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The efficacy of cryotherapy plus oral curcumin in the treatment of genital warts

Nasrin Saki, MD [1,2]
Seyedeh Yasamin Parvar, MD [1,3]
Saba Fazel, MD [3]
Fatemehsadat Pezeshkian, MD [3,4*]

1. Molecular Dermatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
2. Department of Dermatology, Shiraz University of Medical Sciences, Shiraz, Iran
3. Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
4. Burn and Wound Healing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

*Corresponding author:
Fatemehsadat Pezeshkian, MD
Division of Thoracic Surgery, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA
Email: fpezeshkian@bwh.harvard.edu
Yasaman.pezeshkian@yahoo.com

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Genital warts are epithelial tissues infected with human papillomaviruses, the most prevalent sexually transmitted disease worldwide. Topical treatments focus on removing warts rather than eliminating the virus. Curcumin, as a therapeutic option, has been shown to have antiviral activity in treating a variety of skin diseases, including vitiligo and psoriasis. The present study compared the effectiveness of cryotherapy plus oral curcumin to cryotherapy alone in treating genital warts. This randomized, double-blinded, placebo-controlled trial was performed on patients diagnosed with genital warts, who were divided into two groups. Patients underwent 5-7 sessions of cryotherapy plus oral curcumin or placebo. Outcome measures included the number of warts, the visual analog scale (VAS), and the Persian version of the Dermatology Life Quality Index (DLQI). The data were analyzed using SPSS software, version 21.

Twenty-seven patients with a mean age of 34.3 ± 10.3 years were included in each group. The median number of genital warts, DLQI, and VAS improved significantly in both groups. The effect of curcumin was more prominent in a short period, although it was not statistically significant compared to the placebo group. Using curcumin as an adjuvant drug in conjunction with cryotherapy was shown to be ineffective in treating genital warts. According to The Dermatology Life Quality Index, clinical improvement was observed; however, it was not statistically significant. Further studies should be carried out with higher doses of oral curcumin or topical vaginal creams containing curcumin to determine the role of curcumin in treating genital warts.

Keywords: genital warts, curcumin, HPV, cryotherapy, clinical trial

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INTRODUCTION

HPV-related genital warts have a global incidence of 10-20%, which continues to rise each day, and are considered the most common sexually transmitted disease worldwide [1,2]. Genital warts are presented in various shapes and numbers. They appear in asymmetric and polymorphic shapes, involving moist surfaces in the anogenital area [3]. Warts can induce skin irritation, pain, erythema, and discomfort in infected patients [1,4].

Specialists are still endeavoring to discover a definite cure for genital warts since the currently

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available treatment options primarily focus on removing the warty tissues rather than eliminating the virus [1,2]. Removal methods that are utilized are either topical solutions or creams such as Imiquimod and Podophyllotoxin, or procedures including cryotherapy, electrocautery, and lasers, which are more invasive but effective, especially when warts are large [2,5-7].

In preclinical studies, curcumin has been shown to have antiviral and antimicrobial properties. Its anti-inflammatory, antioxidant, and anti-apoptotic properties were proven to help prevent and manage various diseases, including rheumatoid arthritis, psoriasis, and vitiligo, with outstanding safety [8-10]. Overall, these properties rendered curcumin a viable treatment option for treating genital warts.

Surveying the published online data and reviewing curcumin's treatment potential prompted the need to find an alternative painless method for treating genital warts that reduces the number of sessions required as well as their adverse effects. This study compared the efficacy of cryotherapy plus oral curcumin to cryotherapy alone in treating genital warts.

METHODS

This randomized, double-blinded, placebo-controlled trial was conducted in the Dermatology clinic of Faghihi Hospital, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). This clinical trial was carried out according to the declaration of Helsinki and CONSORT guidelines. According to the study by Luk *et al.,* [11] the sample size was calculated as 24 patients in each group, with a 95% confidence interval, 80% power, and 1:1 allocation ratio. The inclusion criteria consisted of all patients who were new cases of HPV and were diagnosed with external genital warts, sized less than one millimeter, sexually active, and aged between 18-60 years.

The exclusion criteria included a history of any topical treatment for warts, having a systemic disease such as gallstone, liver and kidney failure, immunodeficiency, hypertension, diabetes, being pregnant or breast-feeding, receiving cardiovascular drugs, antidepressants, anticoagulants, chemotherapeutic agents, immunosuppressive drugs, and any drug that might affect wound healing, and patients with subclinical human papillomavirus.

After signing an informed consent form, patients were blindly assigned to either a placebo or curcumin using the blocking randomization method. All packs of curcumin and placebo were similar in appearance and had a unique code that was blinded to the patients. Sequestration of randomization was done using the sequence of opaque sealed envelopes technique. In this trial, a trained general physician performed 5-7 sessions of cryotherapy at one-week intervals for both groups [12]. Cryotherapy was performed by admitting liquid nitrogen to a temperature of -196 °C for two freeze-thaw cycles and spending 7-10 seconds for each wart. The cryogen spray, manufactured by the Sarmadaran Company in Iran, was the same for both groups.

