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ORIGINAL ARTICLE

An open comparative study of nail drilling as adjunctive treatment for toenail onychomycosis*

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ABSTRACT

Introduction Novel treatment regimens are being developed to improve drug penetration through the nail plate. This study investigated the efficacy of nail drilling regimens for the treatment of onychomycosis. **Methods** Participants were assigned to holes with combination (oral plus topical terbinafine) therapy (Group 1), holes with topical terbinafine (Group 2) or topical terbinafine only (Group 3). Measurement of clear nail and mycology was performed at baseline and at weeks 4, 10, 16, 22 and 28. Mixed linear models were used to compare mean percent clear nail. Mycological cure rates were also tabulated for each group. Tolerability and adverse events were documented. **Results** Ninety-eight participants were enrolled (106 nails). Both groups with holes had significantly higher percentage of clear nail compared with topical terbinafine alone. Although no significant difference between the two groups where holes were drilled in the nail plate, Group 1 demonstrated improvement over Group 3 earlier than Group 2 (visit 2 versus visit 4). Group 1 also had the highest mycological cure rates. **Conclusion** Treatment with holes plus topical terbinafine produces significantly greater improvement in toenails' appearance and higher mycological cure rates compared to treating the dorsal aspect of the nail plate with topical terbinafine alone.

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Introduction

Onychomycosis is a fungal infection of the nail plate and nail bed caused by dermatophytes, yeasts and non-dermatophyte molds (1). Current onychomycosis treatment options include oral and topical antifungal agents, lasers and devices to thin or debride the nail plate (2). Topical treatment is often preferred by patients as it circumvents many of the health risks associated with oral therapy. However, the presence of hard keratins in the nail plate results in poor drug delivery through the thickness of the nail plate and treatment can be lengthy. Debridement of the nail plate is one of the methods used to enhance transungual drug delivery that has been shown to decrease treatment time when combined with topical therapy (3).

Although treatment protocols involving the use of devices to thin or debride the nail plate have previously been studied, the utility of drilling holes into the nail plate to improve drug delivery is only beginning to be investigated. de Morais et al. describe promising preliminary results with a treatment protocol where amorolfine nail lacquer was applied to mycotic nails that had been fractionally ablated with a 2940 nm erbium yttrium aluminum garnet (Er:YAG) laser; however, the cure rates from this study have yet to be reported (4). The objective of the current study was to evaluate the efficacy and safety of therapeutic regimens that involve drilling of the nail plate to produce holes to facilitate the passage of topically applied terbinafine compared to application of topical terbinafine only to the dorsal surface of the nail plate for the treatment of mild to moderate toenail onychomycosis.

Materials and methods

This parallel, three-arm trial was conducted from May 2013 to January 2014 at Lev Yasmin Medical Center in Netanya, Israel. Eligible participants were 18 years of age or older and had mycologically-confirmed (potassium hydroxide and culture), mild to moderate ($\leq$ 75% nail involvement) distolateral subungual onychomycosis (DLSO) of the toenail caused by a dermatophyte. Participants with lunula involvement, who were allergic to terbinafine, or who were pregnant or lactating were not eligible to participate. This study was approved by the Institutional Review Board Helsinki Committee and all participants provided written informed consent prior to study initiation.

Participants were assigned to one of three treatment arms: (1) holes with combined oral and topical terbinafine; (2) holes with topical terbinafine or (3) topical terbinafine. For participants allocated to either of the holes arms, at the first visit after baseline, an automatic device manufactured by Ex-It Medical Devices Ltd. (Figure 1) was used to drill two horizontal lines of holes just proximal to the border between the diseased and healthy portions of the nail. Holes were drilled into the healthy part of the nail so that medication would be delivered to the diseased portion of the nail in accordance with the direction of nail growth, drilling the nail otherwise may facilitate the spread of fungi into the healthy portion of the nail.

Holes had a diameter of 1.8 mm and were spaced 2 mm apart (Figure 2). The nail plate is comprised a superficial dry compartment and a deeper humid compartment; the nail drilling device used in this study is able to detect when it has reached the more humid portion of the nail plate. It drills rapidly until a pre-defined

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Figure 1. Nail drilling device.

