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Relative Efficacy and Safety of Homologous Autoimplantation in Multiple and Recalcitrant Verrucae Vulgaris

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Abstract

Background: Warts are benign tumors involving skin and mucous membrane that are caused by human papillomavirus (HPV). Several treatment modalities are available for treating multiple warts, but without any significant response or cost-effectiveness. **Aims:** This study aimed to evaluate the safety and efficacy of autoimplantation therapy in the treatment of recalcitrant and multiple warts. **Methods**: A total of 40 patients of multiple warts (more than five warts per patient), palmoplantar warts, recurrent warts, and resistant warts were enrolled in this study. A small piece of warty tissue was introduced in the wound with the help of 26 no. needle. Patients were assessed monthly and resolution after 3 months was considered complete clearance. **Results:** Out of 40 patients, 26 (65%) patients showed complete clearance at the end of follow up. 10 (25%) patients had grade 2 improvement, 2 (5%) had grade 3 improvement. **Conclusions:** Autoimplantation of wart using the pared stratum corneum of wart is a safe, efficacious, less painful, and in-office procedure for the treatment of multiple, recurrent, and palmoplantar warts.

Keywords:- Autoimplantation, Recalcitrant, Warts.

INTRODUCTION

Warts are the infectious proliferation of skin and mucous membranes, benign in nature, caused by DNA virus, Human Papilloma Virus (HPV) belonging to papillomaviridae. It can affect any age group or sex. Infection is acquired most frequently from the abrasive skin where viral proteins remain latent for months. In viral infections, most frequently there is stimulation of production of cytotoxic T cells following destruction of cell membrane by viral proteins, which then destroy infected cells. However, in HPV, there is no cell lysis hence no release of viral proteins thence no antigen presentation. This is reason of chronicity and recurrence of warts.[1]

Warts cause physical as well as psychological distress in patients. Although spontaneous resolution has been reported but destructive modalities like use of salicylic acid, trichloroacetic acid, cryotherapy, laser ablation, electrocautery and radio frequency have been the mainstay of treatment for years but these are painful, with high chances of secondary

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infection, scarring, high recurrence rate along with inability to treat multiple warts.[2]

To overcome these shortcomings, an effort to stimulate immune system against the pathogen via immunotherapy was tried with the help of various agents such as zinc sulfate, imiquimod, intralesional candida antigen, BCG vaccine, MMR vaccine, PPD, Vitamin D. These act via mounting delayed type hypersensitivity response and hence production of Th1 cytokines which in turn activate cytotoxic and Natural Killer cells and thence eliminate infection. These have the added benefit of clearing distant warts along with local lesions.

Autoimplantation is a novel, one- time procedure in which warts are treated by stimulating immune response against HPV. We have here evaluated the safety and efficacy of autoimplantation therapy in the treatment of recalcitrant and multiple warts.

MATERIAL AND METHODS

This study was conducted in outpatient department of tertiary care hospital. A total of 40 patients of multiple warts (more than five warts per patient) who fulfilled the following criteria were enrolled in the study.

Inclusion Criteria:

- Patients of both sexes between the ages 15-50 years.
- Patients having multiple verruca vulgaris (>5 warts).
- Duration of warts of 3 months or more or recalcitrant warts.

Exclusion criteria:

- Patients not willing to undergo the procedure.
- Patients of age <15 years and >50 years.
- Patients with warts other than verruca vulgaris.
- Immunocompromised patients, patients with tuberculosis, cutaneous malignancies, seropositive for HIV, hepatitis B, hepatitis C and diabetes.
- Pregnant or lactating women.
- Patient with history of intake of immunomodulatory drugs.
- Patients with acute febrile illness
- Patients with history of convulsions, meningitis, asthma, allergic skin disorders and coagulopathies.
- Patients who have received any other treatment of warts in the last 1 month.

Aims and Objectives

- To evaluate efficacy and safety of homologous autoimplantation in treatment of multiple and recalcitrant verruca vulgaris.
- To evaluate the adverse effects associated with the therapy used.

