Journal of Novel Physiotherapies

Samhan and Abdelhalim, J Nov Physiother 2015, 5:2
http://dx.doi.org/10.4172/2165-7025.1000252

Research Article Open Access

Terbinafine Hydrochloride 1% Iontophoresis for the Treatment of Toenail Onychomycosis: A Randomized Placebo Controlled Study

Ahmed Fathy Samhan[1,2*] **and Nermeen Mohamed Abdelhalim**[1,2]

[1]*Physical Therapy Department, New Kasr El-Aini Teaching Hospital, Faculty of Medicine, Cairo University, Egypt*

[2]*Physical Therapy and Health Rehabilitation Department, College of Applied Medical Sciences, Prince Sattam bin Abduaziz University (Formerly Salman bin Abdulaziz University), Saudi Arabia*

[*]**Corresponding author:** Ahmed Fathy Samhan, PhD PT, Physical Therapy and Health Rehabilitation Department, College of Applied Medical Sciences, Prince Sattam bin Abduaziz University (Formerly Salman bin Abdulaziz University), Alkharj, Saudi Arabia, Tel: 00966545159701; E-mail: ahmedsamhan44@yahoo.com

Received: March 01, 2015, **Accepted:** March 11, 2015, **Published:** March 18, 2015

Abstract

Background: Successful topical treatment with deep penetration of toenail Onychomycosis remains hard as the delivery of effective degrees of antifungal drug to the site of action is very difficult.

Purpose: To evaluate the efficacy and safety of terbinafine hydrochloride 1% iontophoresis for treatment of toenail Onychomycosis.

Methods: Forty patients (23 males and 17 females) with mean age 46.15 ± 7.72 years and with mild-to-moderate toenail Onychomycosis of the big toe, were enrolled in a randomized placebo controlled study. All patients were assigned randomly into two groups of equal number: study group received terbinafine hydrochloride 1% iontophoresis on the big toenail Onychomycosis with an intensity of 3 to 4 mA/min for 30 minutes, 3 times per week for 4 weeks (12 sessions) and control group received placebo terbinafine hydrochloride 1% iontophoresis. Onychomycosis Severity Index, potassium hydroxide microscopy of a dermatophyte, and visual analogue scale for patient-reported pain during walking wearing shoes had been collected pre-treatment and post-treatment.

Results: Showed significant improvement in the 3 outcomes in study group ($p<0.05$) with non-significant improvement in control group ($p>0.05$). Moreover the analysis between the two groups showed highly significant improvement as the study group would be preferred.

Conclusion: Terbinafine hydrochloride 1% iontophoresis with an intensity of 3 to 4 mA/min appeared to be effective and safe for treatment of mild-to-moderate toenail Onychomycosis after 4 weeks of treatment.

Keywords: Onychomycosis; Terbinafine; Iontophoresis

Introduction

Onychomycosis is a common, chronic fungal infection of the nail plate and nail bed that leads to thickening, discoloration, hardening and crumbling of the nail plate. Toenails are more likely to be infected than fingernails, and infection of both hands and feet may occur and generally causes discomfort to patients and may impact patients' quality of life (QOL) [1]. Toenail Onychomycosis is more than cosmetic problem but patients often experience pain and discomfort, and can affect walking, standing, exercise, or proper shoe fit [2].

The prevalence of Onychomycosis worldwide is about 2-13% and it is fast progressing [3]. It is reported that about 32% of the elderly are suffering from Onychomycosis and the prevalence increases with advancing age [4]. There are many risk factors for Onychomycosis such as diabetes, immunosuppression, elderly, peripheral arterial disease, sports activities and pre-existing dysmorphic nails due to disease such as psoriasis or trauma [5].

The causative organisms in most cases of Onychomycosis are dermatophytic molds such as Trichophyton rubrum and Trichophyton mentagrophytes which represent approximately 85% of cases, nondermatophytic molds represent 15% of cases, and rarely yeasts [6].