Figure 2. Nail drilling method for toenail onychomycosis.

humidity level is reached, thus stopping short of penetrating the nail bed and preventing any pain or discomfort for participants. Nail drilling took approximately 3–5 min to complete. Holes were only drilled once at the start of the study. Participants were instructed to clean the holes with a swab so that they may remain open for the duration of treatment.

Participants in Group 1 were prescribed 250 mg of terbinafine per day for two weeks as steady-state levels are attained following 10–14 days of treatment with terbinafine, allowing an accumulation of terbinafine in the nail plate sufficient to exceed the minimum inhibitory concentration (MIC) (5). This oral dose provides a rapid nail plate accumulation from both transungual and systemic routes to boost the initial MIC at a minimal dose for patient safety to act as a comparator to the slower nail plate accumulation from the topical only arms. Participants in all groups were also instructed to apply terbinafine 1% spray (Novartis Consumer Health, Switzerland) twice daily in the morning and at bedtime for 6 months to the dorsal aspect of the diseased target great toe nail. Although terbinafine 1% spray is not a recognized treatment for onychomycosis, its low viscosity relative to a cream or lacquer lends to better penetration through the holes in the nail plate through to the underlying nail bed. Also, unlike commercially available lacquers, terbinafine spray does not require removal of the applied material prior to subsequent applications. Participants' nails were evaluated at baseline and at weeks 4, 10, 16, 22 and 28 (visits 1–6). At each visit, a trained dermatologist collected nail specimens for mycological testing and measured the percentage of the infected nail that appeared healthy and clear of fungal involvement.

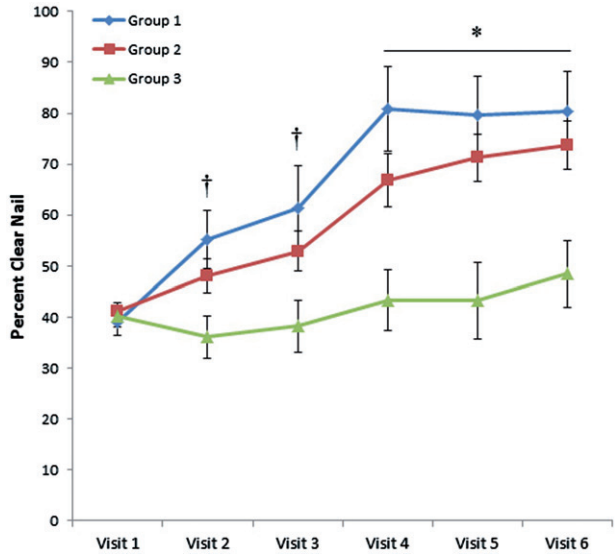

Figure 3. Mean percent clear nail for visits 1–6. Mean percent clear nail (±standard error of the mean) for visits 1–6 in all nails. Group 1, holes + oral and topical terbinafine; Group 2, holes + topical terbinafine; Group 3, topical terbinafine only. †Group 1 significantly different from Group 3 ($p < 0.05$); *Groups 1 and 2 significantly different from Group 3 ($p < 0.05$).

The primary outcome in this study was percent clear nail and the secondary outcome was mycologic cure defined as negative potassium hydroxide (KOH) and culture. Treatment tolerability was assessed using a visual analog scale. Participants were instructed to indicate pain intensity along a Likert scale ranging from 1 to 10, where 1 indicated "no pain" and 10 indicated "worst pain". Adverse events were also recorded.

Proportions of categorical baseline variables were tabulated and chi-square tests were used to compare those variables. Means ± standard deviation of continuous baseline characteristics were calculated and compared using repeated measures ANOVA. Means ± standard error of the mean of percent clear nail in each treatment group for visits 1–6 were calculated and mixed linear models were used to compare means across visits and between treatments, using visits and treatments as the fixed effects. Bonferonni corrections were used when appropriate to compare treatments. Mycological cure rates for each group were also tabulated. A subgroup analysis of mean percent clear nail in each treatment group for visits 1–6 was also performed based on percent nail involvement at baseline (≤ 50% and 51–75%). All analyses were carried out using SPSS software 22.0.0 (Armonk, NY) with 5% significance levels.

