

Original Article

Treatment of difficult-to-treat-dermatophytosis: results of a randomized, double-blind, placebo-controlled study

Sanjeevani Fonseka¹, Dilan Dileepa Jayarathne Bandara¹, Dasun Chathumina Wickramaarachchi¹, Narankotuwe Gedara Kumudu Hasanka Heshani Narankotuwa¹, Pallegoda Vithana Ranjith Kumarasiri²

¹ Department of Pharmacology, Faculty of Medicine, University of Peradeniya, Sri Lanka

² Department of Community Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka

Abstract

Introduction: Difficult-to-treat dermatophytosis is an emerging public health problem in Sri Lanka. Safe, effective and affordable treatment is needed to solve this problem. Therefore this study has assessed the effectiveness and safety of modified Whitfield ointment applied twice daily with oral griseofulvin 500 mg daily given over 8 weeks in patients with difficult-to-treat dermatophytosis.

Methodology: A randomized, double-blind, within-patient-placebo-controlled trial was conducted in patients with clinico- mycologically (history, physical examination, direct light microscopy examination of scales in potassium hydroxide mount) confirmed difficult-to-treat dermatophytosis. Lesions were randomized to receive modified Whitfield ointment (5% benzoic acid and 5% salicylic acid) or emulsifying ointment. All patients were given oral griseofulvin 500mg once daily. The outcome measures were clinical assessment of disease severity, the total surface area of the lesions and the patient's perception of the disease severity at baseline and every two weeks up to a maximum of 8 weeks.

Results: Thirty patients completed the study. At two weeks, there was a statistically significant improvement in modified Whitfield ointment arm in the clinical assessment of disease severity and the patients' perception. There was a 7.59% reduction in the surface area of lesions in modified Whitfield ointment arm and a 5.83% increase in the surface area of lesions in the emulsifying ointment arm at two weeks. The difference between the two arms in surface area changes was not statistically significant ($p = 0.107$, $df = 29$).

Conclusions: A combination of modified Whitfield ointment with griseofulvin is significantly effective, safe and affordable option for treating difficult-to-treat dermatophytosis in the tropics.

Key words: Dermatophytosis; Whitfield ointment; difficult-to-dermatophytosis; griseofulvin.

J Infect Dev Ctries 2021; 15(11):1731-1737. doi:10.3855/jidc.14666

(Received 11 January 2021 – Accepted 18 March 2021)

Copyright © 2021 Fonseka *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Dermatophytosis is a fungal infection in the stratum corneum of the skin affecting 20–25% of the world population. It is caused by species of three genera: *Trichophyton*, *Epidermophyton*, and *Microsporum* [1]. The prevalence of dermatophytosis depends on the host and environmental factors such as climate, humidity, demographic factors of the patient, occupation, genetic predisposition, and socio-economic status [2].

The standard treatment is topical and/or systemic antifungal therapy such as allylamines (terbinafine, naftifine), azoles (fluconazole, itraconazole, terconazole), and griseofulvin [3]. A successful clinical response depends on the susceptibility of the pathogenic organism, the host immune system, drug penetration, patient compliance, and the absence of a protected or persistent focus of infection [4]. However, in the last few years, difficult-to-treat forms of

dermatophytosis are emerging despite the use of multiple topical and systemic therapies in South Asian countries [5]. Difficult-to-treat dermatophytosis consists of recurrent dermatophytosis or chronic dermatophytosis. Recurrent dermatophytosis is defined as reoccurrence of the signs and symptoms within few weeks of apparent cure and chronic dermatophytosis refers to the persistence of the infection despite treatment for over 6 months to one year. The above mentioned scenario can be due clinical resistance or microbiological resistance. Clinical resistance is defined as the persistence or progression of an infection despite appropriate antimicrobial with *in vitro* activity against the organism [6].

At least 3-4% of dermatophytosis is now considered to be chronic, secondary to factors such as obesity, poor hygiene, environmental factors, suboptimal dose or duration of drug therapy, patients with immuno-

compromised status, diabetes mellitus and atopy [4,5,7,8]. In India, 5–10% of new cases of dermatophytosis have been characterized as chronic and recurrent [9].