A pre-informed written consent was taken and recorded. Detailed clinical history followed by general physical examination were recorded on prescribed proforma. Relevant investigations including Hb, TLC, DLC, fasting blood sugar, complete urine examination, VDRL, ELISA for HIV 1 and HIV 2, HBsAg, Anti HCV Ab were done.

Procedure

Donor tissue for autograft was harvested by paring a selected, well developed verrucous lesion. The lesion to be pared was cleaned with povidone iodine to achieve asepsis. Paring was done using a sterile surgical blade no. 11 and a raised warty tissue of size 5 mm was taken. The tissue was then transferred on a sterile surgical swab. Autografting was done on

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upper anteromedial thigh. The site for engraftment was cleaned with povidine iodine, and was infiltrated with 0.5 ml of lignocaine. A subcutis deep stab incision of 3 mm was made using a different surgical blade no. 11, in accordance with resting skin tension lines. Using to and fro motion with 20G needle, a subcutaneous pocket was created. The pared tissue was cleaned with normal saline and introduced deep into subcutis, gently with the help of same 20G needle. The margins of wound were approximated with pressure and closed with the help of a micropore plaster. The patients were advised not to wet or remove plaster for 5 days. Systemic antibiotics were given for 5 days (tab amoxycillin 500 mg + clavulinic acid 125mg BD) and oral analgesics if required. Follow up was done at 4 weeks and subsequently every 4 weekly up to a period of 12 weeks.

Grades of Improvement

Assessment was made on the basis of:
Number and size of lesions
Clearing up of old lesions
Development of new lesions
Grading was done as:
Grade 0 = development of any new lesion or no response
Grade 1= <25% response in old lesions
Grade 2= 25-50% response in old lesions
Grade 3= 51-75% response in old lesions
Grade 4=>75% response in old lesions
The data thus obtained was compiled and was analyzed statistically.

RESULTS

Out of 40 patients, 31 (77.5%) were males and 9 (22.5%) were females. Male: Female= 3.4:1. Maximum number of patients i.e. 20 (50%) were in age group of 21-30 yearsfollowed by 15 (37.5%) patients in age group of 11-20 years of age. The unmarried patients were more in number than married counterparts in both the groups. Unmarried: Married= 2.6:1. The preponderance of unmarried patients may be due to the fact that unmarried people are more conscious about their appearance. The patients with urban background outnumbered those in the rural background with urban: rural ratio of 2.0:1. This can be due to more awareness about the disease and more accessibility to the hospital by the urban population in the community. It may also be due to the reluctancy on the part of the villagers to come to hospital for ailments which according to them is too trivial. Further, urban population is more conscious of their appearance as compared to rural population and hence more prone to seek medical advice for disease.

Table 1: Comparison Of Improvement Of Warts After 4th, 8th& 12th Weeks Of Follow Up (Wilcoxon Signed Ranks Test)

WSR test comparative times group	Negative Ranks	Positive Ranks	Tie	Z Value	P Value	Significance
Grading of Improvement at 2nd visit - Grading of Improvement at 1st visit	0	32	8	-3.601	.000	Highly Significant
Grading of Improvement at 3rd visit - Grading of Improvement at 1st visit	0	40	0	-3.999	.000	Highly Significant
Grading of Improvement at 3rd visit - Grading of Improvement at 2nd visit	0	26	14	-3.286	.001	Highly Significant

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Table 2: Complications In Patients Following Autoimplantation

Complications	**No. of patients**	**%age**
Infection at site of implantation	2	5.00
Post inflammatory hypopigmentation at the site of lesions	8	20.00
Pain during injection	0	0.00
Flu like symptoms	0	0.00
Nil	30	75.00