The current treatment involves oral antifungal drugs such as griseofulvin (Grisactin®), ketoconazole (Nizarol®), and tirbinafine hydrochloride (lamisil®) [7]. Oral therapy with terbinafine HCL is associated with several limitations which include drug interactions, severe side effects, toxicity, and a high rate of recurrence [8]. Topical therapies are the 2nd choices which eliminate the side effects of oral drugs but it can only successful in mild and acute Onychomycosis. Newer nail lacquer formulations such as ciclopirox (Penlac®) and amorolfine (Curanail®) are more effective than traditional topical therapies [9]. Unfortunately, the efficacy of topical application is extremely limited by decreasing in the permeability of the applied medication through the nail into the nail bed and matrix. Topical therapies have been used in combination with oral therapy [10]. As both treatments have limitations, the wealthy treatment in Onychomycosis stays evasive.

The ordinary method for increasing nail drug delivery has been to utilize keratolytic and thiolytic agents which are familiar to enhance the permeability of nail matrix by chemical adaptation of keratin. However, their permeability improvement ability is restricted by the factors such as penetrability of enhancer and the time of its attendance

in the nail matrix might significantly affect the chemical adaptation of keratin [11]. Physical penetration enhancement methods have been successfully used in the transungual delivery of drugs [12]. James et al., fulfilled iontophoresis of prednisolone sodium phosphate through thumb nail and determined the duration of prednisolone in plasma. They also debated the feasibilities of using iontophoresis for treating nail diseases [13]. Furthermore, iontophoresis may have bacteriostatic and fungistatic characteristics [14].

Iontophoresis is a process in which ions in solution are transported across the intact skin by using low intensity electric current. It was also shown that iontophoresis can augment the transport of drugs through the nail plate significantly. The effects of electric current on nails are overturned *in vitro* [15] and *in vivo* [16]; as nail plates will return to normal after iontophoresis treatment.

Terbinafine is a strong synthetic allylamine antifungal drug which is authorized by FDA for use in superficial skin and nail fungal infections [17].

The purpose of this study was to evaluate the efficacy and safety of terbinafine HCl 1% iontophoresis for treatment of toenail Onychomycosis.

Materials and Methods

Study design

The study was designed as a randomized placebo controlled study with pre-treatment and post-treatment evaluation. This study was carried out over the period from May to November 2014 at the physical therapy department of New Kasr El-Aini Teaching Hospital, Cairo University, Egypt.

Subjects

Forty patients (23 males and 17 females) referred to the physical therapy outpatient clinic from dermatologists with the following clinical diagnostic criteria were included: subjects aged 30–60 years with mild-to-moderate toenail Onychomycosis of the big toe which comprise distal and lateral subungual Onychomycosis. Mild-to-moderate toe Onychomycosis was defined as a toenail involvement of 25% to 75% without spikes and without matrix involvement, and nail infection was verified by positive potassium hydroxide (KOH) microscopy. Subjects must be able to follow the medical directions during the study. Exclusion criteria were: subjects who had nail abnormalities, obscuring view of infection-free normal nail (comprising traumatic or onychogryphotic nail) or in whom the infected toenail had less than 2 mm unaffected nail plate section beyond the proximal fold. Also, subjects with severe plantar tinea pedis needing systemic therapy, combined infections (dermatophyte and non-dermatophyte), dermatophytoma thick masses of fungal hyphae between the nail plate and nail bed), those receiving systemic or local anti-fungal therapy within 6 months or 3 months, respectively, and those who used any commercial local nail drug within 1 month. Subjects with severe diabetic foot neuropathy, malignancy, and sensitivity to terbinafine HCl were also excluded.

Institutional Ethical Committee Clearance and written informed consent were taken from subjects. Subjects were assigned randomly using computer generated table of random numbers into 2 groups of equal number 20 subjects for each group. Subjects in study group received active terbinafine HCl 1% iontophoresis to the big toenail Onychomycosis while subjects in control group received placebo iontophoresis. Subjects were told that one group of patients would receive inactive treatment.