Therefore, in the face of drug-resistant dermatophytosis, the need for effective treatment at an affordable cost is rising. Griseofulvin is a time-tested drug for dermatophyte infections that gets concentrated in the keratin layers but rapidly develops resistance in tinea infections. Griseofulvin inhibits microtubule formation of the mitotic spindle and interferes with mitosis in dermatophytes. It is a fungistatic agent against dermatophytes [10].

Whitfield ointment (WO) is an antiseptic ointment that was widely used in the past to treat topical fungal infections but seldom used currently because of the availability of new therapies. The reasons for the underutilization of the Whitfield ointment could be its tendency to irritate the skin (especially in flexures and face) and being less targeted to dermatophytes than the newer therapies. Its efficacy has been shown to be equal to other topical antifungal in several studies [11].

It combines the fungistatic action of benzoic acid with the keratolytic action of salicylic acid. The original formula contains 6% benzoic acid and 3% salicylic acid and World Health Organization (WHO) suggested a modified Whitfield ointment (MWO) with 5% benzoic acid and 5% salicylic acid for tropical countries [12,13]. It is economical and can be manufactured locally.

There are studies done to evaluate the effectiveness of WO as an antifungal agent. A randomized, controlled study involving 120 patients has shown that Whitfield's ointment plus oral fluconazole is as effective and safe as topical 1% butenafine in tinea infections [14].

A study involving 49 relapsed cases of tinea corporis found that systemic terbinafine with topical clotrimazole was more effective than systemic terbinafine with Whitfield's ointment at the end of 4 weeks [11].

In a double-blind trial comparing Whitfield's cream (75 patients) with clotrimazole cream (78 patients) for dermatophyte infection for 6 weeks, Whitfield's cream has been as effective as clotrimazole cream [3]. In this trial, the concentration of salicylic acid and benzoic acid is equal to the MWO used in our study.

In another randomised double-blind study, it has been shown that topical miconazole, clotrimazole, and tolnaftate are superior to Whitfield's ointment in the treatment of superficial dermatophytosis [15].

There is a scarcity of studies on dermatophytosis poorly responsive to standard antifungal therapy which is increasingly becoming a challenge in clinical

practice. The possible approaches are the use of combined systemic antifungals and modified versions of previously used topical treatments such as Whitfield ointment. In countries like Sri Lanka, the treatment option should be affordable and widely available. MWO can be manufactured locally. Therefore, we selected the combination of griseofulvin and MWO because they are cheaper and considered to be as effective as newer therapies. Studies testing the effectiveness of Whitfield ointment in difficult-to-treat tinea infection was not found in electronic literature.

The main objective of this study is to assess the effectiveness and safety of topical MWO applied twice daily with oral griseofulvin 500 mg daily given over 6 weeks in patients of difficult-to-treat forms of dermatophytosis.

Methodology

Trial design

The study was conducted as a randomized, double-blind, within-patient-placebo-controlled trial. Ethical approval was taken from the Institutional Ethics Review Committee (2019/EC/47) and the Clinical Trial registration number is SLCTR/2019/035. Written informed consent was obtained from all subjects and the study was conducted in accordance with the Declaration of Helsinki.

Participants

The participants were males and females aged 16 to 60 years with clinically (history and physical examination) and mycologically (scales of lesions were mounted in 10% potassium hydroxide and examined under a light microscope) confirmed difficult-to-treat dermatophytosis (defined as dermatophytosis which shows relapses or persistence after being treated with 2 or more systemic antifungals for at least 3 months) and with two or more skin lesions.

The following categories of patients were excluded from the study: patients who did not give consent, patients with contraindications for Griseofulvin and MWO, pregnancy, male patients who wanted to father a child within the next 6 months, breastfeeding women, patients with fungal lesions involving the nails and scalp and patients with mental disorders who are unlikely to adhere to treatment procedure of the study.

The patients were recruited from the outpatient dermatology clinic "Skin Center", Sirimavo Bandaranayake Mawatha, Kandy, Sri Lanka. The study was conducted at the Department of Pharmacology, Faculty of Medicine, University of Peradeniya, Sri Lanka from 20/01/2020 to 01/09/2020.