Results

A total of 98 patients participated in this study (106 infected nails). The average age of participants was 52.51 (± 11.19) years. Fifty-five percent of the sample was male and 45% was female. Average nail plate length (diseased and healthy) was 13.05 mm (± 5.03). The majority of the sample (88.8%) was infected with *Trichophyton rubrum*. Approximately 61% of the sample had ≤ 50% involvement and 38.7% had 51–75% involvement. There were no significant differences in baseline characteristics between treatment groups ($p_s > 0.05$) (Table 1).

The average percent clear nail in each treatment group per visit is presented in Figure 3. A significant visit by treatment interaction was found ($F(10, 406.47) = 4.25$, $p < 0.001$), such that both Groups 1 and 2 showed significant improvement in percent clear nail compared to Group 3. Group 1 was significantly different from

Table 1. Participant baseline characteristics.

	Treatment arms				
	Group 1	Group 2	Group 3	Total	*p* Values
Males	14 (60.9%)	22 (55.0%)	18 (51.4%)	54 (55.1%)	0.779
Females	9 (39.1%)	18 (45.0%)	17 (48.6%)	44 (44.9%)	
Total	23	40	35	98	
T. rubrum	21	35	31	87	0.830
T. mentagrophytes	2	5	4	11	
Total	23	40	35	98	
≤50% Involvement	13 (56.5%)	29 (64.4%)	23 (60.5%)	65 (61.3%)	0.811
51–75% Involvement	10 (43.5%)	16 (35.6%)	15 (39.5%)	41 (38.7%)	
Total nails	23	45	38	106	
	Mean (±SD)	Mean (±SD)	Mean (±SD)	Mean (±SD)	
Age	50.52 (±11.61)	51.41 (±11.36)	55.03 (±10.56)	52.51 (±11.19)	0.239
Nail plate length	11.61 (4.77)	14.27 (4.76)	12.47 (5.27)	13.05 (5.03)	0.080

Group 1, holes + oral and topical terbinafine; Group 2, holes + topical terbinafine; Group 3, topical terbinafine only; SD, standard deviation.

Table 2. Mean percent clear nail by visit.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
All nails						
Group 1	39.13	55.12	61.41	80.74	79.67	80.39
Group 2	41.11	48.08	52.91	66.91	71.23	73.73
Group 3	40.13	36.11	38.23	43.32	43.25	48.52
≤50% Involvement						
Group 1	50.00	65.47	76.94	90.19	94.90	92.01
Group 2	50.00	58.70	65.49	77.46	79.20	82.80
Group 3	50.00	41.11	53.80	52.08	53.72	56.21
51–75% Involvement						
Group 1	25.00	41.67	27.25	63.75	59.38	52.50
Group 2	25.00	30.16	32.47	39.95	52.39	56.31
Group 3	25.00	25.44	19.07	31.36	23.81	34.86

Group 1, holes + oral and topical terbinafine; Group 2, holes + topical terbinafine; Group 3, topical terbinafine only.

Table 3. Mycological cure rates by visit number.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
All nails						
Group 1	0.0	0.0	14.3	35.7	46.2	47.1
Group 2	0.0	0.0	2.4	6.3	32.4	34.2
Group 3	0.0	0.0	0.0	0.0	5.0	8.0
≤50% Involvement						
Group 1	0.0	0.0	18.2	44.4	50.0	50.0
Group 2	0.0	0.0	0.0	4.3	34.6	36.0
Group 3	0.0	0.0	0.0	0.0	7.7	6.3
51–75% Involvement						
Group 1	0.0	0.0	0.0	20.0	40.0	40.0
Group 2	0.0	0.0	6.7	11.1	27.3	30.8
Group 3	0.0	0.0	0.0	0.0	0.0	11.1

Group 1, holes + oral and topical terbinafine; Group 2, holes + topical terbinafine; Group 3, topical terbinafine only.

