Efficacy of Autoinoculation in Treatment of Multiple Viral Warts - A Single Arm Study

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ABSTRACT

Objective: To test the effectiveness of autoinoculation of a wart in patients with multiple viral warts.
Study Design: An experimental study.
Place and Duration of Study: Department of Dermatology, Pak Emirates Military Hospital (PEMH), Rawalpindi, from February 2021 to February 2022.
Methodology: Patients above 12 years of age, having more than 5 warts were included. Those getting any other treatment for warts were excluded. The procedure was performed on a total of 70 patients with warts on 3 sites *i.e.* face/neck, palmoplantar and multiple sites. The outcome was categorised into cleared (no wart), partially cleared (reduced number of warts than baseline), and no response (same or increased number of warts than baseline).
Results: Out of 70 patients, 54 (77.1%) patients showed complete response, 6 (8.6%) showed partial response and 10 (14.3%) showed no response at all. Out of 54 patients who showed complete response, 36 (66.6%) were cleared after only one inoculation, fifteen (27.7%) were cleared after two inoculations, and 3 (5.5%) were cleared after three inoculations. The results were statistically significant with p-value <0.05.
Conclusion: Autoinoculation is a simple and minimally invasive procedure which proved to be very effective against all types of warts, with very promising results against palmoplantar warts.

Key Words: *Viral warts, Multiple viral warts, Autoinoculation, Delayed hypersensitivity, Human papilloma virus (HPV), Palmoplantar warts, Immunity.*

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INTRODUCTION

Viral warts are defined as hyperkeratotic papules or verrucous lesions of skin caused by human papilloma virus (HPV). They can involve any part of body including feet, hands, face, genitals or mucosae. There are around 180 types of HPV.[1] Warts on different sites of body are caused by different types of HPV. Depending on the site involved, viral warts can be divided into common warts (face, trunk, arms, legs *etc.*), plantar warts, periungual warts, genital warts and plane warts. Common warts are caused by HPV-2, plantar warts by HPV-1, HPV-2, HPV-4, genital warts are usually caused by HPV-6 & HPV -11, and plane warts by HPV-3 and HPV-10.[1]

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Treatment modalities in practice are locally destructive therapies which include salicylic acid, surgical curettage, chemical ablation, electrocautery, cryotherapy, hyper-thermic therapy, and various types of lasers. All these treatments are performed to destroy warts locally but there is no effect on the immunity against HPV in the host. Some oral medications have also been reported to be effective in the treatment of cutaneous warts *e.g.* H_2 receptor antagonists, zinc sulfate, and oral retinoids.[2,3]

Some topical treatment options are also available like topical 5-Fluorouracil (5-FU), retinoic acid, vitamin D analogues, topical imiquimod, and podophyllin.[4] Virucidal agents are also used which are glutaraldehyde, formaldehyde, formic acid, and antiviral drugs. Anti-mitotic and immunomodulatory agents are also an option. Intralesional injections of candida antigens and interferon alpha are also given.[5,6]

Cryotherapy (freezing) is the most common treatment currently used for viral warts. It is not very painful but can cause dark spots and also needs repetition. Electrosurgery (burning) and curettage (scraping off) are usually combined, which show good results but again treat locally and may require repetition. Chemical peeling is a procedure usually prescribed to treat refractory warts. Patients can apply certain chemicals at home

too. But this carries some risks such as faulty technique or poor compliance. Some dermatologists also suggest intralesional therapies like bleomycin or some other immunotherapeutic agents but these drugs have their own risks and side effects.[7]

Autoinoculation of warts is relatively a newer modality to treat multiple and recalcitrant warts. It is a minor, minimally invasive, and cost-effective procedure.[8,9] Inoculation of an excised wart can expose HPV antigen to the plasma, triggering a delayed hypersensitivity reaction, leading to the clearance of local, and distant lesions.[10,11] Exposure to viral antigens can lead to the development of cell-mediated immunity and virus-specific IgG and IgM antibodies may appear in the body.[12]

Keeping this theory in mind, the fact that the treatments available provide no complete cure, and less literature available on the effectiveness of autoinoculation. This study was conducted with a bigger sample as compared to previous ones, on the patients with warts on three different sites (face/neck, palmoplantar, and multiple sites). The objective of this study was to test the effectiveness of autoinoculation in multiple viral warts.

METHODOLOGY

An experimental single-arm study was conducted in the out-patient department of Pak Emirates Military Hospital over a period of 1 year (from February 2021 to February 2022). Ethical approval was obtained from ethical review committee (ERC no. A/28/EC/230/2021). The study was registered at ClinicalTrials.gov with the ID NCT04947332. Sample size was calculated using WHO calculator with the reference effectiveness of 67%[13] and absolute precision 12%. The calculated sample size was 59, we recruited 92 subjects, 22 were dropped during follow-up so data of 70 patients was analysed at the end of the study.