We adopted a “within-patient controlled” design to minimise the influence of confounding factors such as body weight, hygienic practice, adherence to the protocol and comorbidities.

Sample size

In sample size calculation, the alpha value was taken to be 0.05 and the beta value is taken to be 0.05, with an effects size for the existing systemic treatment of difficult-to-treat dermatophytosis of 0.40 (29, 30). The postulated cure rate with the new treatment was taken to be 0.70. Hence, a sample size of 65 was calculated.

$$N = \frac{P1x(100 - P1) + P2(100 - P2)}{(P2 - P1)^2 \int(\alpha, \beta)}$$

$$N = \frac{40x(100 - 40) + 70(100 - 70)}{(70 - 40)^2} \int(0.05,0.05)$$

Where: *N* = 65

Considering a dropout rate/withdrawal rate of 20% the total sample size was calculated to be 78 and rounded off to a value of 80. The interim analysis was done with 34 patients and a significant difference was seen in one treatment arm. Therefore, the trial was halted. The data from patients who have withdrawn from the study were not analysed.

Randomization

The randomization of dermatophytosis lesions to two treatment arms was done by the trial co-ordinator with a toss of a coin (Table 1). One group of lesions received the MWO whereas the lesions on the other group received the emulsifying ointment (EO). All patients were dispensed with oral griseofulvin 500mg tablets once daily.

Allocation concealment and blinding

The investigators who did the clinical assessment were blinded to the allocation of lesions to two groups. MWO and EO were similar in appearance. Fifty grams each of MWO and EO was placed within identical containers by the pharmacist. A random letter sequence generator was used to generate 3 pairs of letters at the

Table 2. Codes allocated to ointment jars.

	Combination of letters	
	Modified Whitfield Ointment	Emulsifying Ointment
01	D	A
02	P	J
03	Z	B

Table 3. Baseline data.

Male patients	23
Female patients	11
BMI (Mean ± SD)	24.48 ± 3.96 kg m ⁻²
Duration of the disease (Mean ± SD) in months	8.15 ± 8.54

beginning of the manufacturing of the ointments. Three letters were assigned to MWO and the remaining 3 letters were assigned EO. The above code was unknown to the investigators. The codes are shown in Table 2.

Implementation

The allocation of the lesions to the two arms (with coded-letters indicating two treatments) was documented on a paper with a human figure and placed within an envelope which contained the trial number, name and address and placed under lock and key. The envelopes were opened at each subsequent visit only by the pharmacist before dispensing the treatment.

Intervention

A copy of the diagram of lesions was given to the patients to ensure that the appropriate treatment was carried out on the appropriate group of lesions. The patients needed to apply the ointments twice daily as instructed.

Both ointments were prepared in the laboratory of Department of Pharmacology, Faculty of Medicine, University of Peradeniya according to WHO guidelines. All patients received oral Griseofulvin 500mg (Griseofred®, Fredun Pharmaceuticals Ltd, India) daily for 8 weeks. Detailed instructions on the application of ointments, taking griseofulvin and hygienic measures were given.

Table 1. Randomization of lesions to two study arms.

Distribution of lesions	Coin Toss	Randomization	
		Modified Whitfield Ointment arm	Emulsifying Ointment arm
Generalized	Head	Right side of the body	Left Side of the body
	Tails	Left side of the body	Right side of the body
Confined to a single extremity	Head	Proximal part of extremity	Distal part of extremity
	Tails	Distal part of extremity	Proximal part of extremity
Located unilaterally	Head	Upper half of the body	Lower half of the body
	Tails	Lower half of the body	Upper half of the body

Patients were assessed at every two weeks and when a clinical cure was visible in one set of lesions, the trial was stopped and patients were asked to apply the ointment which was effective for one set of lesions to all lesions for 8 weeks (Clinical cure was taken as the absence of localized itching, visible erythema, papules, maceration and scaling. Residual pigmentation was not taken as an incomplete cure). The reason to continue topical and oral medication was to achieve complete clearance of dermatophytosis.

Outcome measures

The outcome measures of the study were clinical assessment of disease severity, the total surface area of the lesions and the patient’s perception of the disease severity. They were assessed at baseline and every two weeks up to a maximum of 8 weeks.