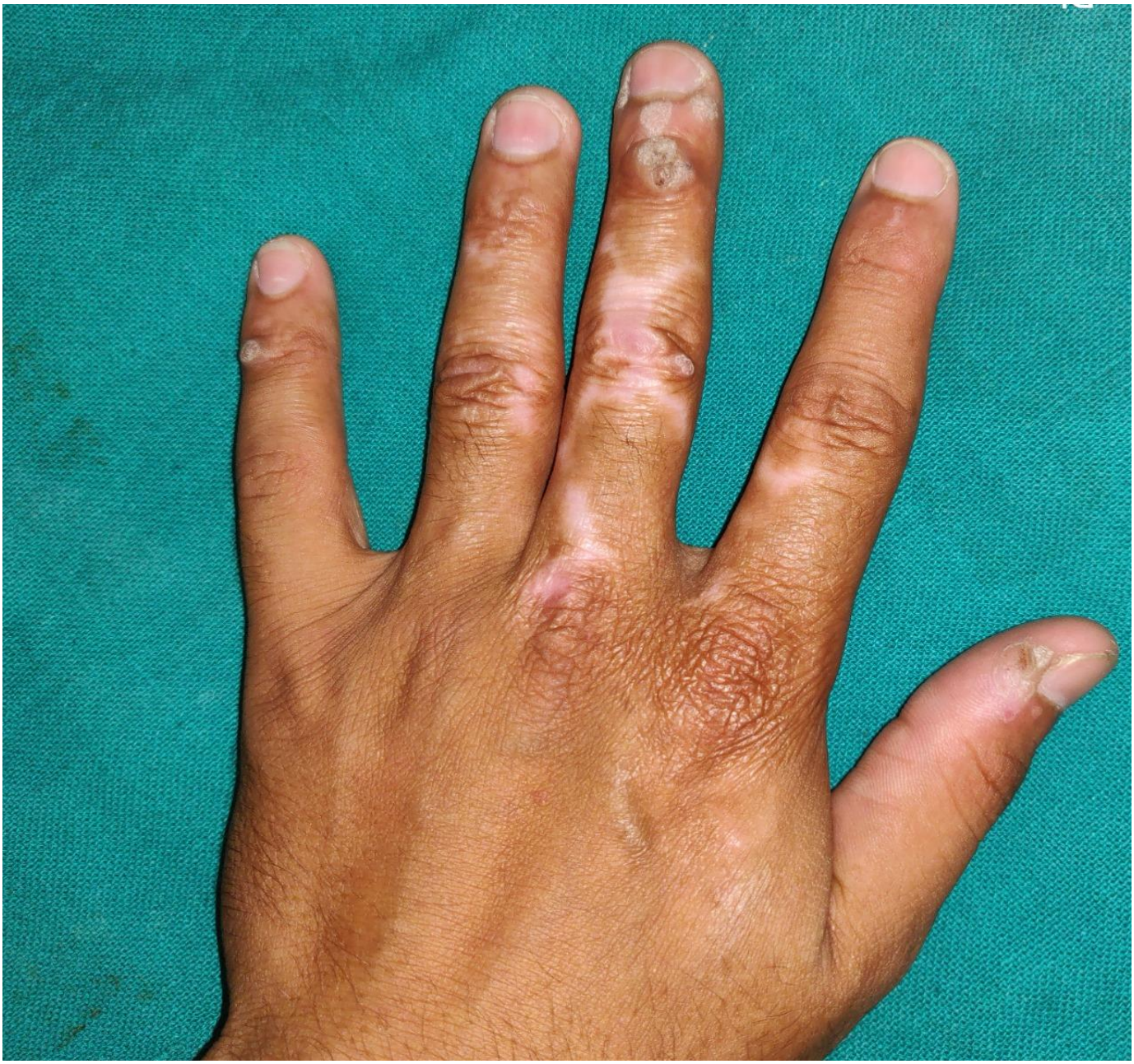

Figure 1: Grade 4 improvement seen in a patient (a) Baseline (b) at 12 weeks

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The duration of disease was variable ranging from 6 months to 36 months but majority of the patients, 27 (67.5%) had duration in range of 0-12 months. Majority of the patients i.e.19 (47.5%) had number of lesions in the range of 0-10 followed by in the range of 11-20 lesions in 13 (32.5%) patients. Majority of the patients 25 (62.5%) had the largest wart of size 0-1.0 cm. Size of the warts was variable ranging from 0.4cm – 2cm. The hands and forearms (dorsal aspect) were most common site involved in both the groups. Majority of the patients were having involvement of the hands only.

On first follow up at 4 weeks, 34 (85%) patients had grade 1 improvement, 2 (5%) patient had grade 2 improvement, none of the patients had grade 3 or grade 4 improvement. Rather 4 (10%) patients developed new lesions having grade 0 improvement.

