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Efficacy of Planter Warts Treatment with Tretinoin Phonophoresis: Randomized Single Blinded Controlled Trial

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ABSTRACT

Objective: To evaluate the efficacy of Tretinoin gel phonophoresis versus topical Tretinoin gel in the treatment of planter warts. **Design, Setting, and Participants:** Prospective, randomized, single-blind, pre–post-test, controlled trial in patients complaining from planter warts selected from Outpatient Dermatology Unit at Railway Hospital between Oct. 2016 and May 2017. Randomized participants were 22 male patients (Group A n=11 and group B n=11) by a blinded and independent research assistant using computer generated randomization card, their age ranging 25-40 years. Patients of Group A received Tretinoin gel Phonophoresis (1MHz Transducer Head, 3W/Cm², 10 minutes, day after day for four weeks), while patients of Group B received Topical Tretinoin gel Application day after day for four weeks. **Main Outcome Measure:** Warts Diameter (by using a diameter caliper) measured at base line, after 6th and 12th session.

Results: With no dropout, analysis of 22 patients indicated significant wart diameter reduction in Group A and Non-significant improvement in Group B.

Conclusion: It could be concluded that Tretinoin gel Phonophoresis might be valuable in the treatment of planter warts.

Key words: Tretinoin, planter warts, Phonophoresis

Introduction

Cutaneous warts are a common presenting complaint in up to 10 percent of children and young adults, warts occur with greater frequency in girls than in boys (Bacelieri and Johnson, 2005). Warts particularly affecting the hands and feet represent one of the most common virus infections of the skin (Plasencia, 2000). Warts typically continue to increase in size and distribution and can be painful depending on their location (e.g. soles of foot and near the nails) and view as socially unacceptable when located on visible areas as face and hands (Clifton *et al.*, 2003).

Warts represent a difficult therapeutic challenge. Response rate with standard therapies i.e. cryosurgery, salicylic acid, electrosurgery, are variable (Kauvar *et al.*, 1995). Treating warts is a therapeutic challenge for the medical field. No single therapy has been proven to be effective at achieving complete remission in every patient. Some of those standard therapies are cryosurgery, salicylic acid and electrosurgery (Sterling *et al.*, 2001). Aggressive destructive treatment modalities (e.g. Cryosurgery and electrocautery) are undesirable due to resultant discomfort, interference with the patient's routine activities and possible blistering or ulceration after treatment. These methods require local anaesthesia and sometimes necessitate a digital block, which can be very painful, especially in the sole of the foot (Loo and Tang, 2009). Warts may even recur in 20% to 40% of cases using surgical excision or electrocautery (Champion *et al.*, 1998) with disadvantage of prolonged recovery time from an often deep and large skin defect which may followed by recurrence producing additional pain, scaring and complications. These complications may also present after carbon dioxide laser treatment. Liquid Nitrogen could be used for treatment of plantar warts but it usually produces a painful burning sensation during the treatment and lasts for 72hours post-treatment (Loo and Tang, 2009).

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Tretinoin is derived from vitamin A, one of a class of substances called retinoids. Retinoid cream disrupts the wart's skin cell growth (Sterling *et al.*, 2001). Systemic retinoids have been used to treat warts because of their ability to alter keratinization and accelerate the clearing of warts by inducing an irritant dermatitis (Al Aboosi, 1994). Previous case studies recommended oral and topical retinoids for the treatment of warts (Brodell and Johnson, 2003).

Phonophoresis (sonophoresis, ultrasonophoresis, ultraphonophoresis) can be defined as the combination of ultrasound therapy with topical drug therapy to achieve therapeutic drug concentrations at selected sites in the skin (Asbill *et al.*, 2000). Many drugs are absorbed through the skin only very slowly, high frequency sonic vibration may accelerate this process (Polat *et al.*, 2011). Current evidence suggests that Iontophoresis and phonophoresis are promising physical therapy methods for enhancing delivery of both dermatologic and non-dermatologic drugs, by varying electrical current or ultrasound frequency (Kassan *et al.*, 1996). Phonophoresis is considered a non-invasive procedure where its effect relies on perturbation of the tissue causing more rapid particle movement and thus encouraging the absorption of the drug (Miller *et al.*, 2012).

