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Study to Evaluate the Efficacy and Safety of Topical Lipid-based Amphotericin B Gel 0.1% in Patients with Cutaneous Mycosis Resistant to Conventional Therapy

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Abstract

The last few years have seen a significant rise in the incidence of cutaneous mycosis infections resistant to conventional therapy. Topical nanostructured lipid formulations of Amphotericin B have emerged as a novel system to tackle this menace. The present study is an open-label, single-arm, prospective study to analyze the efficacy and safety of topical nanostructured lipid-based Amphotericin B gel in treating patients attending Dermatology OPD, Victoria hospital, with cutaneous mycosis resistant to conventional therapy. Thirty patients diagnosed with tinea corporis/cruris resistant to conventional therapy were included in the study. Patients were advised to apply amphotericin B gel 0.1% on the affected area twice daily for four weeks. Outcome parameters like pruritus, erythema, vesicles, desquamation, and KOH mount were noted weekly for the assessment of efficacy and safety. One-way ANOVA was used for statistical analysis. After treatment with Amphotericin B gel, patients showed a statistically significant reduction in pruritus, erythema, vesicles, and desquamation from baseline across time towards the end of 4 weeks ($p<0.05$). Also, the Mean total score of all symptoms, which was 8.3±3.1 at baseline, was reduced to 0.9±0.7 at the end of the 4th week ($p<0.05$). All the patients treated were mycologically negative for KOH mount at the end of the study period. No serious adverse drug reactions were reported to treatment. To conclude, topical nanostructured lipid-based amphotericin B gel in patients with cutaneous mycosis resistant to conventional treatment was efficacious and safe.

Keywords: Amphotericin B Gel, Cutaneous mycosis, Resistance, NLC formulation.

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Introduction

Cutaneous mycosis, caused by dermatophytes, is a common public health problem in tropical nations where the climate is hot and humid.[1] Dermatophyte infect nearly 25% of the world's population, according to the World Health Organization.[2] The last few years have seen a significant rise in the incidence of cutaneous mycosis infections resistant to conventional therapy due to immunocompromised states such as diabetes mellitus, steroid use, HIV infection, lymphomas, etc,.[3] Dermatophytic infections, both chronic and recurrent, cause patients severe social, economic, and emotional distress.[4] Thus, recognising the condition at an early stage and treatment is essential to reduce morbidity and the risk of transmission.[2]

Topical therapy is preferred over systemic therapy in cutaneous mycoses because of the advantages such as lesser side effects, low dose, avoiding drug-drug interactions, better skin permeation, low cost, and better compliance.[3,5,6] Recently, clinical failure and relapses have been observed with commonly used antifungals such as azoles and allylamines.[3] Amphotericin B has always been the gold standard in treating systemic fungal infections.[7]

However, the use of amphotericin B in clinical practice is limited due to its toxicity, which is mitigated by utilizing novel formulations such as topical nano-structured lipid-based amphotericin B gel.[8] The lipid used in this formulation was natural soy phosphatidylcholine which improves percutaneous absorption of the drug and is non-irritating to the skin. Fungal resistance to Amphotericin B is rare when compared to other antifungals.[3]

Considering all these facts, to strengthen the existing knowledge, the present study is designed to evaluate the efficacy and safety of lipid-based Amphotericin B gel topically in patients with cutaneous mycosis resistant to conventional treatment.

Methods

It was an open-label, single-arm, prospective study conducted in the outpatient Department of dermatology, Victoria hospital, attached to Bangalore medical college and research institute. Thirty patients with cutaneous mycoses resistant to conventional therapy were included. The sample size was arrived at, assuming a 95% confidence interval and power of 80%, and a dropout rate of 20%.

Patients of either sex aged above 18 years with a clinical diagnosis of resistant cutaneous mycosis (Resistant to four weeks of conventional topical antifungal therapy such as azoles, imidazoles, and allylamines), confirmation done with a skin scraping positive for KOH (Potassium hydroxide) mount, who gave informed consent were included in the study. Patients with extensive cutaneous mycoses, patients with a known history or clinical evidence of severe cardiac, pulmonary, gastrointestinal, renal, hepatic, neurological disease or uncontrolled diabetes mellitus, those with a history of hypersensitivity to amphotericin B, and pregnant and lactating mothers were excluded from the study.