The disease severity was clinically assessed by the Principal Investigator (using a 4-point Likert scale with respect to erythema, induration, scaling, pustules, vesicles, maceration and papules (1= absent, 2 = mild, 3 = moderate, 4 = severe)).

The surface area of the lesions was measured by the tracing paper and the grid method. A transparent disposable sheet (oil paper) was placed on the top of the lesion and the margin of the lesion was marked with a

marker pen. Each lesion was traced separately. A grid with 1 cm² squares was placed on the top of the marked paper and the number of squares within the outline of the lesion was then counted. The fractions of the squares in the grid covering the traced area were added up and rounded off to get a full number of squares.

A visual analogue scale for patients’ perception was filled by the patient. It consisted of 10 points. Zero was the best outcome and 10 was the worst outcome. The patient was asked to rate the itching, irritation, scaling, size of the lesions and overall improvement separately according to the scale.

Statistical methods

The area of the lesions was compared with paired sample *t*-test. Clinician and patient assessment were analysed with the Mann-Whitney U test. A descriptive analysis of the clinical features and adverse events were carried out.

Results

Thirty-four participants were recruited at the time of interim analysis (i.e. 50% of the sample size). All the participants had dermatophytosis in the body but none had involvement of palms and soles. Figure 1 shows the recruitment and follow-up of the patients. Baseline data are shown in Table 3.

There was no statically significant difference between the two treatment arms at baseline in relation to all three outcome measures (Table 4).

The trial was discontinued in 28 patients at two weeks because of obvious improvement in one treatment arm and the effective treatment was applied on all lesions for the remaining six weeks.

At two weeks, there was a statistically significant improvement in MWO arm in the clinical assessment of disease severity and the patients' perception (Tables 4 and 5).

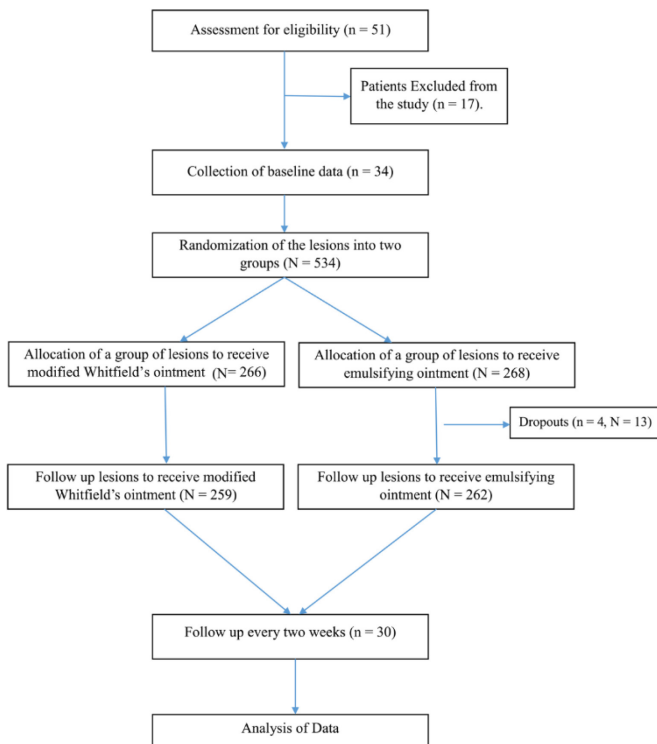
There was a 7.59% reduction in the surface area of lesions in MWO arm and a 5.83% increase in the surface area of lesions in the EO arm at two weeks (Table 6). The difference between the two arms in surface area changes was not statistically significant (*p* = 0.107, *df* = 29).

Regarding adverse events, 11 patients had mild stinging sensation when applying the MWO and none stopped the treatment due to adverse effects of the treatments.

Discussion

The results of this study showed that MWO with griseofulvin is a significantly more effective treatment

Figure 1. Recruitment and follow-up of the patients.



n: number of patients; N: number of lesions.

for difficult-to-treat dermatophytosis compared to EO with griseofulvin (improvement in clinical assessment of disease severity and patients' perception of disease severity). Out of the 30 patients who had a clinical cure, 28 in the MWO arm showed a significant improvement at 2 weeks. In this within-patient-controlled study, patients were not willing to continue the ineffective treatment once they realised the difference. Only two patients in the MWO arm had to continue treatment for 4 weeks to show a clinical cure.

