



Effectiveness of Black Peel with 1% Clotrimazole Cream vs Oral Terbinafine in the Treatment of Onychomycosis-Randomized Controlled Trial

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ARTICLE INFO

Keywords: Onychomycosis, Terbinafine, 1% clotrimazole, Black peel.

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Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 04-03-2025 Revised: 05-06-2025

Accepted: 18-06-2025 Published: 30-06-2025

ABSTRACT

Background: Onychomycosis accounts for 90% of all the toe nail infections and 30 % of all cutaneous fungal infections.(1) The management of this disease is challenging, as on one end there is increasing evidence of growing fungal resistance against available antifungals; and on the other end the majority of the effected individuals are old aged and have comorbidities limiting the use of systemic treatment in such cases.(2) In such circumstances there is an increasing need for exploring newer treatment options for onychomycosis. The aim of the study was to compare the effectiveness of topical black peel combined with 1% clotrimazole versus oral terbinafine in cases of onychomycosis. We hypothesized that this topical combination strategy is better than oral terbinafine in this disease. We carried out a randomized clinical trial in the Dermatology OPD of our tertiary care hospital in Pakistan over a period of 06 months i.e., from March to August 2024. **Methods:** 90 patients suffering from onychomycosis meeting our inclusion criteria were included in the study after informed consent. Later on, six patients were dropped due to non-compliance issues. Sampling was done by non-probability randomized sampling. Group A was treated by weekly black peel combined with daily 1% clotrimazole cream for 3 months and group B was treated by oral terbinafine 250mg for 03 months. After 03 months of treatment, results were analyzed by observing the change in mean onychomycosis severity index (OSI) and patient satisfaction scores. **Results:** There was lesser OSI in group B (1.43±2.25) as compared to group A (5.32±6.5) after treatment with significant p value of 0.003. The mean difference between the groups was 3.887±1.08. But within each group there was a significant difference in pre-treatment to post treatment OSI (p<0.001 in each group). **Conclusion:** Black peeling combination with topical 1% clotrimazole is a comparable treatment option to oral terbinafine for the treatment of onychomycosis.

INTRODUCTION

Onychomycosis is defined as the fungal infection of the nail unit i.e., nail matrix, nail plate and/or nail bed. The word "onychomycosis" is derived from two Greek words i.e., "Onyx" meaning nail and "Mykes" meaning fungus. The etiology is either dermatophyte infection, non-dermatophyte fungi or yeasts. (3) Amongst dermatophytes, Trichophyton (*T. Rubrum* and *Mentagrophytes*) are the most prevalent cause of nail infection in United States and Europe. (1) While Aspergillus is an example of non-dermatophyte onychomycosis and Candida is a common cause of yeast infecting nail apparatus.

When diagnosing onychomycosis, proper history and examination is essential. All nails should be examined and exclusion of other fungal infections of skin and hair should

be done. This should be followed by nail clippings for fungal hyphae detection, as far as the healthy margin by filing and scraping of the subungual scales. For microscopy 10-20% potassium hydroxide (KOH), 0.025% Congo red or 20 % tetraethyl ammonium hydroxide (TEAH) can be used for processing the sample. KOH preparation microscopy has 95% specificity and 61% sensitivity for such diagnosis. Fluorescence optical stains can increase the sensitivity of microscopy. Cultures are done on Sabouraud glucose agar for 4 weeks at 26-32 degree. For cultures anti-fungal must be stopped for 4-8 weeks before obtaining samples for cultures. Cultures have 99% specificity and 56% sensitivity. In such cases PCR for dermatophyte DNA can detect the dormant fungi. It has 100% sensitivity and specificity in the diagnosis of onychomycosis.(4) Histopathology and dermoscopy can also help with the

diagnosis of onychomycosis. Dermoscopic feature of longitudinal striae in nails has 86.5% sensitivity and 100% specificity in the diagnosis (2,5-7). Artificial intelligence is also being used in different studies for diagnosis of onychomycosis with specificity of 72.7% and sensitivity of 70.2%. (7)

