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Comparison of Two Topical Preparations for the Treatment of Onychomycosis: *Melaleuca alternifolia* (Tea Tree) Oil and Clotrimazole

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Background. The prevalence of onychomycosis, the most frequent cause of nail disease, ranges from 2% to 13%. Standard treatments include debridement, topical medications, and systemic therapies. This study assesses the efficacy and tolerability of topical application of 1% clotrimazole solution compared with that of 100% *Melaleuca alternifolia* (tea tree) oil for the treatment of toenail onychomycosis.

Methods. A double-blind, multicenter, randomized controlled trial was performed at two primary care health and residency training centers and one private podiatrist's office. The participants included 117 patients with distal subungual onychomycosis proven by culture. Patients received twice-daily application of either 1% clotrimazole (CL) solution or 100% tea tree (TT) oil for 6 months. Debridement and clinical assessment were performed at 0, 1, 3, and 6 months. Cultures were obtained at 0 and 6 months. Each patient's subjective assessment was also obtained 3 months after the conclusion of therapy.

Results. The baseline characteristics of the treatment groups did not differ significantly. After 6 months of therapy, the two treatment groups were comparable based on culture cure (CL = 11%, TT = 18%) and clinical assessment documenting partial or full resolution (CL = 61%, TT = 60%). Three months later, about one half of each group reported continued improvement or resolution (CL = 55%; TT = 56%).

Conclusions. All current therapies have high recurrence rates. Oral therapy has the added disadvantages of high cost and potentially serious adverse effects. Topical therapy, including the two preparations presented in this paper, provide improvement in nail appearance and symptomatology. The use of a topical preparation in conjunction with debridement is an appropriate initial treatment strategy.

Key words. Onychomycosis; mycoses; nails; nail diseases; clotrimazole; administration, topical.
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The prevalence of onychomycosis, the most frequent cause of nail disease,[1-3] ranges from 2% to 13%. Onychomycosis is caused by dermatophyte infections, the most common of which is *Trichophyton rubrum*; yeast (*Candida* spp); and occasionally molds. Three treatment modalities are available: debridement to eliminate affected keratin, topical medications, and systemic therapy. Topical therapy may have limited effectiveness because of poor penetration of the medication into the nail.[4,5]

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Oral therapies, beginning with griseofulvin in 1959, have been the "gold standard" treatment for dermatophyte onychomycosis.[6] Unfortunately, cure rates with griseofulvin range from 3% to 38%, and although rates may be higher when combined with toenail avulsion or topical medication or both, no significant follow-up data exist for these combined modalities.[7-9] Ketoconazole is attractive because it presumably treats yeast as well as dermatophyte onychomycosis and shows a cure rate of 50% to 93% at 1 year,[5,10,11] which is much higher than that of griseofulvin. Although side effects are rare, they can include pruritus, idiosyncratic liver dysfunction,[12] and gynecomastia.[10] Furthermore, about 50% of toenail infections recur 4 years after the completion of treatment.[13] Itraconazole has cure rates ranging from 4% to 92% with potentially fewer side effects,[14-18] but thus far,

it has been evaluated only in small studies. Follow-up data beyond 1 year are unavailable. Fluconazole has been used by some physicians for both short- and long-term treatment, but no randomized controlled trials have been performed. Outside the United States, much recent research has focused on oral terbinafine (Lamisil), an active fungicidal agent. Cure rates range from 37% to 82% at 6-month follow-up, with a treatment period as short as 2 weeks[19] to 3 months.[20–24] Once again, long-term results and side effects are unknown. Only the topical form of terbinafine has been approved in the United States.

In light of the varied cure rates, potential adverse effects, high cost, and significant recurrence rate of oral treatment,[25] effective topical therapy would be desirable as primary therapy or for augmentation of systemic therapies. Although the topical imidazole preparations are commonly used,[1] their efficacy has not been assessed in controlled trials. In a limited study, clotrimazole has been reported to be of mild benefit in the treatment of onychomycosis.[26] Other imidazole preparations used in combination with nail removal have resulted in one report of cure in 13 patients.[5]

Nail tinctures and lacquers are also being tested with promising results.[27] The tincture or lacquer is thought to provide better nail penetration. Several recent studies have examined amorolfine 5% nail lacquer.[28–30] One large study (N = 456) realized cure rates in the 50% to 74% range.[30]

