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Promising New Wart Treatment: A Randomized, Placebo-Controlled, Clinical Trial

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Abstract

Background: Warts are common dermatological lesion caused by skin epithelial cells' infection with human Papillomavirus (HPV).
Objectives: This study aimed to assess the efficacy of a new method for the treatment of dermal warts.
Patients and Methods: In this clinical trial study, 60 patients (older than 10 years) with dermal warts living in Baneh city, west of Iran, were allocated into the intervention and control groups using the block randomized method in 2012. In the intervention group, outer layers of the dermal wart carved using scalpel and HD tablet set on it and covered with adhesive. In the second and third days, it was repeated again. All stages in the intervention group were similar to the placebo group. Placebo was prepared by a pharmacologist, which was similar to the HD tablet. In both groups, patients were examined one week and one month after taking the last tablet by the physician in terms of improvement or lack of improvement. Data were analyzed by SPSS software version 18 using chi-square test, Fisher's exact test, Mann-Whitney test and ANOVA for repeated measures.
Results: In the first week after the intervention, warts were changed in 93.3% of the cases; however, no changes were recorded in the control group. One month after follow-up, the mean was 0.4 ± 0.7 in the intervention group and 5.5 ± 4.9 in the control group ($P = 0.0001$). Based on ANOVA for repeated measures and t-test, the average number of warts, before, one week and one month after the intervention was statistically significant for both intervention ($P = 0.009$) and control groups ($P = 0.0001$).
Conclusions: This method is recommended for the treatment of dermal warts, owing to the effectiveness, short duration of treatment, and low cost of topical treatment for dermal warts using HD tablets.

Keywords: Warts, Estrogens, Papillomavirus Infections

1. Background

Warts are common dermatological lesions. They are solid lesions with skinny or gray - brown color and rough surface with a few millimeters of diameter that are single or multiple. They can join together and form plaque and regular, bold and rough surface shapes. They are usually painless; however, they are painful when they are cumulative or around the joints and nail or their surface are full of cleft (1). Previous studies showed that the prevalence rate of warts is different based on different age groups, population and periods of time. In two studies, the prevalence rate was 0.84% in the US and 12.9% in Russia (2, 3). In school children and young adults, the prevalence rate was 12% in the UK (4) and 24% in Australia (5).

Warts are caused by epithelial cells' infection with human papilloma virus (HPV) (6). Human papillomavirus is a small double-stranded DNA virus (55 - 50 millimicron), which can infect squamous epithelial cells and cause cell proliferation. The most common effect of HPV infection is to develop the warts. This tumor is created by pleomorphic viruses and can be created in different areas such as hand and feet skin, genitelia skin and mucous, larynx and the mouth mucosa. The virus infects the basal layer of the epithelium. Stem cells can also be infected. However, viral replication happened in places where keratinocytes have fully differentiated such as layer cells (spinosum and granulosum) (7). These viruses replicate inside of the cells since they do not have cover, they are resistant to drought, freezing and solvents (8).

Based on the anatomical distribution, warts are found on the face, hands, nail, foot and genitalia. Warts are contact and inoculated lesions and transmitted by an indirect contact with contaminated materials or walking barefoot. By aging resistance against HPV will develop. Warts are common in children and young adults and rare in the elderly. Some warts that are resistant to treatment and post-

treatment relapsed and became more widespread. Histologically, warts have the same changes such as acanthosis and hyperkeratosis. Common warts mainly be generated in children and usually on hands (1).

Previous studies have shown that therapeutic methods such as using salicylic acid, cryotherapy, hydroxychloroquine and zinc are effective on warts, but for cimetidine, levamisole or homeopathy consistent evidence was not found (9-12). Gibbs and Harvey in a review study for the topical treatment of warts concluded that only 12 of the 50 studies were of high quality (13). Also, several systematic therapeutic methods were used for warts; however, there are not sufficient evidence-based data on their effectiveness.

The local people of Baneh city in some areas have used contraceptives such as HD tablets for topical treatment of warts. The HD tablet is containing 50 mcg ethinylestradiol and 250 mcg levonorgestrel (or L-norgestrel or D-norgestrel). Estradiol is the most effective estrogen. Estrogens by binding to estrogen receptors in the cytoplasm increase the rates of DNA and RNA and other proteins' construction in target tissues. Levonorgestrel is a synthetic progestin (progestin). It has very strong progesteronic effects, weak androgenic effects and very weak mineralocorticoid effects. Levonorgestrel is the most widely used progestin in Iran and the world (14).

