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A Comparison of the Efficacy and Safety Profiles of Topical Amphotericin B in 30% Dimethyl Sulfoxide Cream Versus 30% Dimethyl Sulfoxide Cream for Treatment of Nondermatophyte Onychomycosis

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KEYWORDS
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ABSTRACT:

Background: Studies on topical amphotericin B cream's safety and efficacy in vivo are scarce, despite the drug's usefulness in treating nondermatophyte onychomycosis in vitro.

Objective: We studied the effectiveness and safety of topical 0.3% amphotericin B in 30% dimethyl sulfoxide cream (amphotericin B cream) in nondermatophyte mold onychomycosis using the vehicle cream 30% dimethyl sulfoxide cream as control

Methods: This randomized controlled study was conducted in patients diagnosed with nondermatophyte mold onychomycosis. They were randomly divided into two groups of ten patients each: one treated with amphotericin B cream with vechicle and the other with the vehicle cream alone. Clinical and mycological cure as well as safety were evaluated.

Results: Only nine patients from the vehicle cream group were available for follow-up, out of the ten patients treated with amphotericin B cream and the vehicle cream in the trial. Distal lateral subungual onychomycosis afflicted the great toenails in 18 (94.7%) of the 19 evaluable cases. Eight (80%) of the patients treated with amphotericin B cream and four (44.4%) of the patients treated with the control (vehicle) cream had a mycological cure. Only 2 (22.2%) of the patients receiving the control cream saw a clinical cure, compared to 7 (70%) of the patients receiving amphotericin B cream. No adverse events were observed.

Limitations: The small sample size and the fact that PCR fungal identification that provides accurate identification of fungal species was not performed are limitations of our study.

Conclusion: Topical amphotericin B cream was both very effective and safe in the treatment nondermatophyte mold onychomycosis. The control (vehicle) cream containing 30% dimethyl sulfoxide also demonstrated some antifungal activity.

Introduction

Yeasts, nondermatophyte molds, and dermatophytes are common causes of onychomycosis.[1]The nondermatophyte mold onychomycosis is becoming more common, particularly in tropical nations where prevalence rates have been observed to range from 24.1% to 51.6%.2–5. Scopulariopsis brevicaulis, Fusarium species, Aspergillus species, Neoscytalidium dimidiatum, and Acremonium species are the most often isolated nondermatophyte molds. Nondermatophyte mold onychomycosis can be treated with topical and oral antifungal medications, as well as chemical or surgical nail avulsion.[1, 6, 8–11] A member of the polyene class of

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antimicrobial substances, amphotericin B is an antifungal with a low risk of resistance and broad fungicidal effects.[12] It attaches itself to ergosterol in the fungal cell membrane to create permeable channels that let ions and metabolites out and ultimately kill the cell.[16–18] In vitro studies have demonstrated the effectiveness of topical amphotericin B against nondermatophyte molds, with minimum inhibitory doses ranging from 0.06 to 1 µg/ml.5, 13–15 Due to its strong lipophilicity, dimethyl sulfoxide is frequently utilized as a medication delivery vehicle to augment its therapeutic efficacy.[19]

Dimethyl sulfoxide is a water-soluble, polar, stable substance with antifungal qualities that is often utilized as a solvent to increase the absorption of antifungal medications. [20, 21] An in vitro, using a nail model, it was demonstrated that amphotericin B prepared directly in 30% dimethyl sulfoxide could attain concentrations significantly higher than the minimum inhibitory doses for nondermatophyte molds.[22] Nevertheless, there haven't been many published in vivo studies using topical amphotericin B for this illness. In this work, we describe the safety and efficacy of topical amphotericin B in 30% dimethyl sulfoxide treatment for onychomycosis caused by nondermatophyte mold.

Materials and Methods

Study design

A randomized, double-blind clinical trial was conducted at Deprtment of dermatology ,venerology and leprosy, Vinayaka Missions Medical College ,Karaikal. The study duration was 18 months. Signed informed consent were taken from all patients. Patients were assigned to two groups using mixed-blocked randomization. The first group received topical amphotericin B cream while the second received the vehicle cream.

Subject

Twenty patients with nondermatophyte mold onychomycosis were enrolled and randomized into two groups of ten each. All patients were over 18 years of age and none had been treated with oral, topical or intravenous antifungal therapies during the preceding 36 weeks. Patients with dermatophyte onychomycosis, mixed onychomycosis or other concomitant nail diseases (such as psoriatic nail or paronychia) and immunocompromised patients were excluded.