The purpose of the study was to determine whether Tretinoin 0.025% gel Phonophoresis helps in diminishing planter warts size and avoid its diameter from increasing when compared with Tretinoin 0.025% gel topical application.

Materials and Methods

Design of the Study:

The study was designed as a prospective, randomized, single-blind, pre–post-test, controlled trial. Ethical approval was obtained from the institutional review board at Faculty of physical therapy, Cairo University before study commencement.

Participants

Twenty two male volunteer patients complaining from planter warts participated in this study. They were selected from the Railway Hospital (Department of Dermatology) between Oct. 2016 and May 2017. These patients were examined by a dermatologist before the study, and those subjects were chosen with ages ranged from 25 to 40 years, male subjects who had individually diagnosed unilateral planter wart. The patients were excluded from the study if they had grouped and mosaic warts, undergoing any medical treatment for treating warts, those suffering from malignancies in the area to be treated, subjects who had any infections other than human papilloma virus at sight of treatment or diabetic patients.

Randomization and blinding

Informed consent was obtained from each participant after explaining the nature, purpose, and benefits of the study, informing them of their right to refuse or withdraw at any time, and about the confidentiality of any obtained information. Anonymity was assured through coding of all data. Participants with unilateral planter wart were randomly assigned into two groups (group A and group B) by a blinded and an independent research assistant who opened sealed envelopes that contained a computer-generated randomization card.

Interventions

The treatment was conducted in the from the Railway Hospital (in Cairo, Egypt), physical therapy department by expert physical therapist. Patients randomly assigned for group A received Tretinoin 0.025 % gel Phonophoresis (using Sonopuls® 434 made in Holland) for teen minutes with $3W/cm^2$ intensity and 1 MHz frequency, after soaking the affected foot in water with added alcohol for softening and easy remove of overlying callus tissue. The affected area was again cleaned with a cotton soaked with alcohol. The ultrasound device was then being set at the desired settings. The

Tretinoin gel was applied on the wart, the ultrasonic head was then placed over the wart and moved in a circular motion three days per week (day after day) for four weeks. Patients randomly assigned for group B received topical application of Tretinoin 0.025% gel after cleaning the wart area with cotton soaked with alcohol three days per week (day after day) for four weeks.

Outcome Measures

Wart diameter were measure by diameter caliper while the patients assumed sitting position with the affected foot exposed, each wart was cleaned with alcohol. The wart's edge was determined by using fine tapped marker. The measuring caliper measured the wart's diameter in centimeters. The measurements were conducted by the same physical therapist 3 times to ensure inter rater reliability, before the first session, after the 6th session and after the 12th session. First measurement (Pre): before the first session of treatment. Second measurement (Post 1): after the 6th session of treatment. Third measurement (post 2): after 12th session. The location and size (in centimeters) of the planter wart were recorded.

Sample size and Statistical analysis

To avoid a type II error, a preliminary power analysis [power ($1-\alpha$ error P) = 0.95, $\alpha = 0.05$, effect size = 1.63, with a two-tailed for a comparison of 2 independent groups] determined a sample size of 11 participants for each group in this study. This effect size was calculated according after a pilot study on 12 participants (6 in each group) considering warts diameter as a primary outcome. In this study, descriptive statistics were expressed as mean, standard deviation and rang for both groups of the study. Repeated measurement ANOVA has been utilized to compare and identify the changes that took place within subjects in each group of the study within different reading times of warts diameter. Bonferroni post hoc test to reveal the differences between the diameter of the warts at pre treatment, post 6th sessions of treatment, and post 12th sessions of treatment was conducted. Statistical Package for Social Sciences (SPSS) computer program (version 22 windows) was used for data analysis. The alpha level was set at 0.05. Analysis was conducted using an intent-to-treat approach.