Institutional ethics committee clearance (BMCRI/PS/105/2016-17 – EC number dated 03.09.2016) has obtained prior to the research procedure. Written informed consent was obtained from all study participants. The outpatients attending the department of dermatology fulfilling the inclusion/exclusion criteria were enrolled in the study. The study drug (Topical nanostructured lipid-based Amphotericin B gel) was purchased from a reputed pharmaceutical company. The study design summary is depicted in Figure 1.

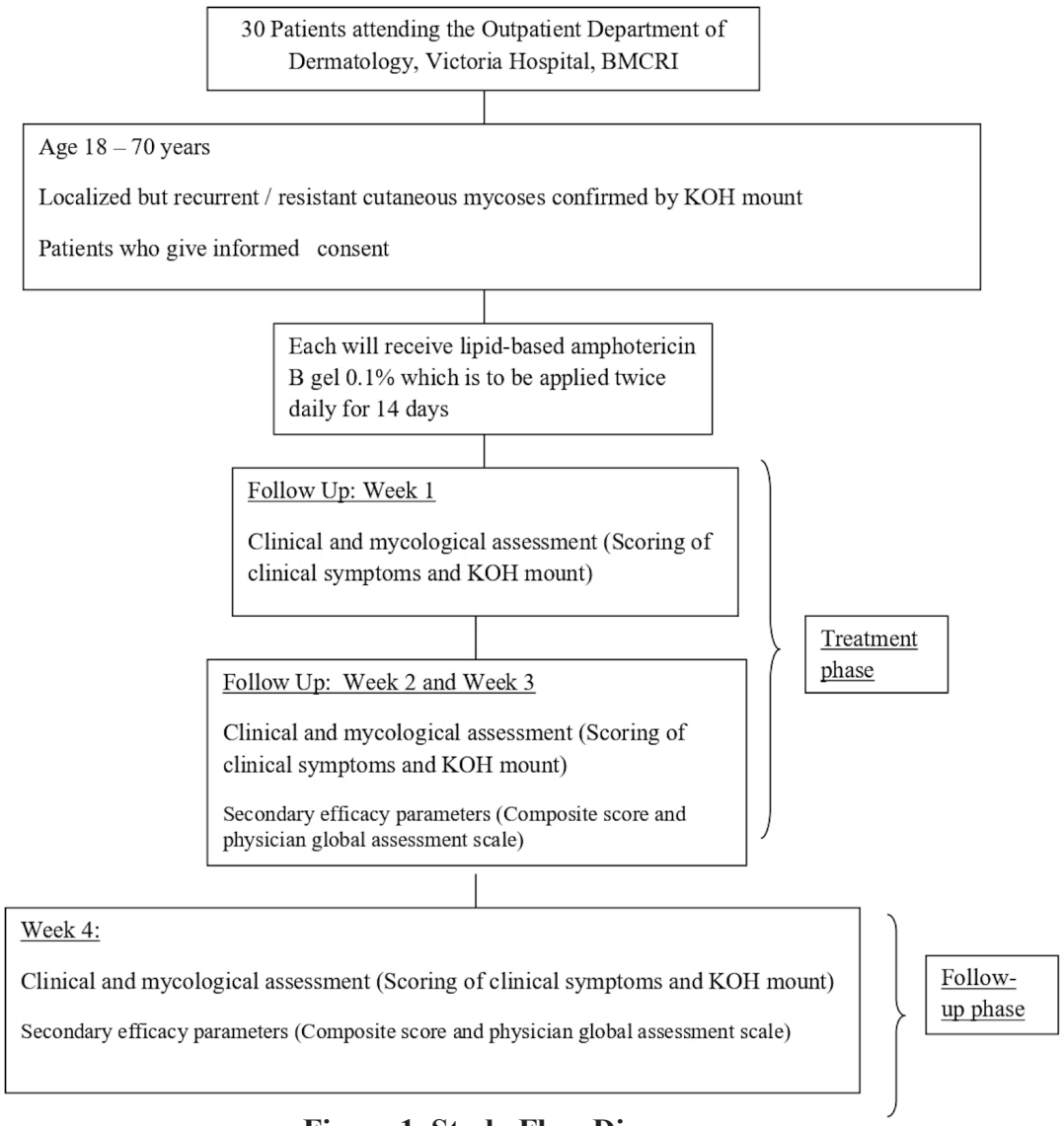

Figure 1. Study Flow Diagram

Primary efficacy was assessed based on a clinical and mycological assessment of tinea lesion at baseline, end of 'Treatment Phase' (1 and 2 weeks), and end of the Follow-up Phase (4 weeks). Clinical assessment is based on the proportion of patients with symptoms and signs of tinea lesions, namely pruritus, erythema, vesicle, and desquamation, and graded as none (0), mild (1), moderate (2), and severe (3) depending on intensity.9 Mycological assessment is based on KOH mount for dermatophytes.

The secondary efficacy was assessed by using the 'Composite Score' of all clinical symptoms (pruritus, erythema, vesicle, and desquamation); and the 'Physician Global Assessment' which was based on three criteria as follows: 1) successful treatment outcome (clinical cure + negative mycology); 2) clinical success (clinical cure + symptomatic relief); and 3) clinical failure (no clinical cure and mycologic improvement); which all assessed at the end of the 'Treatment Phase' and 'Follow-up Phase'.

The safety was assessed by monitoring and recording adverse events reported by the patient at any time of the study (CDSCO adverse drug reaction reporting form).

Results and Discussion