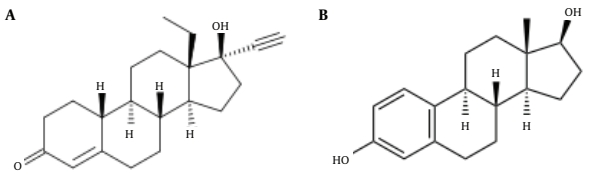

Figure 1. Skeletal Formulae of Levonorgestrel (A) and Estradiol (B)

Estrogen takes into account as mitosis and cell proliferation stimulating factor and in many cells prevents cell death. High dose of estrogen has caused regression of the hormone-dependent breast cancer in the postmenopausal age. In laboratory studies, it has been shown that the apoptotic effect of estrogen is an important factor in reducing the number of some of the cells (15). Regarding the above and experiences of local people in topical use of HD tablets to cure warts, this clinical trial study was designed and conducted to investigate the use of this drug for wart treatment scientifically.

2. Objectives

This study aimed to assess the efficacy of a new method for the treatment of dermal warts.

3. Patients and Methods

This clinical trial study was conducted on people (older than 10 years) living in Baneh city, west of Iran, who had warts on their skin in 2012. Inclusion criteria included persons who had not received any drugs for their wart treatment in the past two months. Exclusion criteria included pregnancy, oral contraceptive contraindications and cancer. A written informed consent was obtained from the subjects or their parents to participate in the study. This study was approved by the ethics committee of Kurdistan University of Medical Sciences (14/3755 Date 2011 JUL) and had been recorded in Iranian registry for clinical trials with registration number: IRCT138712171750N1.

The sample size was 60 patients, 30 people in the estrogen group and 30 in the placebo group. The participants were randomly divided into two groups using 4-block sampling. Photographs were taken from the warts of the intervention group using a digital camera then horny layer of the dermal wart carved using a scalpel and the HD tablet (LD norgestrel 0.5 mg and ethinylestradiol 0.05 mg) set on it and was covered with adhesive. In the second and third day it was repeated again. All stages in the intervention group were similar to the placebo group. Placebo was prepared by a pharmacologist and was similar to the HD tablet. Patients' wart status in both groups was examined one week and one month after taking the last tablet by the physician in terms of improvement or lack of improvement. Data were analyzed using SPSS software version 18, chi-square test, Fisher's exact test, Mann-Whitney test and ANOVA for repeated measures.

4. Results

Results of this study showed that there was no significant difference between the two groups in terms of gender and location of warts ($P > 0.05$). In terms of change in the first week after the intervention, results showed that in 93.3% of the patients of the intervention group the warts were changed, but the control group (placebo group) showed no changes. Also, in follow-up one month after the intervention, 73.3% of the warts in the intervention group were removed, whereas in the control group, warts were not removed ($P = 0.0001$).

Based on ANOVA for the repeated data, the mean number of warts before, one week and one month after the intervention in the intervention group were 6.0 $\pm$ 5.1, 1.9 $\pm$