Procedures

Outcome measures

There were 3 outcome measures, Onychomycosis Severity Index (OSI), potassium hydroxide (KOH) microscopy of a dermatophyte, and visual analogue scale (VAS) for patient-reported pain during walking wearing shoes. The three outcome measures had been collected pre-treatment and post-treatment.

Onychomycosis Severity Index (OSI) is a simple, objective, reproducible numerical system to classify the severity of Onychomycosis. The OSI is calculated as follows: the score for area of inclusion is multiplied by the score for the proximity of disease to the matrix, and 10 points are added for the attendance of a dermatophytoma or subungual hyperkeratosis of >2 mm. The area of inclusion is the percentage of infected onychomycotic nail, 1 point is given if the disease involves 1% to 10% of the nail, 2 points for 11% to 25%, 3 points for 26% to 50%, 4 points for 51% to 75%, 5 points for 76% or more of the nail and no points are gave if no involvement is noted, and the nail is considered clinically cured or inclusion of 1% to 10% may occasionally reveal a "cure" if mycological analysis results are negative for fungus [18]. The proximity of disease to the matrix is calculated as the nail is segmented horizontally into quarters beginning distally and lengthening proximally, it is given a score of 1 to 4, so if the proximal edge is in the distal quarter of the nail, a score of 1 is given; if it extends to the 1st half of the nail, a score of 2; the 3rd quarter, a score of 3; the proximal quarter, a score of 4; a score of 5 is allocated only if there is decisive matrix infection that contains lunula under the proximal nail fold. Dermatophytomas stand for accumulations of fungal hyphae on histological examination, suggestive an aspergilloma [19]. Subungual hyperkeratosis represents thickening of the stratum corneum in reaction to fungal infection, and the height is calculated from the nail bed to the nail plate [20]. If the total score of OSI is 0, it will indicate a "cure"; 1 to 5, mild Onychomycosis; 6 to 15, moderate Onychomycosis; and 16 to 35, severe Onychomycosis [21].

Potassium hydroxide microscopy (KOH)

The diagnosis of infection with some laboratory evidences is essential before treating them with antifungal drugs. Currently available usual laboratory procedures are direct microscopy with KOH and mycological culture. Samples were gathered from the ventral surface of each big toenail and put on a slide. Few drops of 20% KOH were added, incubation was done for 2 h or more up to 48 h until soothing or break down of the sample occurred, and inspected under microscope (20x magnification - Zeiss MI, Thornwood, NY) [22].

Visual analogue scale (VAS)

Subjects rated the pain level during walking wearing shoes for each individually treated toenail on a 0-10 point VAS (0=no pain, 10=excruciating pain).

Treatment Procedures

Group A

is the study group which consisted of twenty toenail Onychomycosis patients who were treated by Chattanooga Ionto™ Dual Channel Iontophoresis System (USA). This system operates on

the principle that electrically-like charges repel each other and delivers ionic drug solutions directly to the body site (skin or nail) being treated and offers; two channels for treatment of two different sites simultaneously and automatic calculation of time based on set dose (1 mA/min. increment from 0 - 160 mA/min) and intensity (0.5 mA and 4 mA). The device was portable with power supply 9 V alkaline battery. The subjects were placed on a bed with the lower leg and the feet were exposed, each infected big toenail was cleaned with alcohol and dried thoroughly. The lead wires were connected to the electrodes. The active electrode polarity was positive as terbinafine HCL was positive ions and the dispersive electrode was the negative electrode. Terbinafine HCl 1% solution (Lamisil® Solution, 1%, Novartis, Switzerland) was injected into the active electrode (Iomed Iontophoresis Electrodes - IOGEL® Drug around Delivery Electrode, Small size) which ensured complete contact between the electrode and the skin surface around the toenail with low impedance, provided a conductive medium similar to ultrasound gel, and was placed in the infected big toenail and the gel dispersive electrode (dispersive pad) was adhesive proximal to the dorsum of the foot. At each treatment session, terbinafine HCl 1% iontophoresis was applied on the big toenail Onychomycosis with an intensity of 3 to 4 mA/min for 30 minutes, 3 times per week for four weeks (12 sessions). Current was increased slowly in order to accommodate for sensation until the maximum current was tolerated by the patient. Subjects were carefully observed at each session to evaluate any side-effects such as pain, erythema or irritation. They might fell itching or prickling sensation during the treatment under the active or the dispersive electrodes. Each electrode was used once and was replaced every session.