The number of patients with grade 1 improvement decreased to 10 (25%) while number of patients increased in higher grades of improvement i.e. 16 (40%) patients had grade 2, 10 (25%) patients had grade 3 and 4 (10%) had grade 4 improvement on second follow up at 8 weeks. No patient had developed new lesions.

On third follow up, at 12 weeks [Figure 1], 2 (5%) patient had grade 1 improvement, 10 (25%) patients had grade 2 improvement, 2 (5%) had grade 3 improvement. The number of patients with grade 4 improvement increased to 26 (65%) patients. No patient had developed new lesions. Improvement in Group A had started from 4th week onwards and was statistically significant. [Table 1]

2 (5%) patient developed infection at the site of implantation, 8 (20%) patient developed post inflammatory hypopigmentation at the site of lesions. Rest of the patient did not show any complication. [Table 2]

DISCUSSION

Autoimplantation is a relatively new technique in dermatology. The technique has been previously used for various diseases using tissues like parathyroid, thyroid, spleen and hematopoietic stem cells. Autovaccination was first described by 3. A treatment option for verruca plantaris.[3]

Similar observations to our study were also reported in different studies by Shivakumar et al (66.67% males), Swaroop et al (72.5% males). Similarly, Lal et al reported mean age of patients as 24.29 years in his study. Shivakumar et al reported that 71.7% of his patients were in the age group of 21-30 years which is in concordance with our study. Swaroop et al also reported the age range of 24-28 years having maximum number of patients.[4,5,6,7,8,9]

Shivakumar et al (2009) conducted an open, non randomized study on 60 patients of multiple warts using autoimplantation therapy. Clinical resolution was seen in 28 patients of verruca vulgaris (70%) and 16 of palmo-plantar warts (80%) within 3 months, accounting for a total clearance rate of 73.3%. It was also observed that majority of the responders (91%) showed resolution of warts within 2 months.[4]

Srivastava et al (2010) conducted a similar study using autowart injection therapy on

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patients with extensive and recalcitrant warts. Out of the 53 patients, 35 patients (66.03%) had complete disappearance of warts, 12 patients (22.64%) had partial improvement and 6 patients (11.32%) did not improve at all.[5]

Nischal et al (2012) used modified technique of autoimplantation by using pared wart tissue (stratum corneum) in 35 patients with multiple, recurrent and palmoplantar warts. Out of this, 27 patients followed up and 20 (74.1%) patients had complete resolution of the warts within 3 months, 1 (3.7%) patient had partial clearance and 5 (18.5%) patients had no improvement. Relapse was seen in 1 (3.7%) patient and no apparent side effects were observed.[6]

Lal et al (2014) a double blind, randomized placebo controlled study in 48 patients to study the effectiveness and safety of autoinoculation in cutaneous warts. Patients were randomly divided into two groups. Full-thickness warty tissue was excised, minced and implanted in a small dermal pocket in the treatment group while warty tissue was only excised but not implanted in the control group, though a dermal pocket was created. The procedure was repeated twice at 4 and 8 weeks and patients were followed up for 12 weeks. Complete resolution was seen in 62.5% in autoinoculation group. Reduction in the number of warts was significantly more in the autoinoculation group than in the control group (P = 0.010) at 8 weeks. Minor adverse effects were noted in 11 (22.9%) of patients. They concluded two sessions of autoinoculation to be an effective therapeutic modality for cutaneous warts.[7]

Gugle et al (2015) studied homologous autoimplantation in 49 patients of warts. They concluded that 49% (24) patients had good response, 28.6% (14) had moderate response, 10.2% (5) had poor response, while 12.2% (6) patients didn't respond at all. 34.69% patients showed clearance. They also observed it to be an easy, minimally invasive and effective treatment option, for multiple, recurrent and recalcitrant warts.[8]

Swaroop et al. (2016) enrolled 40 patients of multiple recurrent cutaneous warts in a prospective open labelled study. Modified technique of homologous autoimplantation was used by paring the wart and implanting it into subcutis. 75% (28) patients showed complete clearance, while 22.5% (9) patients had partial clearance at the end of 3 months follow up. The modality was shown to be effective for multiple, recurrent and recalcitrant warts.[9]