Distal lateral subungual onychomycosis is the most common clinical form of the disease. In this condition infection spreads from distal to proximal matrix spreading from the surrounding skin and reaching the nail by hyponychium. It is characterized by subungual hyperkeratosis and yellow discoloration of the distal end of the nail plate.(3,4,8,9) Proximal subungual onychomycosis is characterized by homogenous white area beneath proximal nail. It is rare and seen in HIV positive patients and patients on immunosuppressants. White superficial onychomycosis (WSO) is characterized by whitish plaque on the nail plate. Black superficial onychomycosis, *Endonyx* and total dystrophic are other variants of the disease. Mixed variety combines two or more of the above variants. (5)

Onychomycosis does not resolve on its own and acts as a source of infection for rest of the body, so it needs to be treated. Treatment strategies include physical measures as per German guidelines i.e., 40% urea assisted nail removal, traumatic nail removal and drilling of the effected part by podiatrist. Topical treatment as per these guidelines should be given in mild to moderate nail involvement i.e., till 40% nail plate involvement and 3/10 toe nails infected. These include amorolfine 5%, ciclopirox 8% and water-soluble terbinafine nail paints.(5) Topical antifungals like Efinaconazole, Tavaborole, Luliconazole, tioconazole have been used with different efficacies in other studies.(10-14) Other options mentioned in literature are carbon dioxide lasers and long pulsed Nd-Yag laser combined with topical medications. (11,14-16). Different peeling agents like black peel, acetic acid, glycolic acid have recently been tried in onychomycosis with mixed results.(17,18) Systemic treatment options are fluconazole, terbinafine and itraconazole. Itraconazole was approved in 1995 for dermatophyte onychomycosis with dosage of 200mg daily for 12 weeks for toenails and two pulses of 200mg twice a day for 1 week separated by 3 weeks for finger nails. (19)Terbinafine was also approved in 1996 for onychomycosis treatment. Dose is 250mg daily for 6 weeks for finger nails and 12 weeks for toenail onychomycosis.(3,5,19)

Sonthalia et al have used black peel i.e., a superficial to medium depth peel often used in treatment of acne, successfully in difficult cases of onychomycosis. It combines 50% black acetic acid with 0.5% salicylic acid, 6% tetrahydrojasmonic acid, 10% bio-Sulphur and 0.1% potassium iodide. They used the peeling protocol in 2 difficult cases with diabetes and congestive cardiac failure. They used the peel once a week for 4 weeks and then fortnightly for next 5 months with daily 8% ciclopirox paint application. In their cases there was complete clinical and mycological cure at the end of 06 months. (18)

V.Chau et al combined fortnightly carbon dioxide laser with 1% clotrimazole twice a day and compared it with itraconazole in cases of onychomycosis. Their results showed better effectiveness of the laser and topical

combination treatment versus oral antifungal in terms of clinical cure and safety profile.(20)

Amongst the effected patients most belong to the strata of co-morbidities like geriatric age group, diabetes, osteoarthritis knees, Chronic venous insufficiency, Peripheral vascular disease, HIV positive patients, renal and bone-marrow transplant recipients, Hemodialysis patients, Patients with lupus erythematosus and oncology patients.(21)Hence oral intake of antifungals is not possible in all cases due to drug interactions, compromised hepatic and renal functions, CYP3A4 enzyme inhibition by itraconazole and other side-effect profile of the oral antifungals.

Based on these comorbidities and limitations of oral antifungals and the results of the above-mentioned studies of Sonthalia et al and V.Chau T et al we decided to compare weekly application of black peel combined with 1% clotrimazole twice a day with oral terbinafine for treatment of onychomycosis. (18,20)

The primary objective of our study was to determine the effectiveness of the above-mentioned protocol in terms of clinical cure as checked by OSI score. The secondary objectives were to determine and compare the patient satisfaction in both treated groups along with comparing the effects of different comorbidities, other factors (presence of Tinea Pedis) and clinical forms of onychomycosis on treatment outcomes.