Group B

is the control group which consisted of twenty toenail Onychomycosis patients who were treated by terbinafine HCl 1% iontophoresis with no current output to subjects (intensity equal zero), as a placebo treatment. The type of device, time of each session and number of sessions were the same as in the study group.

Statistical Analysis

Paired t-test was used to assess the difference within each group in OSI and VAS (parametric variables) for pain level during walking wearing shoes while un-paired t-test was used between both groups in the same variables and also for age. Mann-Whitney U test was used to assess the difference in gender and KOH microscopy (non-parametric variable) between both groups, while Wilcoxon Signed Ranks test was used to determine the significant within each group in this variable. Descriptive statistics (mean and standard deviation) were computed for all data. Data were coded and entered to a statistical package of social science (SPSS, version 20). All p-values less than 0.05 were considered to be statistically significant.

Results

The mean age was 46.15 ± 7.72 years of the study group and was 45.10 ± 8.83 years of the control group. P-value was 0.679 (>0.05) which mean a non-significant difference between both groups in age. Number of males in the study group was 11 (55%) and number of females was 9 (45%), while number of males in the control group was 12 (60%) and number of females was 8 (40%), with a p-value of 0. 752 (>0.05) which mean a non-significant difference between both groups in gender, so there was a homogeneity between both groups in age and gender.

Parameters	Time of evaluation	Study group	Control group	----------
		Mean ± SD	Mean ± SD	P- value
OSI	Pre-treatment	15.7 ± 6.38	15.9 ± 6.18	0.92
	Post treatment	4.6 ± 8.77	14.45 ± 6.95	0.001
	P- value	0.001	0.077	----------
VAS	Pre-treatment	6.55 ± 1.10	6.95 ± 1.15	0.276
	Post treatment	1.25 ± 2.02	5.95 ± 2.46	0.001
	P- value	0.001	0.086	----------

Table 1: Onychomycosis Severity Index (OSI) and VAS for pain level during walking wearing shoes in both groups.

The mean changes in OSI and VAS for pain level during walking wearing shoes for the study group and the control group pre and post-treatment in both groups are summarized in Table 1. Comparison revealed that there were no significant differences in mean changes for all measurements between the two groups pre-treatment ($p > 0.05$) and a high significant difference in mean changes for all measurements between the two groups post-treatment ($p<0.05$). Results of the same two parameters showed that there was a significant difference pre and post-treatment in the study group ($p<0.05$) while there was no significant difference in the control group ($p > 0.05$).

Frequency and percentage of patients with KOH microscopy of the study group and the control group are summarized in Table 2.

Comparison revealed that there were no significant differences in mean changes for all measurements between the two groups pre-treatment ($p>0.05$) and a high significant difference in mean changes for all measurements between the two groups post-treatment ($p<0.001$).

There was a statistically highly significant difference within the study group ($p<0.001$), while there was no significant difference within the control group ($p>0.084$).

KOH	Time of evaluation							
	Pre-treatment				Post-treatment			
	Study group		Control group		Study group		Control group	
	F	%	F	%	F	%	F	%
Positive	20	100%	20	100%	4	20%	17	85%
Negative	0	0%	0	0%	16	80%	3	15%

Table 2: Frequency and percentage of patients with Potassium hydroxide (KOH) microscopy pre-treatment and post-treatment in both groups.