Tea tree oil comes from a shrublike tree in Australia known as *Melaleuca alternifolia*. It was named by Captain Cook, who observed the aborigines brewing these leaves for medicinal purposes. In World War I, it was used in first-aid kits for Australian troops to treat burns, bites, and infections. The active ingredient, Terpinen-4-ol, has both antibacterial and antifungal properties.[31,32] Many brief studies have found this popular home remedy successful in treating a variety of ailments: tinea pedis and onychomycosis,[33,34] trichomonal vaginitis,[35] and acne[36] (the latter the subject of a randomized controlled trial). Tea tree oil is available over the counter at most health food stores at a cost comparable to that of clotrimazole solution. We report a multicenter, randomized, double-blind study to compare the efficacy of two topical preparations, tea tree oil and 1% clotrimazole solution, for the treatment of toenail onychomycosis.

Methods

Either 1% clotrimazole solution or 100% tea tree oil was applied to the affected nail(s) twice daily for 6 months.

Study Participant Criteria

All patients presenting to one of three sites between June 1991 and December 1991 with distal subungual toe onychomycosis proven by culture were enrolled. Patients were excluded if they had had immune-suppressant therapy within the previous 6 months, had used a topical agent on the toenails in the previous 2 weeks, had a history of psoriasis, or had known human immunodeficiency virus (HIV) infection.

Drug Treatment

Patients were randomly assigned to receive 1% clotrimazole solution (Schering-Plough Corp, Liberty Corner, NJ) or 100% tea tree oil (Thursday Plantation Inc, Montecito, Calif). Solutions were received directly from the manufacturers. The Highland Hospital pharmacy filled 60-cc standardized bottles with solutions of clotrimazole and of tea tree oil that appeared identical. The treatment groups were randomized by the pharmacy by means of a computerized random-number generator. The type of medication was blinded to both patient and provider. The patients were instructed on how to apply the medication topically with a swab to all affected nails twice daily. At the 1-, 3-, and 6-month checkups, the patients' nails were trimmed and debrided by the physician, using straight-edged nail clippers. Any adverse reactions were recorded. Compliance was encouraged by mailings and telephone calls, by recording the number of missed applications, and by reminding patients at each of their four visits of the importance of twice-daily medicine application.

Outcome Assessment

There were three primary measures of outcome: culture, clinical assessment, and the patient's subjective assessment (Table 1). At the 6-month visit, repeat nail cultures were performed. The dermatophyte infection test medium was chosen because it achieves better than 97% diagnostic accuracy and has a low false-positive rate.[37,38] All three investigators standardized the method of nail debridement and use of culture medium by organizing a protocol used by other investigators.[37,39,40] The optimal technique for yielding an accurate culture for distal subungual onychomycosis is debriding to the healthy nail, scraping the debris with a curette (No. 15 blade) or small spatula, and inoculating the culture with the debris.[4,40,41] At the time of the 6-month final culture, patients were requested to abstain from using the topical preparation for 48 hours before their visit to prevent false negatives.

At the 1-, 3-, and 6-month visits, the physician

.ble 1. Characteristics of Patients Treated Twice Daily with ɔ Clotrimazole Solution or 100% Tea Tree Oil for Toenail ıychomycosis

ıaracteristics	Patients Treated with Clotrimazole (n = 53)	Patients Treated with Tea Tree Oil (n = 64)
:story of diabetes, %	19	14
:story of trauma, %	8	6
male, %	72	77
:erage age, y	59	61
ail ..ase for more than 1 ye:	92	92
ılture results, %		
Trichophyton rubrum	77	83
Trichophyton mentagrophytes	19	13

ɔTE: *No statistically significant differences were found.*

:corded "full," "partial," or "no" resolution by appear- ıce of the index nail (the nail with the greatest fungal urden at the time of entry into the study). In addition, l patients were telephoned 3 months after the conclu- on of the study. They were asked by a research assistant hether their nail appearance and symptomatology (pru- tis and pain) had resolved, improved, stayed the same, r worsened.

tatistical Analysis

ar 'e size calculations assumed a base cure rate of 0% ısing clotrimazole in order to detect a cure rate vith tea tree oil of at least 30%, with alpha set at .05 one-tailed) and beta set at .8.[42] This calculation yielded . sample size of 52 per group, allowing for 10% loss to ollow-up.

