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ORIGINAL RESEARCH

An Open Label, Prospective, Non-Randomized And Interventional Clinical Study To Evaluate The Efficacy And Safety Of An Autoimplantation Therapy In The Treatment Of Multiple And Recurrent Warts

[1]Dr. Savita Arya, [2]Dr. Bajrang Soni, [3]Dr. Veerbhan Singh

[1]Associate Professor, Department of Skin & VD, SJP Medical College, Bharatpur, Rajasthan, India
[2]Associate Professor, Department of Skin & VD,PDU Medical College, Churu, Rajasthan, India
[3]Associate Professor, Department of Community Medicine, SJP Medical College , Bharatpur, Rajasthan, India

Corresponding Author
Dr. Veerbhan Singh
Associate Professor, Department of Community Medicine, SJP Medical College , Bharatpur, Rajasthan, India
(drmotilalbunkar@gmail.com)

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Abstract

Background: Warts are benign tumours that commonly involve the skin and other epithelial tissues, caused by human papilloma virus infection.[1] A number of therapeutic options for wart are available but there is still a need for a treatment that is promptly effective.

Aims and Objectives: To evaluate the efficacy and safety of an autoimplantation therapy in the treatment of multiple and recurrent warts.

Material and method: The study was an open label, prospective, non-randomized and interventional clinical trial carried out in 128 patients with multiple and recurrent warts. All consecutive treatment-naive patients of both sex and age ranges from 10-55 years with more than five clinically diagnosed cutaneous warts attending the dermatology outpatient department were included. Under local anesthesia and strict aseptic precautions, paired stratum corneum wart tissue was removed and cut in small pieces was gently introduced into the subcutaneous pocket with the same needle on the flexor aspect of non dominant forearm around 2 inches below antecubital crease.

Results: Out of 128 patients, 100 were available for follow-up. Patient showing complete resolution of warts within 3 months were considered as responders. A total of 71 patients showed resolution within 3 months accounting for a total clearance rate of 71%. The earliest response was achieved at the end of 4th week. The filliform subtype had no response with the auto-implantation while mosaic type had 100 % clearance and other sub variants (including palmer, planter and plane) had more than 70% clearance rate. There was no life threatening side effects following auto-implantation.

Conclusion: Our preliminary experience with homologous implantation of wart suggests that this is an inexpensive, safe and probably an effective option against HPV.

Keywords: Autoimplantation, multiple, recurrent warts, delayed hypersensitivity.

Introduction

Warts are benign tumors, caused by human papilloma virus (HPV) infections that commonly involve the skin and other epithelial tissues. Warts present over the skin mimic different morphological forms, depending upon HPV type, body site, immunological status of the patient and environmental influences.[2] Cutaneous warts can occur at any age with varying incubation periods ranges a few weeks to years. Transmission occurs by direct or indirect contact and it can grow anywhere on the body, but most common site are the hands and feet. Although few warts regress spontaneously, but mostly require treatment. Their management is also difficult

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because of resistance to standard therapy or their recurrence nature. The potential for spread to contiguous sites and to contacts along with disfigurement and psychosocial effects result in considerable morbidity and a constant demand for a cure. Although several treatment modalities are available but still the definitive treatment of warts is lacking.

The available treatment options are cryotherapy, lasers, intralesional bleomycin and 5% imiquimod. Some sorts of systemic retinoids, photodynamic therapy and topical sensitizers such as dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE) and diphencyprone (DCP) reported to be effective but no single treatment that is 100% effective. In multiple warts, especially on palms and soles, destructive procedures in the form of cryotherapy and laser are inappropriate and impractical. The immunotherapy (autologous vaccine and Candida antigen) is a promising option in cases of multiple warts and warts at inaccessible sites. However Immunotherapy, cryotherapy and laser are costly modalities in Indian scenario. Furthermore; DCP and SABDE can cause allergic contact dermatitis, urticarial lesions and pigmentary disturbances, while autologous vaccines may have oncogenic potential.

Homologous Auto-implantation is a simple, cheap and easily performed outdoor based technique, with minimal morbidity and no mortality. Although, data regarding the auto implantation study are sparse in Indian population so this study was explored out to know the efficacy and safety of homologous auto implantation in treatment of multiple warts.