Figure 1 shows the mean difference values of OSI pre and post-treatment in both groups. Figure 2 shows the mean difference values of VAS for pain level during walking wearing shoes pre and post treatment in both groups.

Figure 3 shows the percentage of patients with KOH microscopy pre and post treatment in both groups.

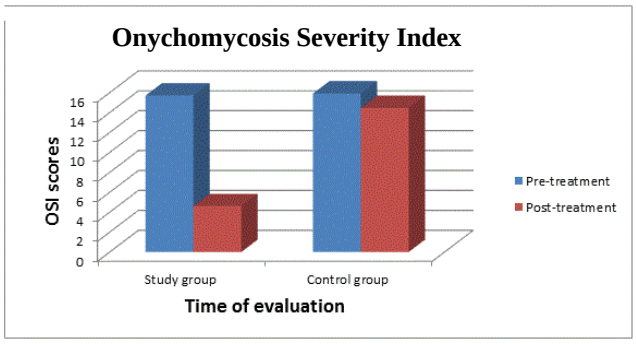

Figure 1: Onychomycosis Severity Index (OSI) pre-treatment and post-treatment in both groups.

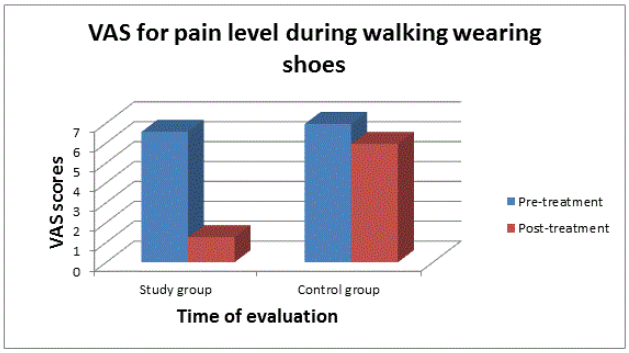

Figure 2: VAS for pain level during walking wearing shoes pre-treatment and post-treatment in both groups.

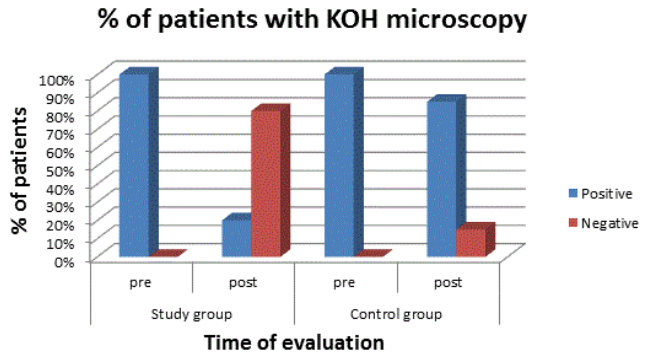

Figure 3: Percentage of patients with KOH microscopy pre and post treatment in both groups.

Discussion

Topical antifungal drugs have generally been distinguished as poorly efficient, mainly because of bad penetration into the toenail. Usually, topical treatment is desirable for patients with Onychomycosis influencing only a few numbers of nails, particularly in cases where the disease time is shorter with least fungal involvement of the distal part of the nail. Despite of its low cure rate, and long treatment duration, it can be used as a choice treatment for those patients who couldn't tolerate systemic therapy. Systemic antifungal drugs are very effective, but may be accompanied with high risk of systemic side effects. The rapid, trans-ungual iontophoretic drug delivery technique with high cure rates and with minimal systemic side-effects for treating toenail Onychomycosis was developed.

The purpose of this study was to estimate the efficacy and safety of terbinafine HCl 1% iontophoresis as a topical antifungal treatment that may improve drug delivery to toenail Onychomycosis. Three parameters were assessed in order to establish improvement: two objective methods (OSI scores & diagnosis with KOH microscopy) and one subjective method (the pain level during walking wearing shoes by VAS).