Group 3 for visits 2–6 ($p < 0.05$ for visits 2 and 3; $p < 0.01$ for visits 4–6), while Group 2 was significantly different from Group 3 for visits 4–6 ($p < 0.05$ for visit 4 and $p < (0)$ 0.001 for visits 5 and 6). No significant differences between Groups 1 and 2 were found ($p > 0.05$).

For nails with ≤ 50% involvement, a significant visit by treatment interaction was found ($F(10, 255.83) = 2.97$, $p = 0.002$). A similar pattern to the analysis of all nails was observed in nails with ≤ 50% involvement, such that Group 2 was significantly different from Group 3 for visits 4–6 ($p < 0.01$) and Group 1 was significantly different from Group 3 for visits 2–6 ($p < 0.05$ for visits 2 and 3; $p < 0.001$ for visits 4–6). No significant differences between Groups 1 and 2 were found ($p > 0.05$) (Table 2).

For nails with 51–75% involvement, the visit by treatment interaction was not significant ($F(10, 143.02) = 1.83$, $p = 0.061$); however, there was a significant effect of treatment ($F(2, 42.37) = 3.84$, $p = 0.029$). Group 1 showed significant improvement in percent clear nail compared to Group 3 ($p = 0.038$), whereas Group 2 did not ($p = 0.145$). Further analysis revealed that Group 1 showed a significantly greater improvement in percent clear nail compared to Group 3 for visits 4 ($p = 0.028$) and 5 ($p = 0.005$). Group 2 showed significantly greater improvement in percent clear nail compared to Group 3 on visit 5 ($p = 0.014$).

Mycological cure rates by visit number are presented in Table 3. Group 1 had the highest rate of mycological cure overall and when nails were divided by percent involvement at baseline.

Treatment was well tolerated. The majority of participants (82%) had no pain, while 8 participants reported pain of varying intensity with 4 (out of 10) being the maximum level of discomfort reported by a single participant. Although pain scores in participants with holes were low, they were significantly different from those reported by participants who received topical treatment only ($p = 0.040$).

Discussion

The purpose of this study was to assess the efficacy of novel therapeutic regimens involving nail drilling for the treatment of toenail onychomycosis. Both groups that had holes drilled into their nails had a significantly higher mean percentage of clear nail compared to nails treated with topical terbinafine only. Nails with holes treated with combination oral and topical terbinafine demonstrated clear growth earlier on in the study (starting at visit 2) than nails with holes treated with topical terbinafine (visit 4 onward). Although the group with holes treated with combination therapy showed greater improvement earlier on in the study, no significant differences between the two holes groups were found. Therefore, when combined with existing onychomycosis treatments, drilling holes into the nail plate significantly improve the cosmetic appearance of the nail (as measured by percentage of clear nail) relative to topical treatment alone.

Similar results were observed for nails with ≤ 50% involvement, such that the holes plus combination therapy and the holes plus topical therapy groups showed significantly greater nail clearance over topical treatment alone. Improvement was observed earlier on in the group treated with holes plus combination therapy compared to the group treated with holes plus topical therapy; however, the holes groups did not differ significantly from one another. Hence in nails with ≤ 50% involvement, drilling holes into the nail plate significantly improved the appearance of the nail over topical treatment alone and a therapeutic regimen consisting of holes plus topical therapy appears to produce esthetic

improvement similar to that which would be observed with a regimen that included oral therapy.

For nails with 51–75% involvement, the group with holes treated with combination therapy showed a significantly higher mean percent clear nail compared to nails treated with topical terbinafine only. The percent clear nail in the holes plus topical terbinafine group was not significantly greater than that observed in the topical terbinafine only group. Also, not only did a larger proportion of nails in the holes plus combination therapy group achieve mycologic cure relative to other treatment groups, but it was also attained earlier on in the study. Insufficient sample size limited our ability to compare mycologic cure rates between groups and may have resulted in a lack of statistical power. However, given that topical terbinafine in combination with nail drilling was not significantly different from topical terbinafine alone and that more severe disease typically warrants oral therapy; the observed effect may be due to the addition of oral treatment and lends to the notion that systemic therapy is warranted for patients with more severe disease (>50% involvement). An important limitation of this study is that participants were only followed-up for 6 months and this period may not be sufficiently long to demonstrate treatment effect, especially considering the slow rate of toenail growth.

