment Interruption Criteria

No clinical improvement, no desire to continue on the part of the patient for any reason, when serious adverse events occurred that required it, whether clinical or documented by complementary analyzes and when there were major violations of the study protocol: lack of adherence to treatment application for > 3 days and/or use of other systemic antifungals other than the indicated treatments.

2.6 Treatments Groups

Group 1: topical OLEOZON® emulsion, Group 2: ketoconazole 2% cream, Group 3: terbinafine 1% cream. The administration was topical, as it was used in the treatment of Epidermophytosis and through this route the effects that support the evaluation of the products have been revealed. Applied the topical OLEOZON® emulsion or creams in a manner that guarantees a thin layer of the medication on the affected area and cover with gauze soaked in the medication.

This study was conduct in outpatient conditions and treatments were applied to the diseased areas twice a day (in the morning and in the evening after bathing) for six weeks.

The use of specific medications such as superficial radiotherapy, mud therapy or systemic antifungals, other than the study treatments, was not permit.

2.7 Efficacy Variable in Post-Hoc Analysis

Significant reduction in all skin lesions (scales, macerated areas, vesicles and erythema) and significant reduction of the presence of dermatophytes (*T. rubrum, T. mentagrophytes, E. floccosum)* at the end of six weeks of treatment versus baseline.

2.8 Criteria for Evaluating the Response

Treatments were considered effective if after six weeks of treatments there is a significant reduction in all skin lesions and significant reduction of the presence of dermatophytes, and if the response is similar, it will be assumed that the treatments are equivalent.

2.9 Safety and Tolerability

Physical examination data (body weight, pulse, and blood pressure), laboratory indicators, and adverse event reporting were included. All adverse events that newly appeared to patients during the trials, disregarding the cause, considered as adverse event. In accordance with their intensity, adverse event were classified as mild, moderate or severe [25].

2.10 Laboratory Analysis

Fasting venous blood samples were obtained. Hematological variables (hemoglobin, hematocrit, red blood cell and leukocyte counts) were determined in a Hematology Complex. Blood biochemical variables (aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, creatinine) were determined by enzymatic methods using reagent kits (Roche, Switzerland) and were performed on automated equipment located in the Clinical Laboratory of both Hospitals.

Microbiological examination: *Tinea pedis* lesions were disinfect with 70% ethanol and their collection was perform by scraping the periphery of the lesion using a sterile scalpel. These samples were collect in a sterile Petri dish.

For direct microscopic examination, a drop of 10% KOH was place on a slide and mixed with a small portion of the material to be examined (skin scraping). The slide was then gently place over a low flame of a Bunsen burner to facilitate clearing and to observe septate hyphae and arthrospores.

Samples positive to direct examination were seeded on Sabouraud Agar supplemented with chloramphenicol using an inoculation loop and incubated at room temperature for 30 days and examined for growth every five days, one replicate of which was incubated. The plates with growth were microcultured. A sterilized glass Petri dish was use for the microculture, the bottom of which was covere with filter paper, on which a "V" shaped glass rod, a coverslip and a slide were place. A portion of supplemented Papa Dextrose Agar with a surface of 1 cm^2 was place on the latter, where small fragments of the isolate to be identified were inoculated on the surface of the lateral edges. The culture medium was then cover with the sterile coverslip and incubated in a humid chamber at 37ºC. Once fungal growth was detected, the coverslip was remove and placed on a slide containing a drop of lactophenol cotton blue. The preparation was observed under the microscope at 100X and 400X magnification [26].

2.11 Method of Randomization

In this study, the block size was predetermined according to the number of intervention groups (3), using a progressive random number table and a vector-generated 1/1 ratio [27]. Treatments were delivered in ascending order after inclusion was confirmed. Therefore, there were no jumps in number allocation. Block randomization was computer-generated. To ensure blinding, none of the participating investigators knew the randomization code, which was administered independently by the National Coordinating Centre for Clinical Trials in Havana, Cuba.

2.12 Sample Size

The purpose of this study was to determine whether topical application of OLEOZON® produced a reduction in all skin lesions and a significant reduction in the presence of dermatophytes equivalent to that produced by ketoconazole and terbinafine, with a potency of 80% and a bilateral α level of 0.05. According to GPower, version 3.1.19.2 (2014), it was estimated that 300 patients were required for inclusion in the study, 100 in each group. Assuming an approximate dropout rate of 10% over the duration of the trial, 330 cases (165 per hospital) were recruited.

2.13 Statistical Analysis

Data were analyzed using to intention-to-treat method, and data imputation was performed using the carryover method. The data were processed using SPSS 21.0, and EPIDAT 3.1 was also used as auxiliary software for specific statistical tests.