Dermatophytes are amongst the most common causative agents of fungal infections worldwide. Mutations in several species of dermatophytes are likely to play a role in the recurrence or resistance of infections. Furthermore, resistance to commonly used topical and oral antifungals has increased alarmingly in the last 4-5 years, especially among the immunocompromised. The growing epidemic of recurrent/chronic dermatophytosis has led to the need for newer antifungals and formulations.[2,6]

The present study was conducted on 13 male and 17 female participants. Only 27 of the total 30 study participants were a part of the study till the end of the study period, and the remaining three participants who were migrant laborers could not be followed-up.

Patients showed a reduction observed through the clinical sign and symptoms score, including pruritis, erythema, vesicles, and desquamation from baseline to 4th week. All the patients who were resistant to conventional treatment, such as azoles, imidazoles and allylamines, were responsive to Amphotericin B gel. The mean readings showed that there was a clinically significant improvement following treatment with Topical Nanostructured Lipid Based Amphotericin B Gel 0.1%, as summarised in Table 1.

Table 1. Mean Scores of Primary Efficacy Parameters at the 1st, 2nd, 3rd and 4th week

Parameter	1st visit (Baseline)	2nd visit (Week 1)	3rd visit (Week 2)	4th visit (Week 4)	p-value
Pruritis	2.78 ± 0.71	1.96 ± 0.71	1.13 ± 0.50	0.56 ± 0.50	0.04
Erythema	2.13 ± 1.00	1.30 ± 0.91	0.86 ± 0.68	0.4 ± 0.67	0.023
Vesicles	1.36 ± 1.03	0.43 ± 0.72	0.03 ± 0.18	0.00	0.035
Desquamation	2.03 ± 1.12	0.83 ± 0.79	0.20 ± 0.40	0.00	0.0001

P-value of < 0.05 was considered statistically significant; p-values were calculated using the One-Way ANOVA test

Secondary efficacy is depicted in Figure 2, showing the composite score for all four symptoms (pruritis, erythema, vesicles, and desquamation) at various visits, which also shows significant improvement from the baseline to the last visit.