MATERIALS AND METHODS

Ethical approval was done by ethical review board of our hospital with the ID of A/29/ERC/03/2024 after scrutiny. Study was conducted in the dermatology outpatient department of our tertiary care hospital over a period of 06 months i.e., 01 March 2024 to 01 August 2024. Study design was "randomized control trial", with two parallel intervention groups. Sample size was calculated by using epi info sample size calculator version 3. Taking 2-sided significance level of 95% and power 90%, our sample size calculated was 20 in each group.(20) But we took sample size of 45 in each group to cater for the suspected dropped out patients.

Inclusion criteria were patients willing to participate in our study, ranging from age group of 15-70 years of both sexes suffering from onychomycosis confirmed by KOH preparation followed by microscopy. Exclusion criteria included onychomycosis effected patient suffering from other pathologies like psoriasis or lichen planus, total dystrophic onychomycosis, pregnant or lactating women, hepatic, or renal disorders, patients already taking anti-fungal and patient's having history of hypersensitivity to drugs or component of black peel being used in the study. 90 patients presenting to dermatology OPD of our hospital were recruited in the study after considering the exclusion and inclusion criteria. Informed consent was taken from the patients. Simple, non-probability randomized sampling in patients divided into two random groups was done, by use of simple lottery method i.e., by giving the patients sealed envelopes of 2 types to choose one blindly from them. Later on, 06 patients were dropped due to non-compliance.

Patients were educated about their respective treatment protocols. The onychomycosis was confirmed by 20% KOH

preparation of nail clippings and subungual scales/debris followed by microscopy. Clinical type of onychomycosis was recorded. Onychomycosis severity index was calculated by multiplying the score for area of involvement ranging from 0-5 by the score calculating proximity of the disease to the matrix ranging from 1-5. Ten points were added for the presence of a longitudinal streak or a patch i.e., dermatophytoma or for > 2mm of subungual hyperkeratosis. Total score of 1-5 correspond to mild disease, 6-15 corresponds to moderate disease and 16-35 corresponds to severe disease. (22)As in some cases more than 01 nail was involved, mean OSI was calculated for such cases. Baseline photography was also done.

For group A daily 1% clotrimazole application was done twice a day, while adding on periodic planned sessions of nail peeling using weekly Black Peel for the next 3 months. First of all, the nails were cleaned by methylated spirit swabs. After safeguarding the nail folds and cuticles with white soft paraffin, a uniform coat of Black peel was applied over the infected toe or finger nails and was allowed to dry for 20 minutes. After which a 2nd uniform coat of the black peel was again painted on the nails. After 20 minutes of the 2nd coat the peel was washed off with plain water at room temperature and area was dried by a clean gauze. Afterwards 1% clotrimazole was applied immediately. Patients were advised to continue applying the cream twice a day till the treatment period. 02 sessions of peeling were done by dermatologist and later the patients were given the peel and were instructed to apply it themselves according to the instructions given. Group B was advised oral terbinafine 250 mg once daily for 12 weeks. Clinical and mycological confirmation of diagnosis, severity assessment and progress were seen in the same manner as with group A. OSI score was calculated after the treatment protocol for both the groups by an independent dermatologist.

Patient satisfaction was also assessed by grading scale i.e., 1. Unsatisfied, 2. Neutral, 3. Completely satisfied.

03 patients from both groups failed to follow the treatment protocol due to non-compliance issues. Data collected was analyzed using IBM SPSS 27.0 (Software Package for Social Science). Frequencies and percentages with means were calculated for numerical demographic variables like age, numbers of nail involved, duration of closed shoe wearing. Chi-square test was use for categorical variables like gender, comorbidities, location, presence of other fungal infections (Tinea pedis, tinea corporis or tinea capitis) and clinical types of onychomycoses (DLSO, WSO or proximal subungual onychomycosis). Chi-square test and independent sample T-test was done to compare the outcomes in the two groups. Paired sample T-test was used to compare the before and after treatment OSI scores in both groups. p-value of less than 0.05 was regarded as statistically significant.