The within-patient controlled design of this study reduced the confounding factors such as weight, hygienic practice, adherence to the protocol and comorbidities that may affect the response to treatment.

There was a technical problem in this study in measuring the change in the surface area of lesions by tracing paper method. Because the active lesion could not be distinguished from the post-inflammatory hyperpigmentation in the healed area through the tracing paper. Post-inflammatory hyperpigmentation tends to last longer in Sri Lankans, who have a type V

Table 4. Clinical assessment of disease severity at the first and second visit.

Symptoms	Visit	Modified Whitfield Ointment arm	Emulsifying Ointment arm	<i>p</i> [#]
		Mean (SD)	Mean (SD)	
Erythema	Baseline	2.71 (1.02)	2.60 (1.01)	0.475
	Two Weeks	1.68 (0.78)	2.19 (0.89)	<i>p</i> < 0.05
Induration	Baseline	2.61 (1.08)	2.58 (1.09)	0.844
	Two Weeks	1.72 (0.78)	2.34 (0.90)	<i>p</i> < 0.05
Scaling	Baseline	2.46 (1.18)	2.46 (1.06)	0.970
	Two Weeks	1.65 (0.78)	2.22 (0.91)	<i>p</i> < 0.05
Pustules	Baseline	1.76 (1.14)	1.84 (1.15)	0.604
	Two Weeks	1.33 (0.64)	1.58 (0.79)	0.027
Vesicles	Baseline	1.77 (1.18)	1.84 (1.18)	0.655
	Two Weeks	1.32 (0.64)	1.62 (0.85)	0.022
Maceration	Baseline	1.83 (1.16)	1.92 (1.16)	0.582
	Two Weeks	1.36 (0.65)	1.60 (0.85)	0.087
Papules	Baseline	1.93 (1.23)	2.07 (1.24)	0.401
	Two Weeks	1.33 (0.64)	1.75 (0.82)	<i>p</i> < 0.05

p value calculated using the Mann Whitney U test; *The disease severity was clinically assessed by using a 4-point Likert scale (1= absent, 2 = mild, 3 = moderate, 4 = severe).

Table 5. Patients' perception of disease severity assessed by visual analogue scale at first visit and second visit.

Symptoms	Visit	Modified Whitfield Ointment arm	Emulsifying Ointment arm	<i>p</i> [#]
		Mean (SD)	Mean (SD)	
Pruritus	Baseline	7.70 (2.37)	7.29 (2.52)	0.198
	Two Weeks	3.15 (3.37)	6.21 (2.95)	<i>p</i> < 0.05
Size	Baseline	9.19 (1.81)	9.03 (1.81)	0.266
	Two Weeks	6.23 (3.51)	7.885 (2.85)	<i>p</i> < 0.05
Scaling	Baseline	5.04 (3.77)	5.48 (3.54)	0.521
	Two Weeks	2.71 (3.14)	4.469 (3.25)	<i>p</i> < 0.05
Irritation	Baseline	6.10 (3.41)	6.17 (3.15)	0.779
	Two Weeks	2.48 (3.35)	4.250 (3.33)	<i>p</i> < 0.05
Overall	Baseline	7.34 (1.64)	7.33 (1.73)	0.979
	Two Weeks	4.07 (2.90)	6.21 (2.43)	<i>p</i> < 0.05

p value calculated using the Mann Whitney U test; * Visual analogue scale consisted of 10 points. Zero was the best outcome and 10 was the worst outcome.

Table 6. Reduction in the surface area of lesions.

Arm	% of surface area reduction	<i>p</i>	df	95% CI
MWO	7.59	0.107	29	3.08-29.94
EO	-5.83			

Values calculated using the paired *t* test; CI: Confidence Interval.

skin (Figure 2). This is a drawback of the study and therefore measuring the surface area by the tracing paper method cannot be considered as a reliable tool for assessment of treatment outcome in dermatophytosis.