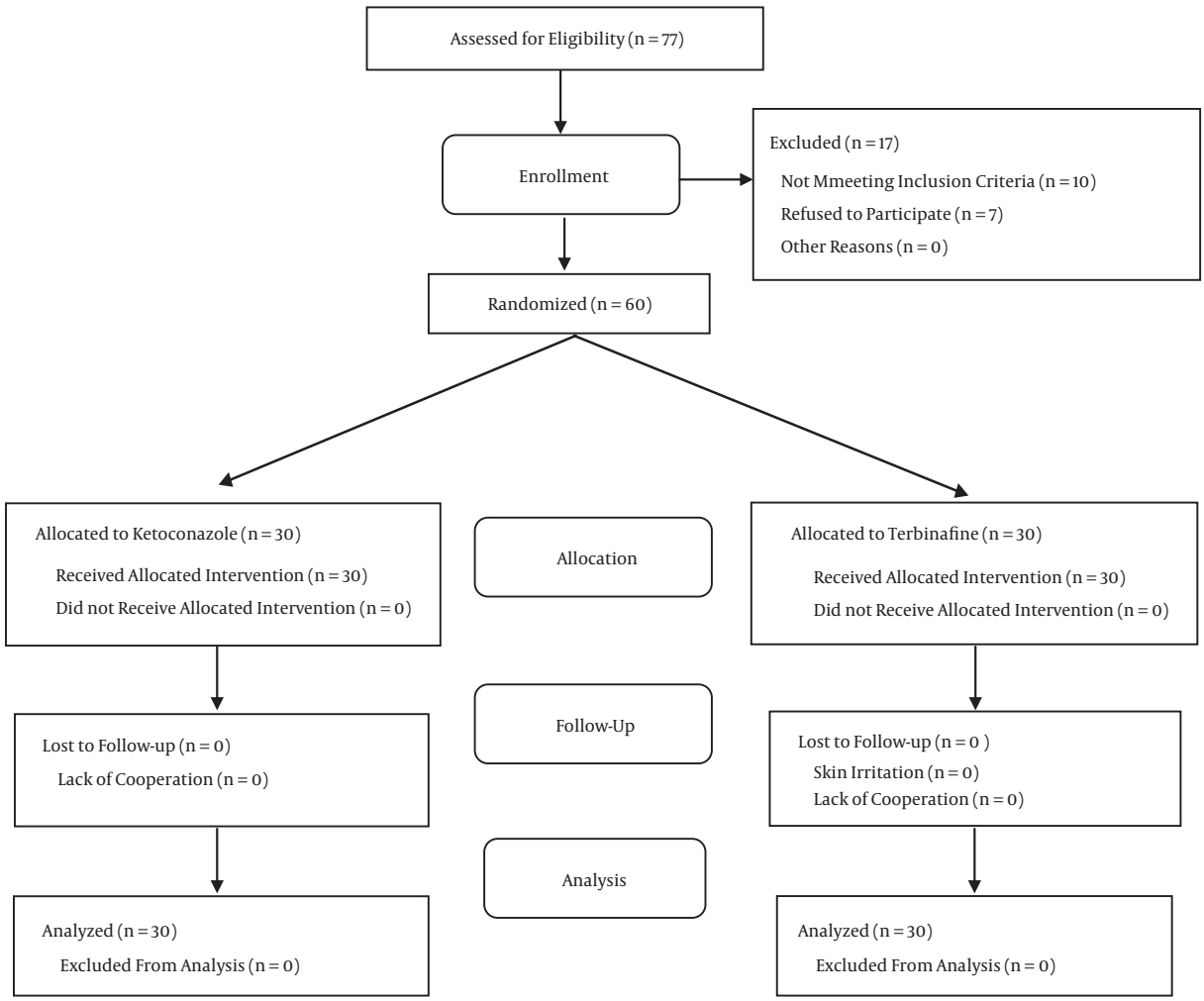

Figure 2. E-Flowchart

1.2, and 0.4 ± 0.7 and in the control group were 5.3 ± 5.1, 5.4 ± 5.0, and 5.5 ± 4.9, respectively (P = 0.009). Also, Based on t-test, the mean number of warts in one week and one month after the intervention in both groups were significantly different (P = 0.0001).

5. Discussion

The main goal of this study was to determine the therapeutic effect of topical application of HD tablets on dermal warts. In this regard, this method is important because none of the treatment methods used to remove dermal warts had been completely effective. Moreover, treatment of dermal warts has more complications, while with HD the treatment would be more cost-effective with less complications.

Our findings showed that in the first week after the intervention, in 93.3% of the patients in the intervention group, warts changed; however, there was no change in the warts' status in the control group. In the intervention group, 73.3% of warts were removed one month after the use of HD tablets, whereas in the control group no warts disappeared. In addition, in the intervention group, the mean number of warts in one week and one month after the treatment was reduced significantly compared to the placebo group. No side effects were observed in the participants of the study.

According to studies about the mechanism of the treatment effect on cell proliferation of breast cancer with estrogen therapy, it seems that in case of creating local concentrations of estrogen in the region, the cells undergo apoptosis. In this study, we observed that in the HD group,

Table 1. Frequency Distribution of Variables in the Intervention and Control Groups[a]

Variables	Intervention Group	Control Group	P Value
Gender			0.15
Male	6 (20.0)	11 (36.7)	
Female	24 (80.0)	19 (63.3)	
Age, y	13.6 ± 2.6	14.1 ± 2.7	
Place of warts			0.33
Hand	27 (90.0)	25 (83.3)	
Hand and face	1 (3.3)	4 (13.3)	
Hand and foot	2 (6.7)	1 (6.7)	
One week after treatment			0.0001
Changed	28 (93.3)	0	
Not changed	2 (6.7)	30 (100)	
One month after treatment			0.0001
Removed	22 (73.3)	0	
Not removed	8 (26.7)	30 (100)	

[a]The values are presented as No. (%) or mean ± SD.

Table 2. Comparison of the Mean Number of Warts in Both Groups

Stage	Intervention Group[a]	Control Group[a]	P Value
Before	6.0 ± 5.1 (4)	5.3 ± 5.1 (2)	0.43
After one week	1.9 ± 1.2 (1)	5.4 ± 5.0 (3)	0.002
After one month	0.4 ± 0.7 (0)	5.5 ± 4.9 (3)	0.0001

[a]The values are presented as mean ± SD (Median).