RESULTS

Mean age of the 84 participants of the study was 46.89 years \pm 13.6 with minimum age of 15 years and maximum age of 70 years.44 patients (52.3%) were male and 40(47.6%) were female. Out of these, 44 males, 21 were in group A and 23 in group B. Out of the 40 females, 21 were in group A and 19 in group B. P-value was 0.662 showing

the age distribution amongst the two groups as insignificant.

Table 1

Demographics and other factors effecting Onychomycosis

Variable	Black peel group (Group A)	Terbinafine group (Group B)	P-value
Age in years			
Mean Age with SD	44.79 \pm 12.1	49 \pm 14.7	0.158
Number of Nails Involved			
Count with SD	2.12 \pm 0.99	2.24 \pm 1.206	0.623
Duration of Wearing Closed Shoes in hours/day			
Hours/Day with SD	5.19 \pm 3.27	4.07 \pm 3.46	0.132
Location of lesions			
Toe nails 60(71.4%)	31	29	0.693
Finger nails 18(21.4%)	9	9	
Both 06(7.14%)	2	4	
Presence of Tinea Pedis			
Present 16(19%)	8	8	1.00
Absent 68(81%)	34	34	
Clinical type of Onychomycosis			
DLSO 65(77%)	33	32	0.988
Proximal Subungual 6(7%)	3	3	
SWO 4(4.76%)	2	2	
Mixed 9(10.7%)	4	5	
Comorbid Conditions			
Nil 37(44%)	22	15	0.592
Diabetes Mellitus 31(36.9%)	13	18	
Peripheral vascular disease 06(7%)	03	03	
Immunosuppression 04(4.76%)	02	02	
More than 01 of the above 06(7%)	02	04	

So, distribution of these demographic variables across both groups is non-significant and hence the observed differences in these variables between the two groups are likely due to random chance and are not a true reflection of a difference in the underlying populations they represent. Following are the results of our primary and secondary outcomes. Mean OSI before treatment in both groups was 9.48 \pm 6.87 and mean OSI after treatment in both groups was 3.106 \pm 5.2 with mean difference of 6.38 \pm 5.6 and 95% CI (5.1-7.6) with p-value of <0.001. Within the groups the difference in OSI with treatment is mentioned below.

Table 2

Primary and secondary Outcomes

	Black peel group Group A	Terbinafine group Group B	p-value
Patient Satisfaction with the Treatment			
Unsatisfied 09(10.7%)	8	01	<0.001
Neutral 14(16.6%)	11	03	
Satisfied 61(72.6%)	23	38	
OSI after Treatment			
Value with SD	4.77 \pm 6.6	1.43 \pm 2.25	<0.001
CI 95%	(1.19-5.4)	(1.17-5.51)	
OSI before and after treatment within each Group			
Mean with SD	4.033 \pm 4.07	8.18 \pm 6.37	Group A- <0.001
CI95%	(2.76-5.30)	CI95% (6.19-10.16)	Group B-<0.001

Figure 1



So, patients in oral terbinafine treatment group were more satisfied with the treatment than the patients in black peel with 1 % clotrimazole treatment group ($p < 0.001$). But, still 54.7 % (23) patients in group A were satisfied as compared to 90.4% (38) satisfied patients in group B, which is acceptable for topical treatment being compared with oral treatment. Similarly mean OSI after treatment in oral Terbinafine group was less i.e., 1.43 ± 2.25 as compared to 4.77 ± 6.6 in black peel group ($p < 0.001$) but within each group comparing OSI before and after treatment yielded significant improvement with $p < 0.001$ in both groups. So although Terbinafine is better treatment option for onychomycosis but black peel with 1% clotrimazole is also a good and comparable treatment option.