Categorical variables were presented in contingency tables with absolute values, proportions, and percentages using Pearson's χ^2 test. In the case of quantitative variables, and to contrast results between the study groups, they were analyzed with a non-parametric ANOVA such as Kruskal-Wallis and comparisons were made in pairs, always evaluating the homogeneity of the variances. For the "before versus after" tests of two means, the McNemar test was used, assuming a normal distribution, as well as the non-significant signed rank test.

For continuous variables, means (means), standard deviations, minimum and maximum values, and 95% confidence intervals were calculated. For discrete quantitative variables, their distributions were analyzed using relative or absolute frequencies or the z test (normal approximation for proportions).

All statistical tests were two-tailed, and the significance level was established a priori at $\alpha=0.05$. Data management and statistical processing were performed at the Data Management and Processing Department of the National Coordinating Centre for Clinical Trials in Havana, Cuba.

3. Results

3.1 Baseline Characteristics

Three hundred thirty-two patients were recruited, of which 300 were included in the active treatment phase. The reasons for non-inclusion were negative mycological examination (9 patients), travel abroad (1 patient) and failure to perform the indicated examinations and analyzes (22 patients).

The main characteristics of the study population are shown in Table 1, with all groups being statistically similar in each of them.

Table 1. Baseline characteristics of the study population

	Ketoconazole (n = 100)		**Terbinafine (n = 100)**		**Topical OLEOZON® (n = 100)**		**Total (n = 300)**	
Age (years) (X, SD)	52 ± 16.1		51 ± 14.9		50 ± 15.3		51 ± 15.4	
Body mass index (kg/m^2) (X ± SD)	26.3 ± 4.2		26.3 ± 4.6		26.5 ± 4.1		26.4 ± 4.3	
Sex	n	%	n	%	n	%	n	%
Male	62	30.5	73	36.0	68	33.5	203	67.7
Female	38	39.2	27	27.8	32	33.0	97	32.3
Personal history								
Overweight (Body mass index ≥25, <30)	44	44.0	35	35.0	40	40.0	119	39.7
Arterial hypertension	40	40.0	40	40.0	34	34.0	114	38.0
Obesity (Body mass index≥30)	18	18.0	27	27.0	22	22.0	67	22.3
Diabetes mellitus	10	10.0	9	9.0	10	10.0	29	9.7
Smoking	12	12.0	6	6.0	10	10.0	28	9.3
Coronary disease	4	4.0	4	4.0	2	2.0	10	3.3
Dyslipidemia	0	0.0	1	1.0	1	1.0	2	0.7
Concomitant medications (CM)								
Patients consuming CM	49	49.0	50	50.0	41	41.0	140	46.7
ACEI	19	19.0	24	24.0	19	19.0	62	20.7
Diuretics	24	24.0	14	14.0	17	17.0	55	18.3
Calcium antagonists	18	18.0	11	11.0	9	9.0	38	12.7
Antidiabetics	9	9.0	4	4.0	8	8.0	21	7.0
Analgesics	2	2.0	6	6.0	5	5.0	13	4.3
β-blockers	7	7.0	1	1.0	3	3.0	11	3.7
Bronchodilators	3	3.0	4	4.0	1	1.0	8	2.7
Antiplatelets	2	2.0	1	1.0	1	1.0	4	1.3
Vasodilators	0	0.0	1	1.0	1	1.0	2	0.7
Antigouty	1	1.0	0	0.0	1	1.0	2	0.7

X: mean, SD: standard deviation, n: number of patients, ACEI: angiotensin-converting enzyme inhibitors
The table includes only those CM consumed by ≥ 2 patients.
All comparison were not signifiant (ANOVA, χ^2 test).

In addition to epidermophytosis, the patients included had other medical conditions, including overweight (39.7%), high blood pressure (38%), obesity (22.3%), diabetes (9.7%), smoking (9.3%), and coronary artery disease (3.3%). The frequency of concomitant therapy use was 46.7%, similar in all groups.

3.2 Analysis of Withdraw

Eleven patients (3.7%) were withdrawn from the study. The causes of treatment interruption were due to adverse events (1 ketoconazole-treated group, 1-terbinafine-treated group, 3 topical OLEOZON-treated group), voluntary abandonment (1 topical OLEOZON-treated group), no clinical improvement (1 ketoconazole-treated group, 1-terbinafine-treated group, 1 topical OLEOZON-treated group), and protocol violation (1-terbinafine-treated group, 1 topical OLEOZON-treated group).