Nondermatophyte mold onychomycosis was diagnosed as per the criteria of Gupta et al. which included positive microscopic examination of nail clippings in 20% potassium hydroxide solution, isolation of nondermatophyte molds on at least two occasions on fungal culture from repeated samplings, exclusion of dermatophytes and histological examination.[6]

Preparation of medication

Amphotericin B was mixed with 30% dimethyl sulfoxide cream to achieve the desired amphotericin B concentration of 3 mg/ml. The 30% dimethyl sulfoxide cream served as control. Both the preparations were stored in identical aluminium tubes at temperatures ranging from 2°C to 8°C. Patients were instructed to apply a pea-sized amount of cream once daily at night to the affected nails and to wrap them in tape overnight to enhance penetration of the medication. No other systemic antifungal agent was given during the study period.

Treatment, follow-up and measurement Patients were directed to apply the medication continuously for 36 weeks. The clinical status, mycological test results, adherence to the drug regimen and adverse events were assessed at 0, 12, 24 and 36 weeks. Subsequent evaluations after the treatment period (clinical status, mycological test results and adverse events) were performed at 48, 60 and 72 weeks. Onychomycosis Severity Index (OSI) was used to determine the extent of onychomycosis.[23]
A "clinical cure" was defined as >95% clinically normal. Two treatment-blinded investigators (CL and SB) conducted the clinical examination.

The assessment of efficacy was based on mycological tests results with “mycological cure” being defined as negative potassium hydroxide test and fungal culture results.[24]

Statistical analysis
Descriptive statistics were applied to the data analysis. Fisher's exact test was utilized to evaluate the variations between
the variables that are categorical. Mann-Whitney U-tests and independent t-tests were used to assess the continuous variables with and without normal distribution, respectively. P was considered statistically significant at 0.05. PASW Statistics for Windows

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(version 18; SPSS Inc., Chicago, Ill., USA) was used to analyze the data.

Result

Twenty patients with onychomycosis caused by nondermatophyte mold were chosen for the investigation. Since one of the ten patients in the control group missed the follow-up visits, she was not included in the analysis. Table 1 lists these 19 individuals' clinical features and demographic information. Ten (52.6%) of the patients were male, and the mean (SD) age was 68.9 (8.6) years. The two groups did not differ significantly in terms of predisposing variables, onychomycosis severity, disease duration, or underlying disorders.

Clinical cure was seen in 7 of the 10 (70%) patients who received amphotericin B cream but in only 2 of 9 (22.2%) patients treated with the vehicle cream. The mycological cure rates for amphotericin B were also higher than for the vehicle cream (80% vs. 44.4%). The two mycological failures in the amphotericin B cream group had Neoscytalidium spp. onychomycosis. No adverse events were reported during the 72 weeks of the study in either group.

Table 1: Demographic data and clinical characteristics of patients diagnosed with nondermatophyte **onychomycosis**

Parameters	Total (*n*, 19)	pical amphotericin B cream (*n*, 10)	Vehicle cream (*n*, 9)	*P*-value
Sex				
Male	**10 (52.6)**	**5 (50.0)**	**5 (55.6)**	**1.000**
Female	**9 (47.4)**	**5 (50.0)**	**4 (44.4)**	
Age (years), mean±SD	**68.9 ± 8.6**	**70.7±6.8**	**66.9±10.3**	**0.351**
Disease duration (months), median (min, max)	**41.0 (9.0,124.0)**	**42.5 (10.0,87.0)**	**41.0 (9.0,124.0)**	**0.191**
OSI score, median (min, max)	**3.0 (1.0,13.0)**	**1.5 (1.0,12.0)**	**3.0 (1.0,13.0)**	**0.511**
Predisposing factors for onychomycosis				
Hyperhidrosis of the feet	**5 (26.3)**	**4 (40.0)**	**1 (11.1)**	**0.303**
Impaired circulation	**2 (10.5)**	**2 (20.0)**	**0**	**0.474**
History of foot trauma	**7 (36.8)**	**4 (40.0)**	**3 (33.3)**	**1.000**
History of contact with pets	**7 (36.8)**	**3 (30.0)**	**4 (44.4)**	**0.650**
Big toenails	**18 (94.7)**	**9 (90.0)**	**9 (100.0)**	**1**
Third toenails	**1 (5.3)**	**1 (10.0)**	**0**	
Depth of nail involvement				
<1/3	**16 (84.2)**	**8 (80.0)**	**8 (88.9)**	**1**
1/3–2/3	**3 (15.8)**	**2 (20.0)**	**1 (11.1)**	
Fungal culture results				
***Neoscytalidium* spp.**	**15 (78.9)**	**7 (70.0)**	**8 (88.9)**	**0.582**
***Fusarium* spp.**	**4 (21.1)**	**3 (30.0)**	**1 (11.1)**	
Concomitant fungal foot infection	**12 (63.2)**	**6 (60.0)**	**6 (66.7)**	**1**