DISCUSSION

We in our quest to search for a good, simple, cost-effective and feasible treatment option other than systemic antifungals and physical modalities like lasers have tried to prove the effectiveness of a peeling agent i.e., weekly application of black peel with 1% topical clotrimazole, by comparing it with standard FDA approved oral terbinafine in the treatment of onychomycosis. We have derived the ideology of this trial from the work of Sonthalia et al who used this innovative peel successfully in 02 old aged patients having congestive cardiac failure and diabetes with achievement of complete clinical and mycological cure after 6 months of this weekly peeling agent and 8% ciclopirox daily.(18)

Different chemical peeling agents i.e., glycolic acid, phenol, salicylic acid and trichloro acetic acid in different strengths have been used to enhance the aesthetic appearance of the nails by removing the surface changes induced by cosmetics.(17) But Black peel is different as it not only exfoliates the surface of the nail and enhances the penetration of topical anti-fungal but the specific characteristics of its constituents play major role in healing mycosis in nails. Black acetic acid derived from rice has been used in Korea for centuries for its antimicrobial properties.(23,24) Salicylic acid exfoliates and has its own antimicrobial and anti-inflammatory properties especially breakage of biofilms.(17,18) Jasmonic acid is a phytohormone and its major metabolite i.e., methyl-jasmonate has been used to eradicate fungal pathogens on plants such as *Penicillium digitatum*.(25–27) Report have shown its efficacy in eliminating *Candida* and *Aspergillus Niger* in humans.(18,27) It has also anti-cancer properties.(28) Sulphur has been used for centuries in animals for antimicrobial properties and humans have used Sulphur-rich natural water sources to heal skin conditions. The mechanism is proposed to be the conversion of Sulphur into hydrogen sulphide in the deep dermis by interaction of oxygen radicals and later to pantothenic acid i.e., Vitamin B5.(29) Potassium iodide has also been used before in neutrophilic dermatosis and fungal infections like sporotrichosis. Its mechanism of action includes conversion to iodine in body by neutrophil myeloperoxidase.(30–32)

The results of our study are comparable to the results of the RCT done by Chau et al who combined fortnightly carbon dioxide laser with daily 1% clotrimazole topical application with oral itraconazole and topical 1% clotrimazole. The clinical improvement in the laser group was superior to the itraconazole group in their study i.e. $p < 0.001$. The clinical improvement in both of our treatment groups was significant i.e., $p < 0.001$. They used SCIO-Scoring Clinical index for onychomycosis but we used OSI for grading clinical improvement. (22) Different clinical trials conducted for treatment of onychomycosis have also used OSI across the globe.(33–35)

Another study compared topical 30% resin lacquer daily application with 5% amorolfine and oral terbinafine showed comparable results to our study with mycological cure rates of 13%, 8% and 56% respectively in these three groups ($p < 0.002$). (36)

A study conducted in Pakistan comparing oral Terbinafine with pulsed itraconazole in toenail onychomycosis has

shown that 51.6% patients improved in total with 71.9% in the terbinafine group and 31.2% in itraconazole group ($p=0.002$).⁽³⁷⁾The results are comparable to the terbinafine arm in our study in which mean improvement was 8.18 ± 6.3 ($p<0.001$) in OSI. Similarly, in their study mean age was 52.67 ± 9.09 with maximum age of 67 and minimum of 35. Mean age was 46.89 ± 13.6 with minimum age of 15 years and maximum of 70 years in our study. So, both studies show that middle aged people are more affected by the disease in our country. 36.9% patients in our study had diabetes which is comparable to 29.7% diabetic patients in their study.⁽³⁷⁾

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Limitations of Our Study

- We did not record the side effects
- Treatment duration in the peel group should be longer i.e., 6-9 months
- Mycological cure was not ascertained

CONCLUSION

We conclude that black peel with 1% clotrimazole is a comparable treatment option if not better than oral terbinafine. It can be used in special onychomycosis populations who cannot tolerate or don't want to take oral treatment.

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