3.3 Analysis of Efficacy

Morphologically, 93.3% of the patients had skin lesions characterized by scales (280 patients), 91.7% had mixed lesions (275 patients), 65.7% had vesicles (197 patients), 51.3% had erythema (154 patients) and 36.3% had macerated areas (109 patients) (Table 2).

Table 2. Effects on skin lesions of the patients studied

Skin lesions	Ketoconazole (n=100)				Terbinafine (n=100)				Topical OLEOZON® (n=100)			
	Baseline		Week 6		Baseline		Week 6		Baseline		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%
Vesicles	62	62.0	0**	10.0	67	67.0	1**	10.0	68	68.0	3**	9.0
Scales	91	91.0	20**	20.0	92	92.0	20**	20.0	97	97.0	17**	17.0
Macerated areas	36	36.0	2**	14.0	44	44.0	6**	17.0	29	29.0	9**	14.0
Erythema	59	59.0	2**	10.0	41	41.0	4**	8.0	54	54.0	6**	23.0
Mixed	92	92.0	2**	2.0	91	91.0	5**	19.0	92	92.0	8**	30.0

n: number of patients. **p<0.001 Comparison versus baseline (McNemar test). The comparisons between groups were not significant (χ^2 test)

A significant reduction in skin lesions was observed in all groups at the end of six weeks of treatment (Figure 1). However, no significant differences were observed between groups in any of the comparisons made.

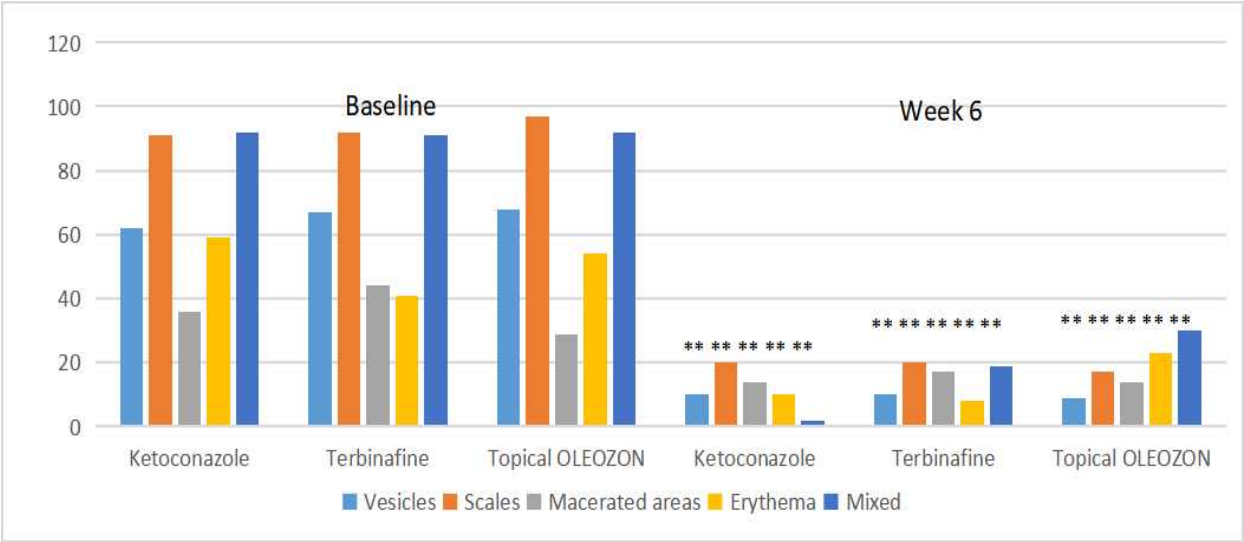

Figure 1. Effects on skin lesions of the patients studied.

Note: **p<0.001 Comparison versus baseline (McNemar test). The comparisons between groups were not significant (χ2 test).

T. *mentagrophytes* (23.3%) was the dermatophyte most frequently identified as the causal agent in the patients studied, followed by *E. floccosum* (12.7%) and *T. rubrum* (11%), Yeast (7%), *Microsporum sp* (0.3%), and other dermatophytes (45.7%) (Table 3).

Table 3. Effects on dermatophytes of the patients studied.