The original Whitfield's ointment contains benzoic acid and salicylic acid in a ratio of 2:1 (usually 6%:3%). Salicylic acid is keratolytic and may irritate the skin in hot climates. Low percentages of salicylic acid do not remove the stratum corneum sufficiently for benzoic acid to penetrate the deeper layers. Benzoic acid has antiseptic properties and it is also an irritant. Therefore, Whitfield ointment with 5% benzoic acid and 5% salicylic acid combination may be slightly more effective than the original one in tropical countries [13]. The accelerated shedding of the stratum corneum due to the keratolytic action of the MWO increases the removal of keratinocytes infected with dermatophytes. In this study, patients reported mild burning sensation

(11 patients), which did not lead to discontinuation of the drug therapy.

After the completion of the study, participants were instructed to come back if there is recurrence of the lesions. Two participants returned three months after the completion of the trial. They were again given the same treatment.

Combinations of systemic and topical antifungal treatment are recommended for difficult-to-treat dermatophytosis by experts [16]. The first line systemic antifungals recommended are itraconazole and high-dose terbinafine. The second line treatment options are griseofulvin and fluconazole [16]. Azoles are recommended as topical antifungals. Our study supports the use of MWO with oral griseofulvin which is a much cheaper treatment option.

Conclusions

A combination of MWO with griseofulvin is an effective, safe, and affordable option for treating difficult-to-treat dermatophytosis in the tropics. Further studies paying attention to different concentrations of benzoic acid and salicylic acid, a reliable and objective method of measuring the surface area of dermatophytosis and recurrence and relapse after the completion of treatment will be useful.

Acknowledgements

The author would like to acknowledge Mrs A.M.I.R.K Athauda and Mr R.M.U.G.A.B. Rathnayake at Department of Pharmacology, Faculty of Medicine, University of Peradeniya, Sri Lanka for their contribution to the clinical trial.

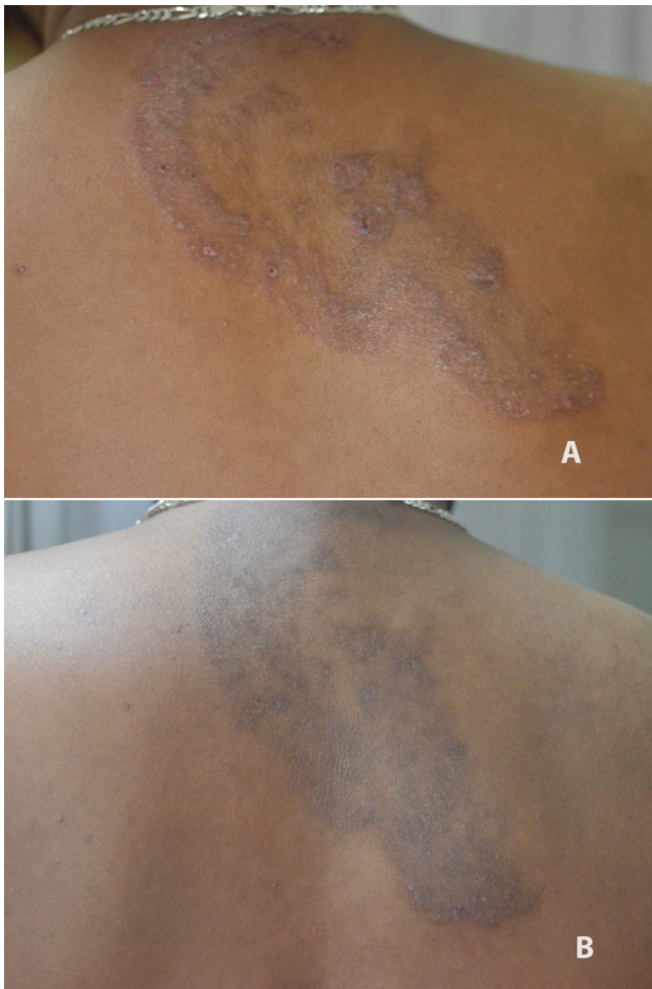
Funding

The research was funded by University of Peradeniya (Grant No: URG/2019/16/M)