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Concurrent foot deformity	**8 (42.1)**	**4 (40.0)**	**4 (44.4)**	**1**
Clinical cure rate	**9 (47.4)**	**7 (70.0)**	**2 (22.2)**	**0.07**
Time to clinical cure (months), mean±SD (*n*=9)	**10.6±4.6**	**10.4±5.3**	**11.0±0**	**0.786**
Mycological cure rate	**12 (63.2)**	**8 (80.0)**	**4 (44.4)**	**0.17**
Time to mycological cure (months), mean±SD (*n*=12)	**8.8±5.2**	**9.5±6.0**	**7.5±3.4**	**0.482**

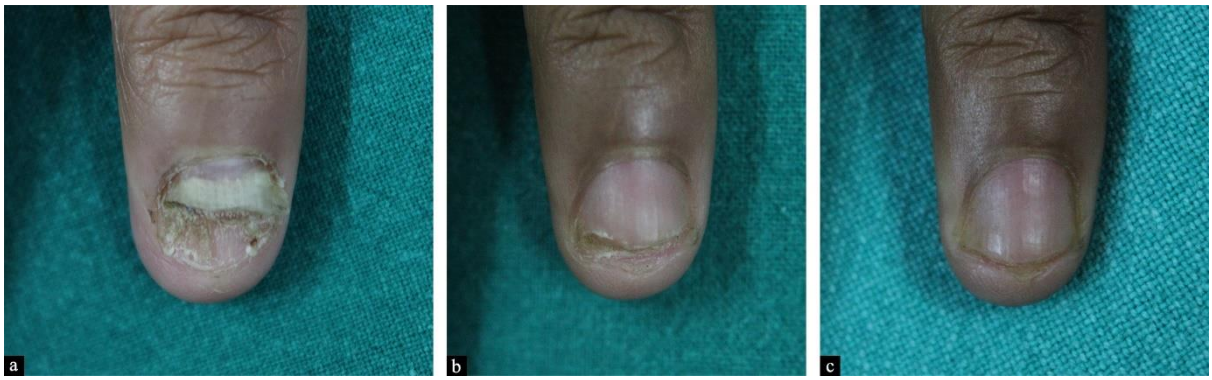

Figure 1: Finger nail with onychomycosis treated with amphotericin B in 30% dimethyl sulfoxide at (a- day 1,b-after 4 months,c-after 6 months)

Discussion

Studies on the topical treatment of nondermatophyte mold onychomycosis are few. Earlier reports have noted a 44% mycological response rate with 8% ciclopirox nail lacquer in 18 patients with Neoscytalidium spp. onychomycosis at 12 months and 89.3% mycological cure with 5% amorolfine nail lacquer in N. dimidiatum onychomycosis.[25, 26] In the latter study, a mycological cure of 32% was noted in those patients receiving only 40% urea cream with occlusion.[26] Combined treatment of nondermatophyte mold onychomycosis with 5% amorolfine nail lacquer and neodymium-doped yttrium aluminum garnet (Nd: YAG) 1064-nm laser resulted in only a marginally higher mycological cure rate of 65% as compared to 60% in those using 5% amorolfine nail lacquer alone.[27]

Amphotericin B has excellent in vitro activity against nondermatophyte molds.[5,13-15] In a study from Switzerland mycological cure was achieved with 0.2 % topical amphotericin B in 50% dimethyl sulfoxide in 7 (87.5%) of 8 treatment-resistant nondermatophyte mold onychomycosis patients at 12 months.17This compares well with the mycological cure rate of 80% in our study, although we used 0.3% amphotericin B in 30% dimethyl sulfoxide cream.[27]

The mycological and clinical cure rates of 44% and 22%, respectively, with the 30% dimethyl sulfoxide vehicle cream was an unexpected finding in our study. Dimethyl sulfoxide has both keratolytic [28,29] and antifungal properties and has been shown to inhibit the growth of dermatophytes and yeasts in vitro.[21,30,31]

Limitations

Limitations of the study include the small sample size and the non-availability of PCR fungal identification which provides accurate identification of fungal species was not used in this study. As all cases were the distal lateral subungual type, treatment response according to clinical type of onychomycosis could not be identified. Although all four cases of fusarium spp onychomycosis responded to amphotericin B in our study, it is difficult

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to draw any firm conclusions owing to the small numbers. Validation through a larger sample size is needed to conclusively demonstrate the effects of not only amphotericin B, but also the 30% dimethyl sulfoxide vehicle cream for nondermatophyte mold onychomycosis treatment.

Conclusion

Amphotericin B in 30% dimethyl sulfoxide was effective and safe in the treatment of nondermatophyte mold onychomycosis. However, the vehicle cream containing 30% dimethyl sulfoxide also showed some effectiveness in nondermatophyte mold onychomycosis

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