Results

One hundred seventeen patients (CL = 53; TT = 64) were randomly assigned to a treatment group. Strict random assignment was adhered to throughout the study. The baseline characteristics of the treatment groups did not differ significantly (Table 2). Cultures were positive (excluding contaminants not considered positive) for predominantly two species: *Trichophyton rubrum* (80%), *T mentagrophytes* (16%), and other (4%).

Five (4%) of the 117 patients were dropped from the study because they had moved or their telephone had been disconnected (4 of 53 CL; 1 of 64 TT). Adverse reactions included erythema and irritation (most common) and edema. Adverse reactions occurred in 7% (3 of 53 CL; 5 of 64 TT), resulting in four (3%) of the original 117 participants dropping out of the study.

Table 2. Results of 6 Months of Treatment with 1% Clotrimazole and 100% Tea Tree Oil

Result	Clotrimazole Treatment Group n (%)	Tea Tree Oil Treatment Group n (%)
Culture negative at end of therapy	4 (11)	7 (18)
Full or partial resolution at end of therapy	22 (61)	24 (60)
Full or partial resolution 3 months after conclusion of therapy	27 (55)	33 (56)

NOTE: *No statistically significant differences were found.*

Chi-square statistical analysis failed to reveal any significant differences between the two treatments for the culture being negative at 6 months, clinical assessment at 6 months, or telephone follow-up 3 months after study completion (Table 1).

Discussion

This multicenter, double-blind, randomized clinical trial was designed to assess and compare the efficacy and tolerability of topical application of 1% clotrimazole solution vs 100% tea tree oil for the treatment of toenail onychomycosis. The two preparations were comparable in efficacy of cure, clinical assessment, and subjective improvement. Their cost is also comparable. One half to two thirds of the study patients showed improvement in both clinical assessment and subjective rating of nail appearance and symptomatology.

Our study yielded results similar to those of other studies.[43] Cure rates in the 10% to 15% range have been found with a propylene glycol–urea–lactic acid solution,[44] and with ciclopiroxolamine.[45,46] Even higher cure rates have been found with other treatments: 30% to 60% with urea-bifonazole solution[47–49]; 42% with naftitine hydrochloride gel[50]; 64% to 84% with amorolfine,[51] and 50% to 74% with amorolfine lacquer.[30]

The principal limitation of the study was the 35% loss to culture follow-up. However, in a comparison of the participants who either did or did not show up for the 6-month culture, no statistically significant differences were found at the 3-month posttreatment telephone follow-up. Given the improvement reported at telephone follow-up in both groups (those who did and those who did not attend their 6-month visit), the lack of follow-up does not appear to be related to outcome. A

potential limitation of this study was that no photographs were taken of the nails, but this is unlikely to have led to bias since this factor affects each group equally. Some investigators have discouraged the use of the dermatophyte infection test medium for culture[41,52] because of the potential for contamination, but in our study, this concern was resolved by using nail debris rather than nail clippings.[37,38]

Three additional interventions may have improved the outcome: simultaneous use of multiple oral and topical agents, longer treatment times, and a keratolytic agent, such as DMSO, or other agents that improve nail penetration of the medication.

One potential reason for the poor long-term benefits of any therapy is that it may be treating only a manifestation of underlying disease(s), such as generalized immune suppression or peripheral micro- or macrovascular disease. In a study of 400 patients, Forck[53] looked at the "relationship between blood circulation of the skin and the development of fungus disease" and found a greater than 50% reduction in blood flow in patients with tinea pedis and onychomycosis as compared with patients without these disorders. If onychomycosis is a symptom of an underlying process, then treatment aimed at eradication of a pathogen[54] may be unrealistic. A more appropriate goal may be the amelioration of symptoms and the improvement of nail appearance.

Topical and oral therapies have high recurrence rates. Oral therapy has the added disadvantages of high cost and potentially adverse side effects. Topical therapies, including the two preparations presented in this paper, provide significant improvement in nail appearance and symptomatology for over one half of all subjects. The use of a topical preparation in conjunction with debridement is an appropriate initial treatment strategy.

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