Material and method

The study was an open label, prospective, non-randomized and interventional clinical trial carried out in 128 patients from January 2014 to June 2015 at the department of dermatology, venereology and Leprology of government medical college and attached group of hospital, Kota, Rajasthan, India. The clearance from the institutional ethics committee was obtained before starting the study. All consecutive treatment-naive patients of both sex and age ranges from 10-55 years with more than five clinically diagnosed cutaneous warts (except genital wart) attending the dermatology out-patient department were included. The written informed consent was also taken before enrollment to study.

The patients of age less than 10 years, pregnant or lactating females, patients with active infection other than warts, history of allergic skin disorder (generalized eczema or urticaria), primary or iatrogenic immune-suppression eg: diabetes mellitus, patient on corticosteroid therapy or anti-cancer medications, patient with HIV infection, bleeding disorders and refusal to consent were excluded the study.

The pre-treatment evaluation included a detailed medical history, a thorough general physical examination and local examination of warts including site, size, number and consistency were carried out. Investigations include complete blood count with differential and platelet count, haemoglobin and biochemical investigations including liver function test, renal function test and random blood sugar and HIV serology.

The homologous auto implantation was done in all the study patients.

Technique of auto implantation

A well-developed verrucous papule was chosen as a donor wart. Under local anesthesia and strict aseptic precautions, paired stratum corneum wart tissue was removed and placed on a sterile swab. An area on the flexor aspect of non-dominant forearm around two-three inches below the antecubital fossa was chosen as a recipient site. Under local anesthesia with aseptic precautions, a subcutaneous pocket was created with the help of 16 gauge needle. The harvested paired wart tissue cut in small pieces was gently introduced into the subcutaneous pocket with the same needle and secured with a Band-Aid plaster. The donor area was also dressed. Systemic antibiotics were given for a period of 5 days. The dressing was removed after 5 days.

All study patients were subjected to follow up after two weeks for the first month and then monthly for six months. A base line photograph of the every study subject was taken before auto implantation for comparing the response in follow up visits.

Outcomes of the study

Resolution of warts within a period of three months after the procedure was considered as successful treatment. Either non responders or resolution after three months was considered as failures.

The primary outcome was the status of the lesion, as defined good response or no response / worsening based on the above criteria. **The secondary outcomes** were the various adverse effects recorded during the study period and the treatment required thereof.

Statistical analysis

The data collected was analyzed by using Microsoft Excel, Microsoft Access and Graph Pad in Stat computer software. All tests of significance were two-tailed, and $p < 0.05$ was considered to reflect significance.

Results

A total of 128 patients were enrolled in the study. Out of them, 100 patients were available for follow-up. The

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baseline demographic characteristics are shown in table no.1.

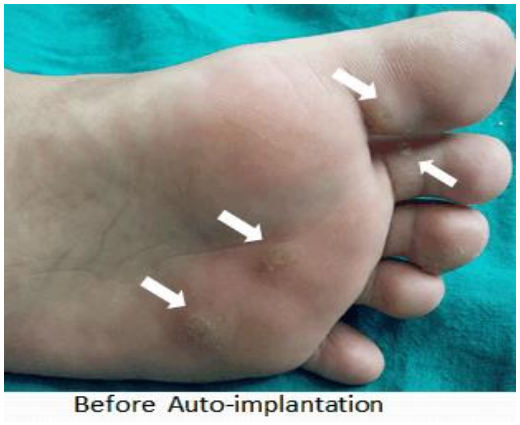
Table No.1. Demographic profile of study populations

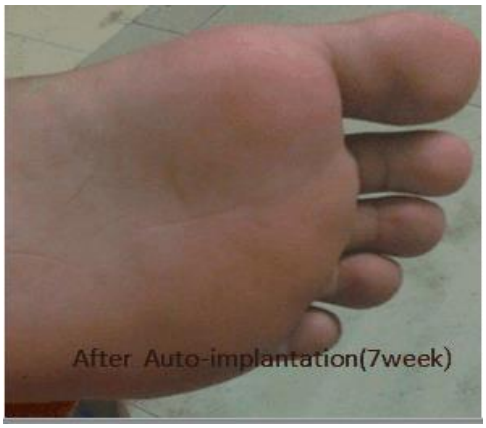
Demographic characteristic	No. of patients (Out of total 100)	Clinical Characteristic	No. of patients (Out of total 100)
1. Age:		**1. Symptoms:**	
<20 yrs.	30	Pain	13
21-40 yrs.	64	Disfigurement	70
>40 yrs.	06	**2. Type of warts:**	
2. Sex:		Common	27
Male	68	Filliform	02
Female	32	Mosaic	02
3. **Duration of wart:**		Palmer	08
Less than 1 yr.	93	Palmo-planter	02
1 to 3 yrs.	05	Plane (Facial)	17
More than 3 yrs.	02	Planter	36
		Sub-ungal/ peri-ungal	06