References

1. Sardana K, Kaur R, Arora P, Goyal R, Ghunawat S (2018) Is antifungal resistance a cause for treatment failure in dermatophytosis: a study focused on tinea corporis and cruris from a tertiary centre? *Indian Dermatol Online J* 9: 90-95.
2. Shenoy MM, Jayaraman J (2019) Epidemic of difficult-to-treat tinea in India: current scenario, culprits, and curbing strategies. *Arch Med Health Sci* 7: 112-117.
3. Gooskens V, Pönnighaus JM, Clayton Y, Mkandawire P, Sterne JA (1994) Treatment of superficial mycoses in the tropics: Whitfield's ointment versus clotrimazole. *Int. J. Dermatol* 33: 738-742.
4. Dogra S, Uprety S (2016) The menace of chronic and recurrent dermatophytosis in India: is the problem deeper than we perceive? *Indian Dermatol Online J* 7: 73-76.

Figure 2. Dermatophytosis on type V Skin.



A: before the treatment procedure; B: after two weeks.

5. Rengasamy M, Chellam J, Ganapati S (2017) Systemic therapy of dermatophytosis: practical and systematic approach. *Clin Dermatol Rev* 1: 19-23.
6. Verma S, Madhu R (2017) The great Indian epidemic of superficial dermatophytosis: an appraisal. *Indian J Dermatol* 62: 227-236.
7. Sharma R, Adhikari L, Sharma RL (2017) Recurrent dermatophytosis: a rising problem in Sikkim, a Himalayan state of India. *Indian J Pathol Microbiol* 60: 541-545.
8. Singh S, Verma P, Chandra U, Tiwary NK (2019) Risk factors for chronic and chronic-relapsing tinea corporis, tinea cruris and tinea faciei: Results of a case-control study. *Indian J Dermatol Venereol Leprol* 85: 197-200.
9. Chen E, Ghannoum M, Elewski B (2021) Treatment-resistant tinea corporis, a potential public health issue. *Br. J. Dermatol* 184: 164–165.
10. Gupta A, Mays R, Versteeg S, Piraccini B, Shear N, Piguet V, Tosti A, Friedlander S (2018) Tinea capitis in children: a systematic review of management. *J Eur Acad Dermatol Venereol* 32: 2264–2274.
11. Rahangdale V, Deshmukh S, Madke B, Singh AL, Vaishnavi (2020) Effect of Salicylic Acid 3%+ Benzoic Acid 6%(Whitfield's Ointment), Clotrimazole 1% Cream, and Systemic Terbinafine on Mild-to-Moderate Tinea Corporis: A Randomized Comparative Study. *Int J Recent Surg Med Sci* 6: 49–52.
12. Whitfield A (1920) Whitfield's ointment. *Arch Derm Syphilol* 1: 684–684.
13. Bakker P, Woerdenbag H, Gooskens V, Naafs B, van der Kaaij R, Wieringa N (2012) Dermatological preparations for the tropics. University of Groningen, The Netherlands: Beta Science Shop 268 p.
14. Thaker SJ, Mehta DS, Shah HA, Dave JN, Kikani KM (2013) A comparative study to evaluate efficacy, safety and cost-effectiveness between Whitfield's ointment+ oral fluconazole versus topical 1% butenafine in tinea infections of skin. *Indian J Pharmacol* 45: 622-624.
15. Sivayathorn A, Piamphongsant T (1979) Topical antimycotic agents for the treatment of superficial dermatophytoses in Thailand. A double-blind study. *Mykosen* 22: 21–24.
16. Rajagopalan M, Inamadar A, Mittal A, Miskeen AK, Srinivas C, Sardana K, Godse K, Patel K, Rengasamy M, Rudramurthy S, Doga S (2018) Expert consensus on the management of dermatophytosis in India (ECTODERM India). *BMC Dermatol* 18: 6.

Corresponding author

Dr Sanjeevani Fonseka, MBBS, MD, PhD

Department of Pharmacology, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka, 20400

Phone: +94 718074979

Email: sanjeevani.fonseka@yahoo.com

Conflict of interests: No conflict of interests is declared.