Results

A total of 22 patients with unilateral planter wart were eligible for inclusion. They were randomized for study intervention (figure 1). All randomized patients completed the trial. There was no significant statistical difference between groups at baseline regarding age (table 1). Within group comparison (Table 1) showed that there was significant improvement of the wart diameter in both groups after 6 and 12 sessions in comparison to pre treatment measures. There was no significant difference between both groups in Diameter of the Warts at pre treatment values ($P>0.05$). While there was a significant difference between both groups (table 1) in Diameter of the Warts at post 6th sessions and post 12th sessions of treatment with $p<0.01$ with better results in group A. The results of Group A showed that, the percentage of improvement of the diameter of wart after the 6th session was 45.6%. While after the 12th session the percentage was 73.4%. The results of Group B after 6th session showed that, the percentage of improvement of the diameter was 18.08%. While after the 12th session the percentage of improvement was 28.7%.

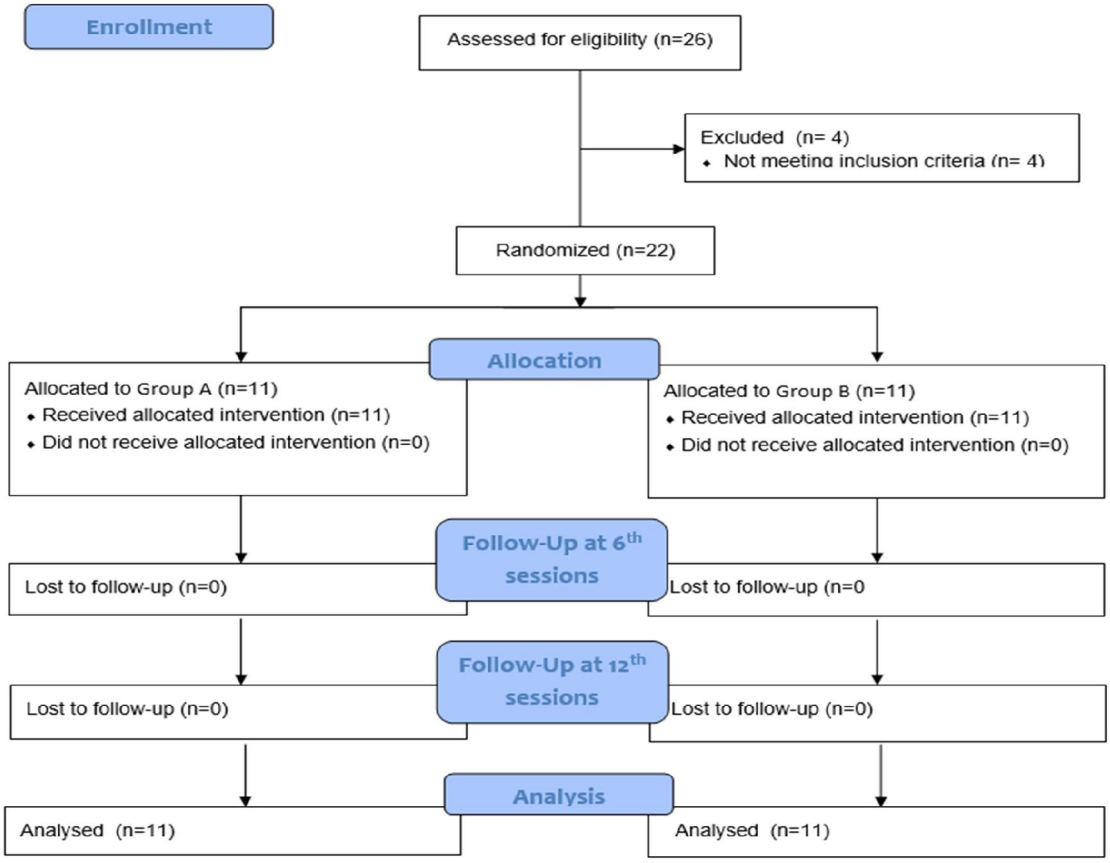

Fig. 1: Study flow chart.