The inclusion criteria were patients older than 12 years and those having at least 5 or more warts. Children less than 12 years old and patients with less than 5 warts were excluded from the study, however, there was no upper limit for the maximum number of warts. Patients receiving any other treatment for warts currently or who have received any treatment in the last 4 weeks were excluded from the study. Written informed consent was obtained after explaining the procedure and possible outcomes to the patients. Baseline count of warts was recorded.

A feasible (easy to approach and excise) wart was selected as donor wart from any part of the body preferably extremities. The volar surface of forearm or medical surface of lower leg was selected as recipient site depending upon patient's preference. Both donor wart and recipient sites were cleaned with pyodine and local anaesthesia (2% lignocaine) was given. The selected wart was excised, cleaned, minced into very small fragments. A subcutaneous pocket was made on the recipient site (forearm or leg both can be used for any type of warts) and the minced wart was inoculated there. Then, the pocket was stitched with prolene sutures (3.0/4.0) and sterile dressing was applied. After the procedure, oral and topical antibiotics were advised for a period of 5 days. Each patient was followed up at 4, 8, and 12 weeks. Lesions were counted and compared with baseline count. Procedure was repeated after 4 weeks in patients with no or partial response, up to three inoculations.

Procedure was performed on patients with warts on 3 sites *i.e.* face/neck, palmoplantar, and multiple sites. The outcome was categorised into cleared (no wart), partially cleared (reduced number of warts than baseline), and no response (same or increased number of warts than baseline).

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 23.00. Chi-square test was applied between the two categorical variables *i.e.* site of warts and the clinical response and was applied between number of inoculations and the clinical response. The categorical variables were expressed as n (%). The value of $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 70 patients were included in the study. Out of these, 16 patients (22.9%) had warts on face/neck, 45 patients (64.3%) had palmoplantar warts, and 9 patients (12.9%) had warts on multiple sites. After procedure of autoinoculation, 54 (77.1%) patients showed complete response, 6 (8.6%) showed partial response, and 10 (14.3%) showed no response at all.

Forty-five patients had palmoplantar warts, out of these 39 (86.6%) were completely cleared, 3 (6.6%) were partially cleared, and 3 (6.6%) showed no response. Sixteen patients with warts on face/neck were inducted, out of these, 9 (56.2%) patients were completely cleared of warts, 1 (6.25%) was partially cleared and 6 (37.5%) showed no response. Nine patients had warts on multiple sites of body like face, genitals, and other areas. Out of these, 6 (66.6%) patients were completely cleared, 2 (22.2%) were partially cleared, and 1 (11.1%) showed no response as shown in Table I.

Out of 54 patients who showed complete response, 36 (66.6%) were cleared after only one inoculation. Fifteen (27.7%) were cleared after two inoculations, and 3 (5.5%) were cleared after three inoculations as shown in Table II.

Pictures of a fully recovered patient before and after treatment are shown in Figure 1a and Figure 1b.

Few mild and transient side effects were reported by some patients, which included itching, swelling, and recipient site infection. Out of the 60 patients who showed complete or partial clearance, itching was reported in 55 (91.6%) patients. Some patients complained of local inoculation site infection in 5 (7%) patients in spite of antibiotics, and transient swelling of all warts in 2 (2.8%) of patients.

DISCUSSION

Viral warts are common in every age group all over the world affecting 10% of the population.[14] Warts are also associated with immunosuppressive states. They spread by direct/indirect contact or trauma. Immune response of human body against HPV remains naturally low.

Table I: Site of warts and the clinical response cross-tabulation.

Site of warts	Clinical response			p-value
	Cleared	Partially cleared	No Response	
Face / Neck	9 (16.6%)	1 (16.6%)	6 (60%)	0.019*
Palmoplantar	39 (72.2%)	3 (50%)	3 (30%)	
Multiple	6 (11.1%)	2 (33.3%)	1 (10%)	
Total	54	6	10	

Chi-square test: p-value <0.05 is considered significant.

Table II: No. of inoculations and the clinical response cross-tabulation.

No. of Inoculations	Clinical response			p-value
	Cleared	Partially cleared	No response	
1	36 (66.6%)	2 (33.3%)	6 (60%)	
2	15 (27.7%)	1 (16.6%)	2 (20%)	0.022*
3	3 (5.5%)	3 (50%)	2 (20%)	
Total	54	6	10	

Chi-square test: p-value < 0.05 is considered significant.