The intervention group received a nano micelle containing 40 mg of oral curcumin daily (Minoo. Co., Iran). The placebo groups received daily pharmacology department-approved capsules in the same packs as curcumin. The participants took curcumin or placebo daily for two months since their first visit.

After every two cryotherapy sessions, or every two weeks, the outcome was evaluated by counting the number of warts visible on the genital area, using a visual analog scale (VAS, 0-10), and the Persian version of the Dermatology Life Quality Index (DLQI, 0-30).

The comparison between intervention and placebo groups was made using the Chi-square test. Mann Whitney U-test was also used to compare means between two groups based on the median number of lesions. The data were analyzed using the SPSS software version 21, and *P*-values less than 0.05 were considered statistically significant.

RESULTS

From December 2020 to May 2021, 54 participants (14 men and 40 women) entered the study and completed the treatment plan. The mean age of the participants was 34.3 ± 10.3 years old. To avoid selection bias, patients were assigned to each group using the simple randomization method, and both groups were adjusted according to age, sex, and wart severity. There were no significant differences between the two groups regarding the median number of genital warts during the study (Table 1).

The obtained results indicated that curcumin had a greater effect in a shorter period of time. The effect of genital warts on the patient's quality of life increased

Table 1. Median and interquartile range [IQR] of the number of genital warts, Dermatology Life Quality Index, and Visual Analog Scale at each visit

Follow up	Number of genital warts			Dermatology Life Quality Index			Visual Analog Scale		
	Placebo N = 27	Curcumin N = 27	*P*-value* (Between groups)	Placebo N = 27	Curcumin N = 27	*P*-value* (Between groups)	Placebo N = 27	Curcumin N = 27	*P*-value* (Between groups)
Baseline	12.0 (7.0-20.0)	13.0 (6.0-23.0)	0.862	0.0 (0.0-3.0)	0.0 (0.0-3.0)	0.593	5.0 (3.0-7.0)	4.0 (2.0-6.0)	0.183
One month later	3.0 (0.0-12.0)	3.0 (0.0-11.0)	0.664	-	-	-	8.0 (5.0-10.0)	7.0 (5.0-10.0)	0.652
Two months later	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.805	8.0 (6.0-10.0)	8.0 (7.0-10.0)	0.570	10.0 (9.0-10.0)	10.0 (8.0-10.0)	0.814

*Mann Whitney U-test; P value less than 0.05 was considered statistically significant.

significantly over time ($P < 0.001$). The Wilcoxon test showed that although there was no difference between the two groups in the case of median VAS scores, the patients' satisfaction increased significantly over time in both groups. Gastrointestinal problems were the only adverse effects, which was observed in one patient, who left the study during follow-ups.

DISCUSSION

In light of the available data and ongoing pharmaceutical processings, curcumin, a natural herbal antioxidant, had the potential to act as an anti-HPV agent by down-regulating HPV oncogene expression via various mechanisms [13]. Psomiadou *et al.* conducted a novel treatment on a woman with a vaginal cuff wart that did not improve despite applying imiquimod cream three times a week. She administered this regimen for two cycles of therapy, which resulted in the deterioration of her clinical condition accompanied by symptoms of medicament intolerance, such as burning and itchiness of the affected area. After two months of discontinuing the imiquimod regimen, a vaginal cream containing a mixture of curcumin, Indian grapefruit (AMLA), aloe vera, docosanol, lactic acid, and CM-β glucans was administered for six months. After three months, a significant lesion regression of the vaginal cuff wart was observed in the patient's clinical and colposcopy findings along with a negative pap smear test and colposcopy results. Even after two years of follow-up, this therapy was still beneficial with no reported side effects. This finding prompted us to evaluate this novel technique further in a clinical trial [14]. In the phase II randomized controlled trial, a polyherbal vaginal cream containing curcumin was topically used daily for 30 days, except during menstruation. Although an increase in the clearance of all types of HPV was observed, it was not statistically significant [15]. In the present study, we found that utilizing 40 mg of oral curcumin every day as an adjuvant drug alongside cryotherapy had the same result compared to those who had only undergone cryotherapy. Nevertheless, adjuvant use of curcumin was observed to induce a more prominent result in a shorter time. However, curcumin's efficacy in HPV eradication was dose-dependent. It could be used in high doses of up to 8000 mg per day for three months with no significant toxicity [16,17].

Furthermore, we assessed the quality of life before and after treatment. Remarkably, no statistically significant improvement was observed after treatment; however, their quality of life was improved clinically. Genital warts propose a cosmetic issue for infected patients and have the potential to impair emotional and sexual aspects of quality of life [18]. Another study investigated the effect of genital warts on the quality of life in late adolescence observed that sexual dysfunction and sexually related distress were prominently higher in the presence of genital warts than the general population, [19] which was consistent with the findings of the present study.

With regard to the present study, some limitations should be addressed. As this study was one of the first clinical trials to evaluate the effect of curcumin in managing genital warts, we confronted a lack of data (such as the number of partners and history) as well as sex equality (since women with genital warts outnumbered men). Moreover, as cryotherapy is one of the effective conventional methods of physically removing warts, its effect might mask the efficacy of curcumin. Finally, we only assessed the clinical progress in the first and last sessions and did not document the progress in the interim.