Figure 3 shows the mycological assessment results of all the study participants. Study participants had no signs of fungal growth on the KOH mount by 4th week of treatment. Only one patient complained of burning and redness. It was mild, self-limiting, and did not require discontinuation of therapy.

The topical preparation of Amphotericin B was found to be effective to be used in the treatment of various mucocutaneous fungal infections. The development of the resistance towards Amphotericin is considered to be rare compared with other agents, because mutations in critical membrane sterol, by which the drug acts, are associated with the fall in virulence, hence, the evolution of resistance to Amphotericin B will be hindered by a tradeoff between the drug tolerance and the ability to cause disease.[7,10]

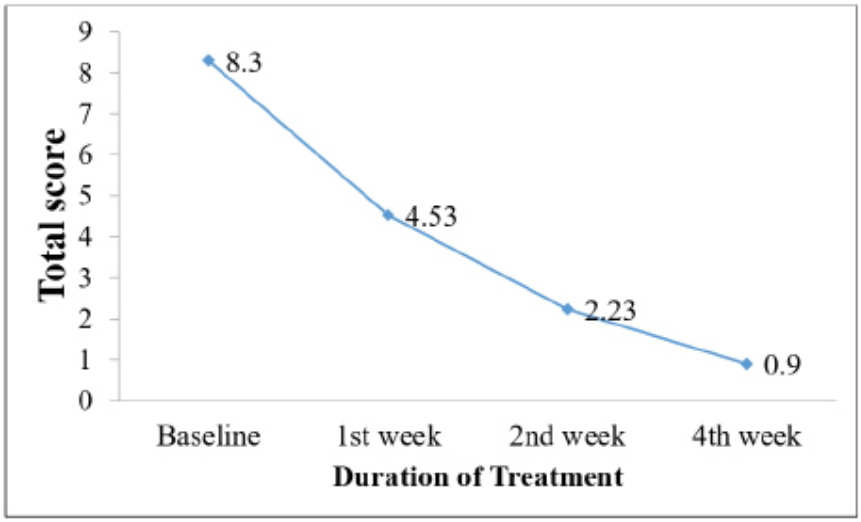

Figure 2. Changes in the Mean of Composite Score for All the Four Symptoms (Pruritis, Erythema, Vesicles and Desquamation) at Serial Visits during the Study

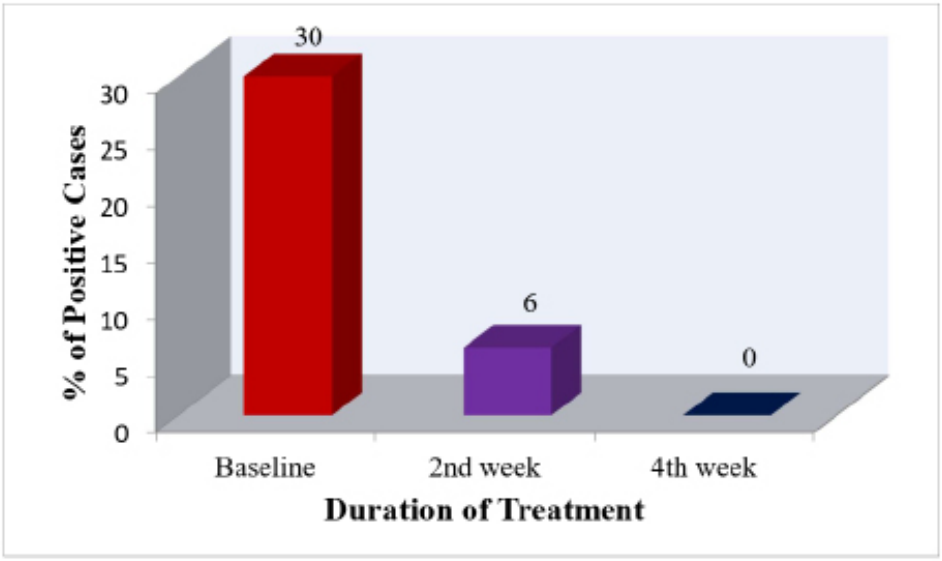

Figure 3. Number of Patients with Positive Cases after KOH Mount at Different Stages of the Study

In the present study, patients treated with Amphotericin B gel had a statistically significant decrease in pruritus, erythema, vesicles, and desquamation from baseline through the end of the four-week trial ($p<0.05$). Also, the mean total score of all symptoms, which was 8.3±3.1 at baseline, was reduced to 0.9±0.7 at the end of the 4th week, which is statistically significant ($p<0.05$). There was a clinically significant improvement following treatment with Topical Nanostructured Lipid-based Amphotericin B Gel 0.1%.