Table 1: Age and wart diameter comparison within group and between groups

		Group A (n=11) Mean±SD (P-value)	Group B (n=11) Mean±SD (P-value)	Mean Difference	P-value
Age		30.186±3.94	30.09±4.59	0.09	0.961
Wart Diameter	Pre	0.79 ± 0.23	0.94 ± 0.34	0.145	0.255
	Post 1	0.43 ± 0.22	0.77 ± 0.29	0.345	0.005
	Post 2	0.21 ± 0.19	0.67 ± 0.25	0.464	0.0001
Within group Bonferroni post hoc test	Pre vs Post 1	(0.000)	(0.002)		
	Pre vs Post 2	(0.000)	(0.000)		
	Post 1 vs Post 2	(0.000)	(0.076)		

Discussion

This study was conducted to determine the efficacy of Tretinoin 0.025% gel Phonophoresis versus Topical Tretinoin 0.025% gel Application in the treatment of planter warts. Results found that there was a statistically significant difference between both groups with better improvement in the warts diameter in group A (Phonophoresis group).

The actual exposure to tretinoin that are topically applied is negligible, as only a small percentage - up to 6% - of topically applied tretinoin is absorbed into healthy skin (Menter, 2000). Low-frequency ultrasound (low-frequency sonophoresis) increases skin permeability, thereby facilitating delivery of macromolecules (A Tezel *et al.*, 2001). Sound waves may easily cause substances of large molecular sizes to penetrate the depth of 4 to 6 cm (Williams, 2003). Ultrasound exposure for 3–5 minutes with 1 MHz frequency and 1.5 W/cm2 intensity increased transdermal

permeation of mannitol and physostigmine across hairless rat skin in vivo by up to 15-fold with nearly-completely elimination of lag time typically associated with transdermal drug delivery (Levy *et al.*, 1989). So, significant reduction in the diameter of warts over the period of the study in Group A (Phonophoresis Group) compared to Group B (Topical Group) may be attributed to the application of the Phonophoresis as an enhancer for transdermal delivery of the Tretinoin 0.025% gel.

The exact mechanism is not known, drug absorption may involve a disruption of the stratum corneum (SC), lipids allowing the drug to pass through the skin (Baker *et al.*, 2001). Alvarez-Román *et al.* (2003), reported that lipid extraction also plays a role in low-frequency sonophoresis. They reported that about 30% of the stratum corneum lipids were removed during low-frequency sonophoresis. Mitragotri (2007) theorized and found supporting evidence that ultrasound caused cavitation in the lipid bilayer of keratinocytes, resulting in structural disorder and permeability. Ultrasound cause disruption of SC lipid bilayers by moderate level of disruption decreases the structural order of lipid bilayers and increases solute diffusion coefficient or higher level of disruption, lipid bilayers may loose structural integrity and facilitate penetration of the coupling medium. As a result, ultrasound, enhance penetration of low-molecular weight drugs (Mitragotri, 2001).

Conductivity enhancements with phonophoresis explained experimentally by observed spherical collapses or microjets near the surface of the stratum corneum. Bubble collapses by both types of cavitation events only close to the stratum corneum surface (∼50 μm) are contribute to sonophoresis (Ahmet Tezel and Mitragotri, 2003).

Another mechanism by which ultrasound improve penetration of drugs is its heating effects. The thermal effects of sonic energy are easily monitored through temperature measurements Temperature changes of approximately 5°C are necessary to cause measurable changes in cell membrane permeability. Also the higher ultrasound energy frequency lead to higher epidermal concentrate and so higher enhancements of drug delivery (Bommannan et al., 1992).

The current results are contradicted with unpublished work by Kamar *et al.* (2015) who study the effect of adapalene gel 0.1% (another retinoid) phonophoresis in treatment of plantar warts with no significant deference between the effecte of topical adapalene gel 0.1% and adapalene phonophoresis on the wart diameter. This difference may be due to the different retinoid used in our study.

The study results are limited to the exact parameters used, sample selection, psychological status of the patients and individual differences in the patients and their effects on the degree of treatment achievement, and the rate of recovery. However, further studies should be conducted with different parameters of the ultrasound device and check if it may lead to faster and better results without complications. Also, it is recommended to compare delivering different wart drugs iontophoretically and/or phonophoretically.

Conclusions

Finally, according to the previous discussion and the results of the present study, it could be suggested that, Tretinoin 0.025% gel Phonophoresis could be considered a valuable modality of the treatment of planter warts compared to Topical Application of Tretinoin 0.025% gel. Tretinoin 0.025% gel Phonophoresis can be considered as an effective, safe and non-invasive maneuver for treatment of planter warts.

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