CONCLUSION

Using curcumin as an adjuvant medication along with cryotherapy appeared to be ineffective in treating genital warts. The quality of life was observed to improve clinically but was not statistically significant. Therefore, further studies should be carried out with a higher dose of oral curcumin or topical vaginal creams containing curcumin to evaluate the role of curcumin in treating genital warts. Moreover, curcumin's potential ability to reduce cervical cell cancer should be considered, and longitudinal studies are required to determine curcumin's role in cancer prevention over time.

Authors' Contributions

NS and SF designed the study and collected the data. SP carried out the statistical analysis. SP and FP drafted the manuscript. All authors read and approved the final version of the manuscript and have never been published or are under consideration for publication elsewhere.

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Funding Source

None.

Conflict of Interest: None declared.

Ethical standards

The Ethics Committee of Shiraz University of the Medical Sciences approved the present study (code: IR.SUMS.MED.REC.1398.334). This study was conducted in compliance with the Declaration of Helsinki. All the required information about the study, treatment, and adverse effects were given to the participants. Then, written informed consent was obtained from all the patients before being included in the study. Patients could leave the trial any time they desired. We confirm that all figures and tables are original and generated by the authors. We would also like to undertake that we have read the plagiarism policy and have submitted the article with complete responsibility.

Data availability statement

The present study and SPSS file findings are available on request from the corresponding author. They are not publicly available due to privacy and ethical restrictions.

REFERENCES

1. Leslie SW, Sajjad H, Kumar S. Genital warts. StatPearls [Internet]. 2021.
2. Yuan J, Ni G, Wang T, et al. Genital warts treatment: beyond imiquimod. Hum Vaccin Immunother. 2018;14(7):1815-9.
3. Salman S, SA Shehata M, Ibrahim AM, et al. Efficacy of retinoids alone or in combination with other remedies in the management of warts: a systematic review and network meta-analysis. Dermatol Ther. 2021;34(2):e14793.
4. Hunter Handsfield MDHH. Clinical presentation and natural course of anogenital warts. Am J Med. 1997;102(5, Supplement 1):16-20.
5. Solanki JS, Waghmare S, Gautam M, et al. Review of treatment modalities in the management of Genital Warts: review of treatment modalities in the management of Genital Warts. J Pakistan Assoc Dermatol. 2022;32(4):726-33.
6. Halim HM, Ahmed SFAE, Eyada MM. Effectiveness and

safety of topical application of diphenylcyclopropenone versus podophyllin in treatment of genital warts. Int J STD AIDS. 2023;34(9):641-8.

7. Iranmanesh B, Khalili M, Zartab H, et al. Laser therapy in cutaneous and genital warts: a review article. Dermatol Ther. 2021;34(1):e14671.
8. Patel SS, Acharya A, Ray RS, et al. Cellular and molecular mechanisms of curcumin in prevention and treatment of disease. Crit Rev Food Sci Nutr. 2020;60(6):887-939.
9. Salehi B, Stojanović-Radić Z, Matejić J, et al. The therapeutic potential of curcumin: a review of clinical trials. Eur J Med Chem. 2019;163:527-45.
10. Malathi S, Pavithra PS, Sridevi S, et al. Fabrication of nanopatterned PLGA films of curcumin and TPGS for skin cancer. Int J Pharm. 2020;578:119100.
11. Luk N, Tang WY, Tang NL, et al. Topical 5-fluorouracil has no additional benefit in treating common warts with cryotherapy: a single-centre, double-blind, randomized, placebo-controlled trial. Clin Exp Dermatol. 2006;31(3):394-7.
12. Jahic M. Cryotherapy of Genital Warts. Mater Sociomed. 2019;31(3):212-4.
13. Mishra A, Das BC. Curcumin as an anti-human papillomavirus and anti-cancer compound. Future Oncol. 2015;11(18):2487-90.
14. Psomiadou V, Iavazzo C, Douligeris A, et al. An alternative treatment for vaginal cuff wart: a case report. Acta Medica Cordoba. 2020;63(1):49-51.
15. Basu P, Dutta S, Begum R, et al. Clearance of cervical human papillomavirus infection by topical application of curcumin and curcumin containing polyherbal cream: a phase II randomized controlled study. Asian Pac J Cancer Prev. 2013;14(10):5753-9.
16. Bano N, Yadav M, Das BC. Differential inhibitory effects of curcumin between HPV+ ve and HPV–ve oral cancer stem cells. Front Oncol. 2018;8:412.
17. Hsieh C. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001;21(2895):e2900.
18. SEGEDI LM, BJELICA A. The quality of life of women with genital warts. Med Pregl. 2019;72.
19. Erol Koc EM, Akkaya H, Ozaksit MG, et al. The impact of genital warts on sexual function and sexuality-related distress in late adolescence. Int J Impot Res. 2022:34(8):790-4.