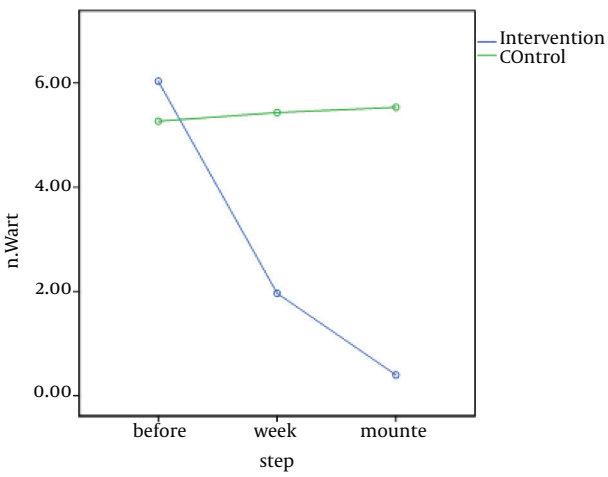

Figure 3. The Mean Number of Warts in Both Groups

by placing HD tablet on sore, some of wart surface tissues became necrotic and finally the entire wart became necrotic and removed without leaving scar; therefore, we can say that the skin warts have improved by a similar mechanism.

Limitations of this study include: lack of similar studies about the use of medications such as estrogen and progesterone in the treatment of skin diseases as well as problems of follow-up of the study subjects in the villages, also the less experienced researchers, and demographic data and patients' history of treatment duration were not fully recorded. Strength of this study is its novelty.

It is recommended that similar studies be conducted with controlled doses of estrogen. Owing the effectiveness of topical treatment of dermal warts using HD tablets, short duration of the treatment and low cost, this method is recommended for the treatment of dermal warts.

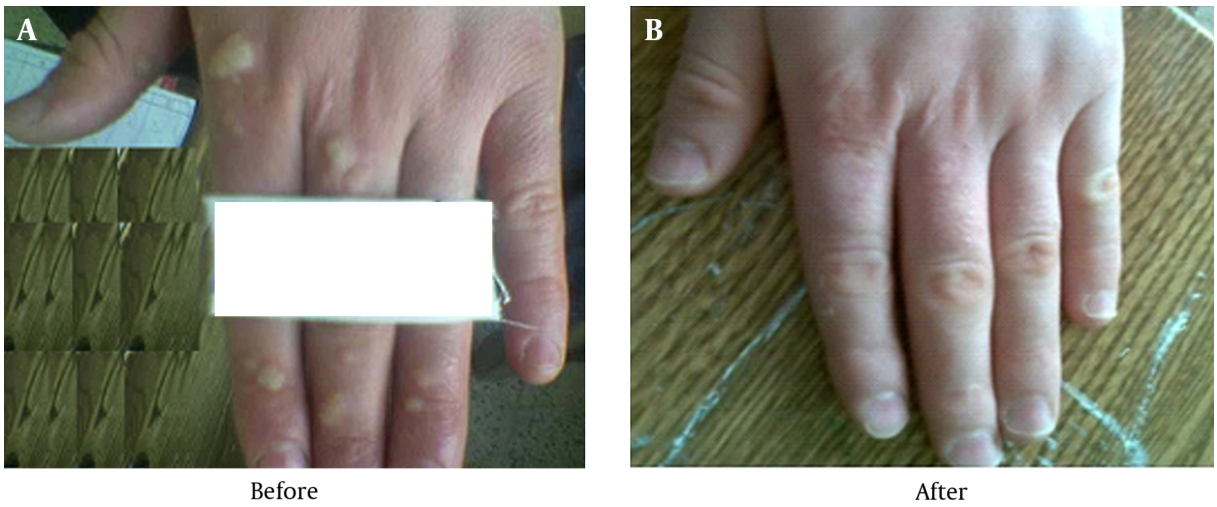

Figure 4. The Patient's Hand in the Intervention Group. A, Before; B, After

Acknowledgments

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Footnotes

Authors' Contribution: Study concept and design: Razyeh Ahmad Zadeh, Shokrollah Zandi; acquisition of data and design: Razyeh Ahmad Zadeh, Shokrollah Zandi; analysis and interpretation of data: Fardin Gharibi, drafting of the manuscript: Shokrollah Zandi; critical revision of the manuscript for important intellectual content: Sayedeh Reyhaneh Yousefi; statistical analysis: Fardin Gharibi, administrative, technical, and material support: Shokrollah Zandi; study supervision: Shokrollah Zandi.

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