In the present study patients received terbinafine HCl 1% iontophoresis on the big toenail Onychomycosis with an intensity of 3 to 4 mA/min. The procedure was under complete supervision of a physical therapist to detect any side effects. In comparing with the previous studies, the time of iontophoresis session was shorter (30 minutes) and the overall period of treatment was 4 weeks (short duration of treatment). The data analysis revealed that the study group which received active terbinafine HCl 1% iontophoresis therapy showed highly significant improvement in OSI scores that was used to classify the severity of Onychomycosis, KOH microscopy which used to diagnose the presence of dermatophyte infections which cause toenail Onychomycosis, and VAS which reported the pain level during walking wearing shoes, before and after treatment. On the other hand data analysis of the control group which received placebo terbinafine HCl 1% iontophoresis showed non-significant improvement in the same three parameters. Moreover the analysis between the two groups showed highly significant improvement in favor to the study group. Toenail Onychomycosis was improved after treated by terbinafine HCL 1% iontophoresis only for 30 minutes, 3 times per week for four weeks (12 sessions) without any detected side effects with high

terbinafine permeation across the nail plate under the influence of electric charge, as terbinafine HCl has a positive charge and was connected to the positive electrode of the iontophoretic unit to be rebelled to penetrate the nail bed. This is most likely due the fact that terbinafine HCl 1% iontophoresis is noninvasive, safe, short treatment period, and can be easily completed within few minutes per treatment session without any side effects. Patients of control group received active terbinafine HCL 1% iontophoresis as in study group after the end of the study to benefit from the procedure.

Nail is different from skin as it is a thick, hard keratin membrane with low lipid content (≤1%) [23]. Iontophoresis includes delivery of ions across a membrane using an electromotive force. The principal pathway for iontophoresis in skin is known to be the follicular route, which it disappeared in nail. However, a hydrated nail is known to swell and behave more like a porous hydrogel matrix [24]. Drug diffusion through the hydrated keratin of a nail may be improved by iontophoresis. Factors which are responsible for this improvement comprise electro-repulsion/electrophoresis- interaction between the electric field and the charge of the ionic permeant; electro-osmosis convective solvent flow in pre-existing and newly created charged pathways; and permeabilization/electroporation- electric field-induced pore induction. In contrast to passive transport, iontophoresis significantly enhanced drug penetration through the nail [25]. Murthy et al., studied the effect of iontophoresis on the permeability of salicylic acid across human nail plate. They applied diffusion study using Franz diffusion cell. The results reported that extreme increase in the permeability across nail plate as compared with the routine method of penetration [26].

Terbinafine is a well-established broad-spectrum antifungal drug with unique clinical efficacy integrated with good tolerability. Terbinafine HCl, a strong antifungal agent from allylamine antifungals, was chosen as a model drug because it is very impressive in treatment of dermatophyte infections and it is a drug option for treatment of Onychomycosis [27]. Recently, terbinafine HCl 1% iontophoresis has become one of the most effective therapies for toenail Onychomycosis. The findings of the present study are generally in line with earlier reports of positive outcome treatment of toenail Onychomycosis with terbinafine HCl 1% iontophoresis in the previous studies.

Initial studies reported that implementation of current (0.5 mA/cm²) could significantly increase the trans-ungual delivery of terbinafine. An increase in the implemented current or duration of current application increased the trans-ungual delivery of terbinafine. Terbinafine permeation through the nail and drug percentage in the nail correlated well with the used electrical dose. Light microscopy trials proven the ability of iontophoresis to drive a charged molecule across the nail plate. The results of Nair et al., indicated that iontophoresis could be developed as a potential technique for Onychomycosis therapy [28]. In another study by Nair et al., they reported that a short current time (max 60 min) and a safe current intensity (max 0.5 mA/cm²) would be preferred. With their applicator technique, treating more than finger/toe infections at the same time using a multiunit power supply should be possible. They concluded that local iontophoretic delivery of terbinafine to the nails would be able to result in much higher drug load levels compared to systemic delivery [29].