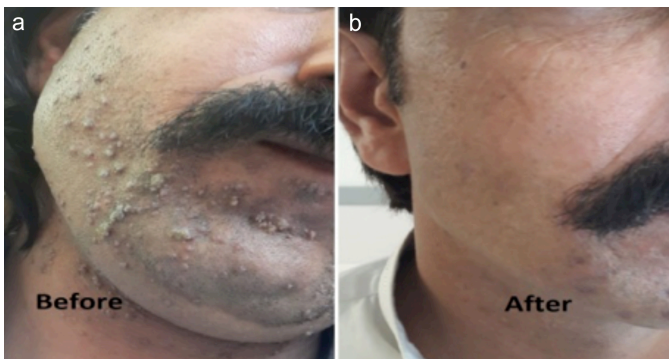

Figure 1: (a) Before the procedure of autoinoculation. (b) Complete clearance of warts after autoinoculation.

HPV also employs several mechanisms to reduce innate and cell-mediated immunity, thus causing host immune evasion and persistent infection.[15] They can cause itching, pain, and cosmetic concerns. Around 60% warts may regress spontaneously in 2 years but may recur, thus require treatment.[13] Malignant change in these lesions is rare but may progress to squamous cell carcinoma in immunocompromised patients and in organ transplant recipients.[16]

Common warts are usually present on the hands and flat warts on the face. Plantar warts appear on the soles of the feet, which look like calluses and may grow inward. They are painful and cause difficulty in walking. Genital warts occur as a result of sexually transmitted infections. They can appear on penis, vagina or vulva. Some warts are formed around (periungual) or under (subungual) the fingernail or toenail. Palmoplantar warts are the commonest ones.[17]

Viral warts although not life-threatening can pose cosmetic concerns, pain, itching, patient dissatisfaction, and can lead to recurrence, involvement of multiple sites, psychosocial issues, and rarely malignant changes.[18] Multiple treatment options are available including locally destructive therapies and virucidal agents like acyclovir (oral) and cidofovir (IV/intralesional), but complete cure is not obtained with them. Recently a new treatment modality has been introduced which is excision and then autoinoculation of a wart in subcutaneous tissue of forearm.

Few studies have been conducted to test the effectiveness of this procedure. A study conducted on 48 subjects in India showed that autoinoculation was more effective than placebo. Complete resolution occurred in 62.5% of cases.[10] In another study conducted in Egypt with sample size of 50, autoinoculation of warts was compared with intralesional injections of bleomycin, and 40% of patients showed complete clearance in whom autoinoculation was performed but according to authors the procedure was more effective in patients were having less than 12 warts.[19] Another study comprising of 15 subjects, was conducted recently and complete resolution was seen in 67% of patients after 12 weeks.[13] A similar study was conducted in Kolkata, India on 83 patients of viral warts. Out of these, 57 (69.5%) patients were completely cured after 3 inoculations.[20]

After autoinoculation in the present study, 54 (77.1%) patients showed complete clearance, 6 (8.6%) showed partial clearance, and 10 (14.3%) showed no response at all. Out of 54 patients who showed complete response, 36 (66.6%) were cleared after only one inoculation. 15 (27.7%) were cleared after two inoculations, and 3 (5.5%) were cleared after three inoculations. Rapid clearance of warts was observed mostly in young patients including soldiers, students, and athletes. No recurrence was reported till 3 months after complete clearance of warts.

The procedure of autoinoculation also happened to be cost-effective as compared to currently used treatment modalities. Since there is no recurrence of warts yet reported after the procedure there are less sessions required to completely cure warts.

Few complications of the procedure were reported, itching being most common. This could be the sign of development of immunity against HPV and delayed hypersensitivity reaction.[21]

Autoinoculation of wart can be recommended as first-line treatment for recurrent and recalcitrant palmoplantar warts, however, further studies are recommended for facial and genital warts with larger sample size. This procedure can also be compared with other treatment modalities which are

already in practice for viral warts. Further studies based on the serological response of the body against HPV can also be conducted.

Lack of control group is the limitation of this study. The autoinoculation is not compared with any other treatment option. The serological response of the patients is not measured in this study.

CONCLUSION

Autoinoculation is a simple and minimally invasive procedure which proved to be very effective against all types of warts, with very promising results against palmoplantar warts. This procedure can be used as first-line treatment for palmoplantar warts.

ETHICAL APPROVAL:
Ethical approval was obtained prior to initiation of the research work from the ethical review committee of PMEH, Rawalpindi. (ERC No. A/28/EC/230/2021).

PATIENTS' CONSENT:
Written informed consent was obtained from patients to participate in the study and to publish the data concerning this case.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
MWS: Concept, design, acquisition, and data collection.
NI: Concept, acquisition, and review.
MI: Drafting, data analysis, and intellectual content.
AA: Data analysis.
JH: Intellectual content.
UAA: Data collection.
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