Out of 100 cases of auto-implantation 68 were males and 32 were females (M: F 2.13:1) and the majority of cases (64 %) were in the age range of 20- 40 years. Pain (13 patients) and disfigurement (70) were two main clinical presentation symptoms. The majority of patients (36%) had planter type of warts followed by common (27%) and plane wart (17%). The filliform, mosaic, and palmo planter warts were exclusively found in males in our study. Most of study patients had their disease duration less than 1 year (93, 93%). All the demographic and clinical data noted, are summarized in Table 1.

Table No.2. Response of auto-implantation therapy with the types of wart

Type of wart	**Response**	
	Complete response (%)	**No response/ Failure (%)**
Common	16/27 (59.20%)	11(40.80%)
Filliform	00/2(0.0%)	2(100%)
Mosaic	2/2(100%	00(0.0%)
Palmer	7/8(87.50%	1(12.50%)
Palmo-planter	1/2(50%)	1(50%)
Plane (Facial)	12/17(70.50%)	5(29.50%)
Planter	29/36(80.50%)	7(19.50%)
Sub/ peri-ungal	4/6(66.77%)	2(33.33%)





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The overall response was achieved in 71% of patients after three months of auto-implantation; the earliest response was achieved at the end of 4th week. The filliform subtype had no response with the auto-implantation while mosaic type had 100 % clearance and other sub variants (including palmer, planter and plane) had more than 70% clearance rate. There was no life threatening side effects following auto-implantation. The most common side effects were pustule (6%) and nodule formation (4%). None of the patients showed recurrence at the site of implantation while the distant site wart found in one patient.