In a preliminary study by Amichai et al., 38 patients were divided randomly into two groups, group A was treated with terbinafine and an iontophoretic patch and group B was treated with terbinafine without iontophoresis. Treatment was overnight wear (6-8 hours), every day, 5 days per week, for 4 weeks. Results showed a significant clinical response in patients of group A. They concluded that the delivery of terbinafine under an electrical current of 100 μA/cm² appears to be efficacious and safe for the treatment of nail Onychomycosis [16]. In another study by Amichai et al., iontophoresis was introduced through porcine and human nail *in vitro* to evaluate its efficiency in increasing transference of terbinafine HCL. They reported that an optimal electrolyte concentration (1% NaCl or KCl) is needed for an effective transference. They concluded that iontophoresis was effective in increasing the trans-nail delivery of terbinafine [30].

The findings of the current study suggested that terbinafine HCl 1% iontophoresis appeared to be effective and safe for the treatment of toenail Onychomycosis as shown by improvement of OSI scores in the study group compared with the control group. This effect could be reinforced by negative reaction of KOH microscopy as well as by the reduction of pain scores during walking wearing shoes in VAS. It might be possible that successful toenail Onychomycosis treatment would result from developing a topical treatment technique (iontophoresis) that will be able to give a high cure rates with short durations treatment.

Conclusion

Terbinafine hydrochloride 1% iontophoresis with an intensity of 3 to 4 mA/min appeared to be effective, safe, and well tolerated for the treatment of mild-to-moderate toenail Onychomycosis after 4 weeks of treatment.

References

1. Finch JJ, Warshaw EM (2007) Toenail Onychomycosis: current and future treatment options. Dermatol Ther 20: 31-46.
2. Potter LP, Mathias SD, Raut M, Kianifard F, Tavakkol A (2006) The OnyCOE-t™ questionnaire: responsiveness and clinical meaningfulness of a patient-reported outcomes questionnaire for toenail Onychomycosis. Health and Quality of Life Outcomes 4: 50.
3. Murdan S (2007) 1st meeting on topical drug delivery to the nail. Expert Opin Drug Deliv 4: 453-455.
4. Botek G (2003) Fungal nail infection: assessing the new treatment options. Cleve Clin J Med 70: 110-114, 117-8.
5. Tosti A, Hay R, Arenas-Guzman R (2005) Patients at risk of Onychomycosis--risk factor identification and active prevention. J Eur Acad Dermatol Venereol 19 Suppl 1: 13-16.
6. Piraccini BM, Iorizzo M, Antonucci A, Tosti A (2004) Treatment of nail disorders. Therapy 1: 159-167.
7. Ajit C, Suvannasankha A, Zaeri N, Munoz SJ (2003) Terbinafine-associated hepatotoxicity. Am J Med Sci 325: 292-295.
8. Gupta AK, Shear NH (2000) A risk-benefit assessment of the newer oral antifungal agents used to treat Onychomycosis. Drug Saf 22: 33-52.
9. Rodgers P, Bassler M (2001) Treating Onychomycosis. Am Fam Physician 63: 663-67 677-8.
10. Patel RP, Naik SA, Patel NA, Suthar AM (2009) Drug Delivery across Human Nail. International Journal of Current Pharmaceutical Research 1: 1-7.
11. Murdan S (2002) Drug delivery to the nail following topical application. Int J Pharm 236: 1-26.
12. Kassan DG, Lynch AM, Stiller MJ (1996) Physical enhancement of dermatologic drug delivery: iontophoresis and phonophoresis. J Am Acad Dermatol 34: 657-666.
13. James MP, Graham RM, English J (1986) Percutaneous iontophoresis of prednisolone--a pharmacokinetic study. Clin Exp Dermatol 11: 54-61.