Electrical equipment and dental drills have previously been used in conjunction with topical antifungals to thin or debride the nail plate (6–8). In a study by Fukuda and Shiohara, 32 patients with onychomycosis had the diseased parts of their nails removed with a high-speed electrical grinder in addition to being treated with either 1% neticonazole hydrochloride solution (Group A) or 1% butenafine hydrochloride solution (Group B) (6). Mycological evaluations were performed by KOH mount, periodic acid-Schiff stain and culture. After 6 months of treatment, 13.3% of patients in Group A and 17.7% of patients in Group B were completely cured, while 73.3% of Group A and 58.8% of Group B showed improvement with no adverse effects reported. In another study, 146 patients with onychomycosis who were unresponsive to long-term treatment with topical antifungals also had the mycotic portions of their nails removed with a high-speed electrical drilling device and continued topical therapy thereafter (7). Patients' reported a shortened disease duration and considerable improvement in disease morbidity. Sumikawa et al. used an electrical dental drilling device to thin the nail plate in combination with topical therapy to treat toenail onychomycosis in diabetic patients (8). Twenty-four diabetic patients, 8 of whom presented with superficial white onychomycosis and 16 with DLSO, were prescribed topical ketoconazole, terbinafine hydrochloride, bifonazole, clotrimazole or butenafine hydrochloride and underwent nail surface grinding. The Scoring Clinical Index for Onychomycosis was used to evaluate the regimen's efficacy. Though complete cure was not achieved in this study, improvement was observed in 56.3% of patients.

Despite the use of electrical devices to thin or debride the nail plate, the use of holes to improve the efficacy of topical therapy has not been widely investigated. A previous study investigated the use of holes in the nail plate to improve the efficacy of amorolfine 5% nail lacquer (4). Participants were assigned to have either (a) holes created in their nail plates by means of a Er:YAG 2940 nm laser and amorolfine 5% lacquer for 6 months or (b) amorolfine 5% lacquer alone for 6 months. Results from this study have yet to be reported. The authors' did note that patients' experienced pain and bleeding following damage to the nail bed by the laser. The hole-drilling device used in the present study is set to stop drilling once it reaches a pre-specified humidity level, therefore sparing participants of unnecessary pain and trauma. Indeed, the majority of participants in our study reported no pain and none experienced bleeding or nail bed trauma from the drilling procedure.

Overall, nail drilling as an addition to existing onychomycosis treatment regimens produced significantly greater improvement in nails' appearance and numerically higher mycological cure rates compared to topical treatment alone, likely attributable to increased antifungal penetrance through the nail plate. Compliance with these treatment regimens was also higher than with topical treatment alone. Thus, this well-tolerated procedure can provide an additional method to clinicians treating onychomycosis and in particular, may be of value in assisting patients who are otherwise unresponsive to topical treatment. While not all patients will be open to having holes drilled into their nail, this technique may provide an alternative to long-term systemic treatment for those with more serious disease who are unwilling, or who are not candidates for, prolonged systemic treatment. Of patients with 51–75% nail involvement, those that received holes with combination oral and topical terbinafine showed significant percent clear nail as compared to topical alone, while over this short course of treatment, holes and topical did not differ from topical alone. Therefore, short course oral antifungal treatment coupled with nail drilling to increase the efficacy of topical agents may be a more attractive option for those with moderate to severe onychomycosis.

Disclosure Statement

A.S. is a consultant for Ex-it Medical Devices Ltd. A.K.G. has been both an investigator and speaker for Valeant Pharmaceuticals International Inc., Novartis Pharmaceuticals Inc., and Janssen Pharmaceuticals Inc., and has been an investigator Nitric Bio Inc. D.D. and K.A.F. are employees of Mediprobe Research Inc. which conducts clinical trials under the supervision of AKG. B.A., R.F., R.B. and C.R.D. III have no conflicts of interest to declare.

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