A similar study by Sheikh et al.[8] showed that using 0.1% amphotericin B gel as a treatment for cutaneous mycoses, 89.2% (74/83). For mucocutaneous fungal infection, 100% of patients were cured at the end of the treatment.

He concluded that lipid-based amphotericin B gel for patients with cutaneous and mucocutaneous fungal infections was safe, tolerable, and efficacious.[8] Sirohi et al.[11], in their study involving 52 patients with *T. corporis* found out that topical Amphotericin B gel was superior to topical sertaconazole cream concerning early clinical cure.[11]

The present study results was consistent with the above as all the patients treated were mycologically negative for KOH mount at the end of the study period. No serious adverse drug reactions were reported to treatment.

Nanostructured lipid carriers are novel drug delivery systems for treating topical skin infections, especially for antifungal drugs known to be lipophilic. Here the drug is entrapped within a lipid core matrix. Solid lipid nanoparticles are incorporated with the active drug in gel form; when applied, a depot is formed in the lipidic stratum corneum, which releases the drug slowly to the underlying skin layers.

The small size of lipid particles ensures a close contact with the stratum corneum, which increases the amount of drug penetrating the skin, enhancing their bioavailability at the application site. Lipid nanoparticles enhance chemical stability. Also, lipids utilised in this preparation are physiological lipids; this avoids the side effects of topical therapy, such as skin irritation, allergic dermatitis, redness, burning, blisters, and itching.[12-14]

A study conducted by Afzal et al.[15] showed that Amphotericin B incorporated in nanoemulsion formulation shows better in-vitro antifungal activity. In addition, Sanna et al.[13] and Mukherjee et al.[16] research showed that NLC formulations of drugs like econazole and itraconazole had improved therapeutic efficacy with fewer side effects. In vitro antifungal susceptibility studies conducted by Devi et al.[17], Sowmya et al.[18], and Fernandez et al.[19] showed that Amphotericin B incorporated in vesicular lipid bilayer showed an increase in retention, permeation, negligible skin irritation with better in vitro antifungal activity and is highly effective on dermatophyte strains when compared to all other antifungal drugs.

The present study suggested the safety of Topical Nanostructured Lipid Based Amphotericin B Gel 0.1% in patients with dermatophytosis resistant to a full course of conventional topical therapy which is about 1-1.5%.[7] It was well tolerated, consistent with similar studies by Sheikh et al.[8] and Sumedha et al.[11], where no serious adverse events were reported. Topical formulation is thus a safer and more economical way of effective management.[20]

Limitations and Suggestions of Study

The fundamental of the present study determined that the topical Amphotericin use in resistant dermatophytosis is to be reserved only when there is a failure of response to 4 weeks of conventional antifungal therapy. Compared to conventional therapy, Amphotericin B is more expensive, and the occurrence of antifungal resistance to conventional topical antifungal agents is only 1 to 1.5%. We suggest that Amphotericin gel is to be reserved only for resistant cases. Otherwise, rampant use may promote further resistance in the community, limiting its use for more invasive fungal infections.

The study design and small sample size were the shortcomings in our study, which controlled studies with larger sample sizes could overcome. More studies are suggested for corroboration and to help clinicians adopt newer, more effective therapeutic options.

Conclusion

Topical nanostructured lipid-based amphotericin B gel in patients with cutaneous mycosis resistant to conventional treatment was efficacious and safe.

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Conflict of Interest

None declared.

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