14. Kalinowski DP, Edsberg LE, Hewson RA, Johnson RH, Brogan MS (2004) Low-voltage direct current as a fungicidal agent for treating Onychomycosis. J Am Podiatr Med Assoc 94: 565-572.
15. Hao J, Li SK (2008) Transungual iontophoretic transport of polar neutral and positively charged model permeants: effects of electrophoresis and electroosmosis. J Pharm Sci 97: 893-905.
16. Amichai B, Nitzan B, Mosckovitz R, Shemer A (2010) Iontophoretic delivery of terbinafine in Onychomycosis: a preliminary study. Br J Dermatol 162: 46-50.
17. Sachdeva V, Kim HD, Friden PM, Banga AK (2010) Iontophoresis mediated in vivo intradermal delivery of terbinafine hydrochloride. Int J Pharm 393: 112-118.
18. Scher RK, Tavakkol A, Sigurgeirsson B, Hay RJ, Joseph WS, et al. (2007) Onychomycosis: diagnosis and definition of cure. J Am Acad Dermatol 56: 939-944.
19. Roberts DT, Evans EG (1998) Subungual dermatophytoma complicating dermatophyte Onychomycosis. Br J Dermatol 138: 189-190.
20. Baran R, Hay RJ, Garduno JI (2008) Review of antifungal therapy and the severity index for assessing Onychomycosis: part I. J Dermatolog Treat 19: 72-81.
21. Carney C, Tosti A, Daniel R, Scher R, Rich P, et al. (2011) A new classification system for grading the severity of Onychomycosis: Onychomycosis Severity Index. Arch Dermatol 147: 1277-1282.
22. Shenoy MM, Teerthannth S, Karnake VK, Girisha BS, Prasad MSK, et al. (2008) Comparison of potassium hydroxide mount and mycological culture with histological examination using periodic acid-Schiff staining of the nail clippings in the diagnosis of Onychomycosis. Indian J Dermatol Venereol Leprol 74: 226-229.
23. Gupchup GU, Zatz JL (1999) Structural characteristics and permeability properties of thehumannail: A review. J Cosmet Sci 50: 363-385.
24. Walters KA, Flynn GL, Marvel JR (1983) Physicochemical characterization of the human nail: Permeation pattern for water and the homologous alcohols and differences with respect to the stratum corneum. J Pharm Pharmacol 35: 28-33.
25. Murthy SN, Waddell DC, Shivakumar HN, Balaji A, Bowers CP (2007) Iontophoretic permselective property of human nail. J Dermatol Sci 46: 150-152.
26. Murthy SN, Zhao YL, Hui SW, Sen A (2005) Electroporation and transcutaneous extraction (ETE) for pharmacokinetic studies of drugs. J Control Release 105: 132-141.
27. Elewski BE, Ghannoum MA, Mayser P (2013) Efficacy, safety and tolerability of topical terbinafine nail solution in patients with mild-to-moderate toenail Onychomycosis: results from three placebo studies using double-blind vehicle-controlled and open-label active-controlled designs. JEADV 27: 287-294.
28. Nair AB, Vaka SR, Sammeta SM, Kim HD, Friden PM, et al. (2009) Trans-ungual iontophoretic delivery of terbinafine. J Pharm Sci 98: 1788-1796.
29. Nair AB, Kim HD, Chakraborty B, Singh J, Zaman M, et al. (2009) Ungual and trans-ungual iontophoretic delivery of terbinafine for the treatment of Onychomycosis. J Pharm Sci 98: 4130-4140.
30. Amichai B, Mosckovitz R, Trau H, Sholto O, Ben-Yaakov S, et al. (2010) Iontophoretic terbinafine HCL 1.0% delivery across porcine and human nails. Mycopathologia 169: 343-349.