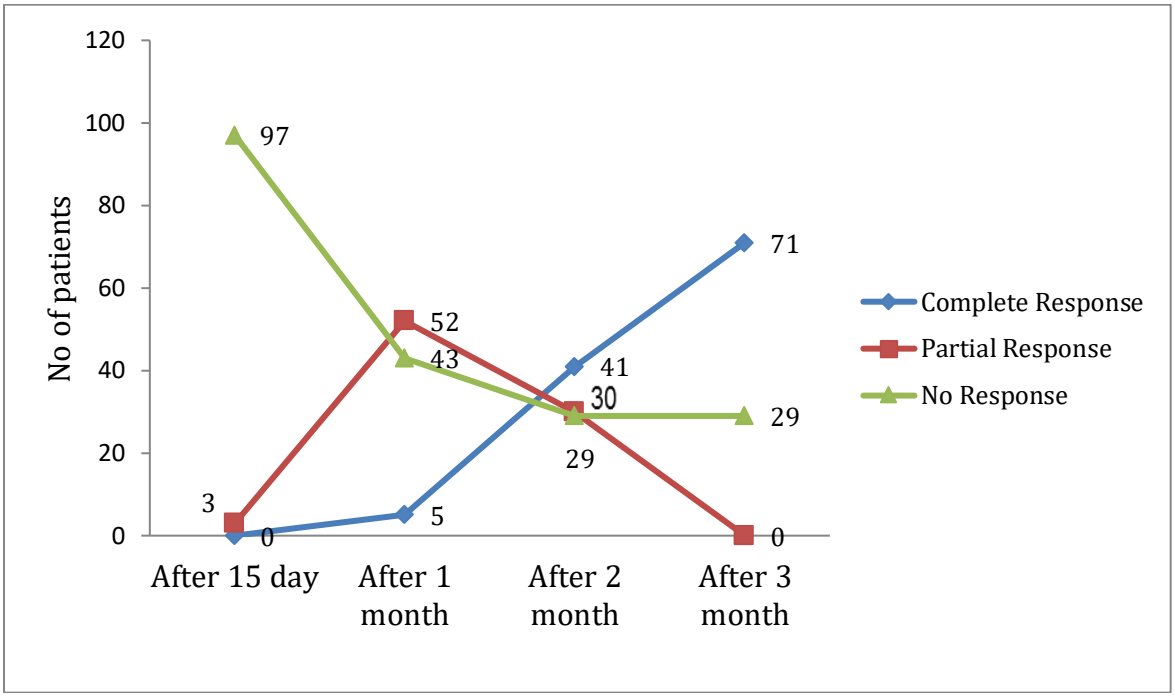

Figure.1. Histogram showing objective response with varying time duration

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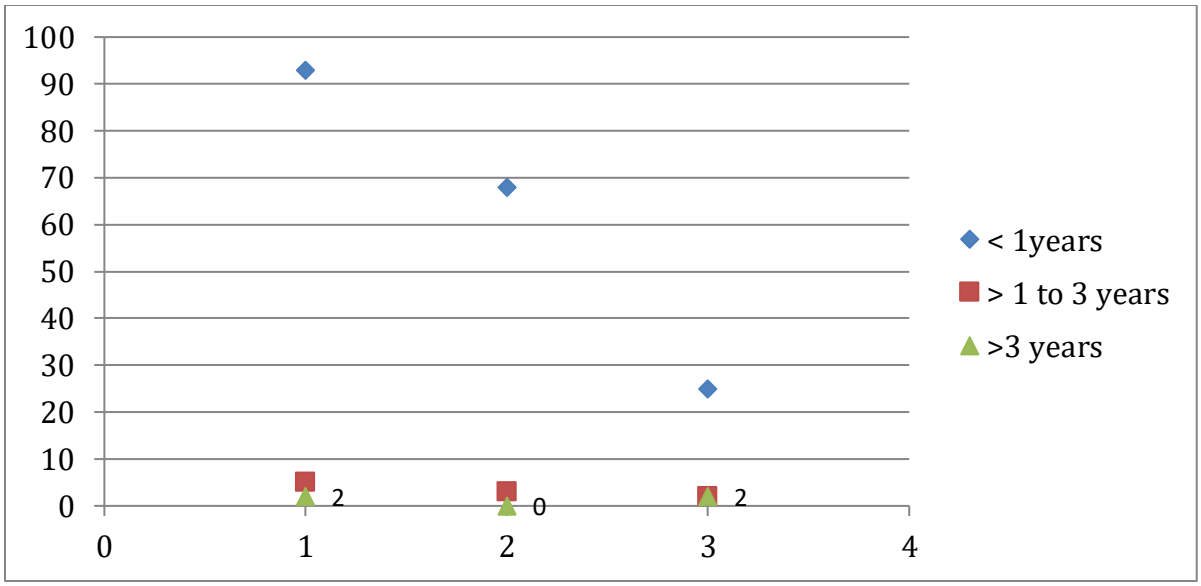

Figure no. 2. Scattered diagram showing relationship between response to treatment and duration of warts

Discussion

Despite numerous therapeutic modalities reported in the literature, treatment of common warts remains a continuing challenge. The treatment is often frustrating for both physicians and patients because optimal treatment with high efficacy and low recurrence has not been explored.[3] Currently destructive modalities are most commonly used treatment for warts but they are painful, associated with disfiguring scarring and have a high recurrence rate.

Evidence suggests that the patient's cell-mediated immunity plays an important role in the treatment of warts.[4]

These include 1) the uncontrolled proliferation of warts, both common and genital, in HIV-infected patients with high viral loads and low T-lymphocyte cell counts, 2) the profusion of warts in solid organ transplant recipients, 3) the innumerable flat warts in patients with epidermodysplasia verruciformis and 4) the significant epidermal and dermal influx of CD4+ lymphocytes in spontaneously regressing warts.[5] This has prompted researchers to search for immunotherapeutic approaches in the treatment of warts. Some of these immunotherapeutic agents include contact sensitizers, imiquimod, intralesional interferon and oral drugs such as levamisole, cimetidine and zinc sulphate.

Intralesional immunotherapy is an approach that employs the ability of the immune system to recognize certain viral, bacterial and fungal antigens that induce a delayed-type hypersensitivity reaction, not only to the antigen but also against the wart virus, which, in turn, increases the ability of the immune system to recognize and clear HPV [6]. Several intralesional immunotherapeutic agents such as BCG[7], Candida[8], Mumps[9], Trichophyton[10], Mycobacterium w[11] , MMR (mumps, measles and rubella) have been used in the treatment of different types of warts with variable efficacy.