Types of Dermatophytes	Ketoconazole (n=100)				Terbinafine (n=100)				Topical OLEOZON® (n=100)			
	Baseline		Week 6		Baseline		Week 6		Baseline		Week 6	
	n	%	n	%	n	%	n	%	n	%	n	%
Trichophyton rubrum	6	6.0	0*	0.0	10	10.0	0**	0.0	17	17.0	1***	1.0
Trichophyton mentagrophyte	35	35.0	5***	5.0	21	21.0	1***	1.0	14	14.0	1***	1.0
Epidermophyton floccosum	12	12.0	2**	2.0	11	11.0	1**	1.0	15	15.0	3***	3.0
Microsporum sp	0	0.0	0	0.0	1	10.0	0	0.0	0	0.0	0	0.0
Yeast	7	7.0	0**	0.0	10	10.0	3*	3.0	4	4.0	1	1.0
Others	40	40.0	5***	2.0	47	47.0	6***	0.0	50	50.0	7***	5.0
Total	100	100.0	12	12.0	100	100.0	11	11.0	100	100.0	13	13.0

Note: n: number of patients. *p<0.05; **p<0.01; ***p<0.001 Comparison versus baseline (McNemar test). The comparisons between groups were not significant (χ^2 test).

The treatments significantly reduced the presence of dermatophytes at the end of the six weeks (Figure 2). However, no significant differences were observed between the groups in any of the comparisons made.

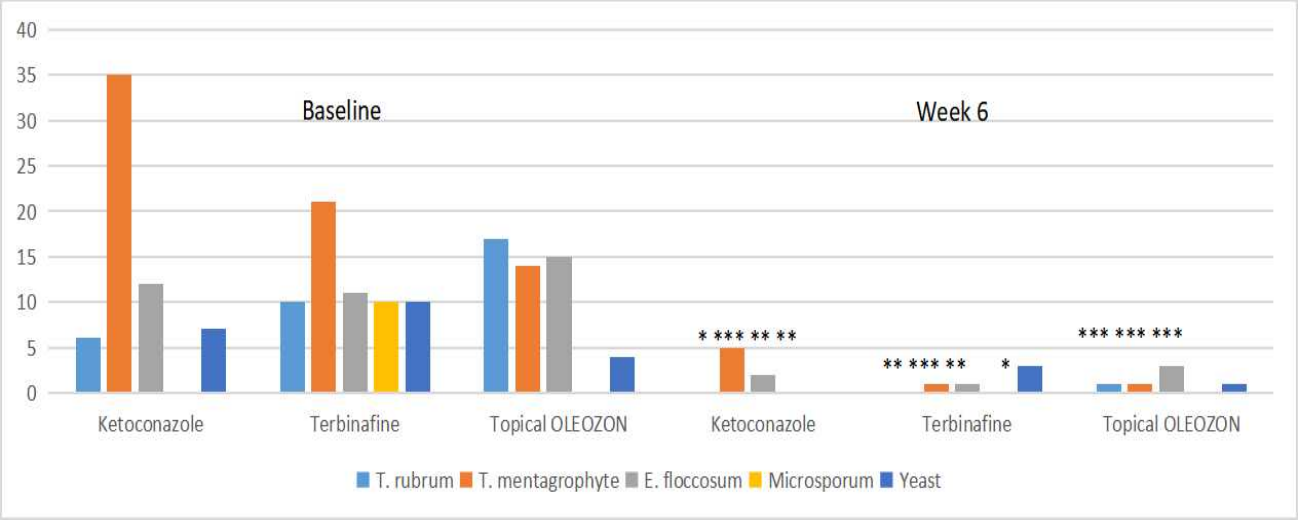

Figure 2. Effects on dermatophytes of the patients studied.

Note: *p<0.05; **p<0.01; ***p<0.001 Comparison versus baseline (McNemar test). The comparisons between groups were not significant (χ^2 test)

3.4 Analysis of Safety and Tolerability

No significant changes were obtained in any of the comparisons made (data not shown for simplicity) in the analysis of the physical examination and laboratory variables.

Seven patients reported adverse events during the study, two of them reported worsening of the lesions, two lymphangitis, two superimposed sepsis and one pruritus, and were classified as moderate due to requiring treatment (two from the group treated with ketoconazole, one from the group treated with terbinafine and four from the group treated with topical OLEOZON. However, all reported adverse events were classified as having a doubtful relationship with the treatments used.

4. Discussion

The present post-hoc analysis demonstrated that topical OLEOZON® applied for 6 weeks reduce skin lesions and dermatophytes in patients with Epidermophytosis, with effects comparable to ketoconazole and terbinafine.

This study included three hundred patients with a clinical and mycological diagnosis of Epidermophytosis.

The sex distribution of the included population showed a predominance of male patients 203/300 (67.7%), and an average age of 51 years, which coincides with what has been reported internationally regarding its epidemiology [28].

In addition to Epidermophytosis, the patients included had other pathological history, which is consistent with what has been described in other studies [29]. The frequency of concomitant therapy use was 46.7%, similar in all groups, with the use of antihypertensives being notable, followed by oral hypoglycemic agents, analgesics, bronchodilators, supplements, antiplatelets, vasodilators and antigouty.