Khatu et al (2017) enrolled 40 patients of multiple warts (more than five warts per patient), palmoplantar warts, recurrent warts, and resistant warts were enrolled in this study. 21 patients of verruca vulgaris (75%) and 10 patients of palmoplantar warts (83.3%) showed resolution within 3 months, accounting for a total clearance rate of 77.5%.[10]

Repeated exposures to viral antigens showed the development of cell- mediated immunity and appearance of virus- specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies.[11,12]

Gulanikar et al (2018) enrolled twenty- five consecutive patients who presented with recalcitrant warts. They were followed up for a period of 1 year and evaluated for clearance of lesions. There was complete clearance in 22

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patients, 3 patients failed to show any clinical improvement.[13]

Sugandhy (2019) enrolled hundred patients with multiple warts (≥ 5), were randomly selected and divided into two equal groups. One group was treated with cryotherapy with liquid nitrogen and the other with homologous autoimplantation. They were followed up for six months and the time taken for clearance of the lesions, compared. Homologous autoimplantation gave a higher cure rate (78%) than cryotherapy (56%).[14,15,16]

Dhanalakshmi Kasi et al(2019) enrolled 50 clinically diagnosed patients of extensive verruca vulgaris. Homologous auto-implantation was done over the uninvolved flexor aspect of the forearm skin after harvesting wart tissue up to the level of the papillary dermis. Patients were assessed monthly and resolution after 3 months was considered as complete clearance. Out of 50 patients, 41 patients came for regular follow up whereas 9 patients didn't turn up for the follow-up. Out of 41 verrucavulgaris patients, 34 showed resolution within 3 months, accounting for a total clearance rate of 82.9%.[17]

Taneja et al (2020) enrolled patients with verruca vulgaris (n = 13), palmoplantar (n = 4), periungual (n = 5) were included in the study. The warty tissue was excised, minced and homogenous tissue implanted in a small dermal pocket in the left forearm. Patients were evaluated every 4 weeks. The procedure was repeated at 4th and 8th week. Response was assessed at each visit and at 12th week. Fifteen cases were recruited. Majority of the patients were diagnosed with verruca vulgaris (87%, n = 13) followed by periungual warts (33%, n = 5) and palmoplantar warts (27%, n = 4). Recurrent warts were present in 73% (n = 11) patients. Average improvement at the end of 12 weeks was seen in 65% cases. Ten (67%) patients showed complete resolution of warts. In two patients, warts increased in number while on treatment. Local site infection was seen in two patients.[18]

Our results were inferior as compared to previous studies by Swaroop et al (with 75% clearance),[9] Nischal et al (with 74% clearance) It may be due to longer follow up in these patients. 81 In our study, partial improvement was seen in 35% of the patients, which is superior to the Srivastava et al,[5] and Swaroop et al,[9] who reported partial clearance rate of 22.64% and 22.5% respectively. Nischal et al,[6] and Shrivastava et al,[5] observed no improvement in 18.5% & 11.32% patients respectively. In our study, however there was no patient who did not respond to this modality of treatment.

CONCLUSIONS

The homologous autoimplantation of warts is a novel immunotherapeutic method for treatment of warts. It is an economical, single sitting procedure with high cosmetic acceptability and minimum downtime as compared to destructive procedures. It can be performed on an outpatient basis without sophisticated equipments and also in patients with multiple warts. No major side effects are seen. However appropriate aseptic conditions have to be maintained as we have to give a surgical incision for implanting the pared tissue. So the chances of infection at the site of implantation are still there. The bandaid plaster have to be kept in place after the procedure. The local anaesthesia used in the

procedure can cause adverse drug reaction if hypersensitivity test is not performed prior to the procedure.

The limitations of our study were that the sample size was small. The control group with placebo to assess spontaneous resolution was not taken. The patients with complete response were not graded separately. Only verruca vulgaris patients were included in the study and other types of warts were excluded from the study. Due to time constraints the follow up period was of 12 weeks but resolution or improvement in grading can occur even after 12 weeks. HPV serotyping, relevant Th1 cytokine profile and antibody titers were not done in our study.

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