Eleven patients (3.7%) were withdrawn from the study, therefore, 289/300 (96.3%) patients included completed the study, a very satisfactory figure since in studies in this type of patients very variable dropout frequencies have been obtained [30]. Yes, added to this is that all patients who completed the study properly applied their medication, the validity of the efficacy and safety data obtained is reinforced.

Treatment adherence was excellent, exceeding 90% and similar across all groups. The patients included correctly applied the prescribed treatments, according to the review of the empty vials and tubes, as well as the questionnaires conducted, with the exception of the eleven patients who were dropped from the study.

At the end of six weeks, treatment with topical OLEOZON® produced a total clinical and mycological cure rate in 78% of patients, similar to the efficacy achieved in the groups treated with ketoconazole (78%) and terbinafine (77%), while another 16% of patients treated with topical OLEOZON® achieved partial clinical cure (presence of improved lesions), similar to that achieved in the groups treated with ketoconazole and terbinafine. Complete mycological cure was achieved in 87% of patients treated with topical OLEOZON®, while complete elimination of dermatophytes was achieved in 88% of patients treated with ketoconazole and in 89% of patients treated with terbinafine.

Morphologically, 93.3% of the patients had skin lesions characterized by scales (280 patients), 91.7% had mixed lesions (275 patients), 65.7% had vesicles (197 patients), 51.3% had erythema (154 patients) and 36.3% had macerated areas (109 patients).

A significant reduction in skin lesions was observed in all groups after six weeks of treatment, with no significant differences between groups in the comparisons made of the variables evaluated.

T. mentagrophytes (23.3%) was the dermatophyte most frequently identified as the causal agent in the patients studied, followed by *E. floccosum* (12.7%) and *T. rubrum* (11%), Yeast (7%), *Microsporum sp* (0.3%), and other dermatophytes (45.7%).

These findings coincide with what has been reported in other studies, in which *T. mentagrophytes* continues to be the fungal agent causing the majority of *Tinea pedis* [31,32].

The treatments significantly reduced the presence of dermatophytes at six weeks. However, there were no significant differences between groups in the comparisons made.

Topical OLEOZON® applied for six weeks showed comparable effects in this clinical study with ketoconazole and terbinafine, efficacy results that coincide with those reported by other authors for these products in this type of patients with Epidermophytosis [18,19,22,33-35].

In this study, the treatments showed a safety and tolerability profile consistent with data reported for these treatments [18,19,22,33-35].

The treatments did not produce alterations in the physical examination parameters or the laboratory variables investigated. No significant differences were observed in the comparisons between groups, and the values for the variables evaluated remained within the ranges considered normal for these variables.

Topical OLEOZON® was very well tolerated, with only four patients reporting adverse events, while two patients treated with ketoconazole and one with terbinafine also reported adverse events. All adverse events reported during the study were classified as moderate because they required treatment, and they were also classified as having a doubtful relationship with the treatments used.

5. Conclusions

Topical OLEOZON® showed comparable effects to ketoconazole and terbinafine in reducing all skin lesions and the presence of dermatophytes in Cuban patients with Epidermophytosis, with a favorable impact on the clinical and mycological cure rate of these patients.

These findings support the potential utility of OLEOZON® as an affordable, well-tolerated alternative in settings where conventional antifungal options may be limited or contraindicated.

Further studies including different designs and treatment time, however, are required to extrapolate the present results to other populations.

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Author Contributions

JCFT: Conceptualization, Investigation, Project administration & Writing-original draft. EAGP: Investigation & Methodology. LAP: Conceptualization, Investigation & Review. YGL: Investigation & Methodology. ESW: Methodology, Resources. MRO: Investigation & Methodology. JADC: Methodology, Resources. ABS: Methodology, Resources. ALC: Supervision & Validation. YRN: Supervision & Validation. YFD: Supervision & Validation. MECH: Methodology, Resources. RUP: Software, Formal Analysis.

Authorship Declaration

We hereby request the evaluation of the work for publication, bearing in mind that it has not been previous published, nor it´s being review by any other journal.

The instructions for the authors and the ethical responsibilities have been take into account, among them, that all author meets the requirements of authorship and all have declared not to have a conflict of interest.

The authors have been involved in the conception and design of the work, or in the collection of data, or in the analysis and interpretation of the data, as well as in the writing of the article or in its critical review and in the approval of the final version for publication.

The authors who prepared the article are employees of a research institution where research is the main function of the entity. The curriculum vitae of all the authors only relates to research activities.

Conflicts of Interest

The authors declare that have no conflict of interest in relation to this work.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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