Autoinoculation may work by activating a delayed hypersensitivity response to the wart tissue antigens, aiding clearance of both local and distant warts. This therapy was shown to be associated with the production of Th1 cytokines.[5] Th1 cytokines TNF-α and IL-1 down regulate the transcription of HPV genes whereas INF-γ and IL-2 stimulate cytotoxic T cells and natural killer cells to eradicate HPV-infected cells.[12]

The most common age group with multiple and recurrent wart found in our study was 20-40 years (64% patients) followed by less than 20 years (30% patients) of age. The mean age for male was 21.53±7.99 and for female was 24.68±7.07. This finding was similar to the study conducted by Nischal et al.[13] The youngest patient was of 10 years age and oldest one was 55 years. The male to female ratio was 2.13:1 (68:32). The mean duration of disease was 10.11±1.5 months, ranging from 15 days to 7 years. Most of study patients had their disease duration less than 1 year (93, 93%), out of them 88 patients had less than 6 months duration.

Majority of patients had no associated symptoms only 13% had associated mild pain at site of warts. This pain was more evident in patients with younger age and also with short duration of disease. Among the types of warts, planter type was most common (36 patients) followed by common (27 subjects) and plane / facial (17 patients) sub types of warts. Other varieties of warts like palmer (8 patients), sub / periungal had 6 patients while filliform, mosaic and palmo-planter were found in 2 subjects in each group, respectively. This observation had much difference with the Shivkumar et al[14] where Verruca vulgaris type of wart present in 40 patients and

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palmo-planter in 20 patients. This difference may be due to geographical distribution. None of the study patients had prior treatment history in Shrivastav et al[15] while our study had 15 patients, of these 15 patients, 11 were male and 4 were female. They have consulted to another physician for same problem and taken treatment for less than two months.

Overall the objective response in view of complete response (clearance or cure) was achieved in 71% (71 patients) of study population while remaining had either partial response or no response. Longhurts B et al[16] observed 69% clearance rate, similar result as to our study.

The complete response was much higher in our study as compared to Viac et al[17] and Usman et al[18] , which showed 45.4% and 44% clearance rate, respectively. While Lal NR et al [19] showed 62.5% of clearance rate, slight lower to our study.

Shivkumar et al [14] and Nischal KC et al [13] showed 73.3% and 74.1% complete response simultaneously, almost equal observation to our study. The earliest complete response was achieved after 4 weeks of auto-implantation (seen in 5 patients). At the end of three months 71 patients had clearance with no recurrence till six months follow up. The clearance rate was much higher and early in patients with painful wart as compared to painless. They showed complete response in two months. A possible explanation of this could be that, these patients had already inflammatory process at site of warts with abundant infiltration of inflammatory cells like lymphocytes. With the help of Auto-implantation we also are activating other inflammatory cytokines eg; Th1 cytokines, TNF-α and IL-1 etc. They further down regulate the transcription of HPV genes whereas INF-γ and IL-2 stimulate cytotoxic T cells and natural killer cells to eradicate HPV-infected cells increase the likelihood of a successful clearance. After the end of treatment 29 patients still had either residual or persistent wart lesion and they termed as catastrophe to auto-implantation.

The subjective response in form of satisfaction to the auto-implantation treatment found in 71% patients while residual 29 patients had disappointment to the treatment protocol. The gratification was more in females as compared to male (F: M, 72:70.6%).

In our study response to treatment was highest (73.11%, 68/93) in patients having warts for ≤ 1year, followed by patients with 1-3 years (60%, 3/5) and none of the patients with more than 3 years duration had complete response. Results showed statistically significant inverse correlation between duration of warts and the treatment response (p= 0.001), i.e. the better cure rate in patients with shorter disease duration. It is well known that warts typically continue to increase in size and distribution and may become more resistant to treatment over a period of time. [20] So early treatment of warts is desirable and waiting for spontaneous resolution might sometimes make the condition more difficult to treat.[21] This observation of our study is contradictory to Lal NR et al [19] who said that "patients whose warts cleared completely had them for a longer duration."

We did not find any statistically significant association between the therapeutic response to auto-implantation and the different clinical variables including age and sex. But response with clinical subtypes of wart had an interesting finding that filliform subtype had no response with the auto-implantation while mosaic type had 100 % clearance and other sub variants (including palmer, planter and plane) had more than 70% clearance rate. Common wart also had approximate 60% cure rate. Our observation was slight higher to Shrivastav et al [15] who showed 66% complete response in recalcitrant wart while slight lower to Shivkumar et al[14] found 80% clearance rate with palmer and planter wart while 70% cure with verruca vulgaris subtype.

We observed recurrence of warts only in single patient during the follow up period of 6 months. A similar observation of absent or low rates of recurrence have also been reported by other related studies (Shrivastav et al [15] , Shivkumar et al[14] and Nischal KC et al[13] . This finding represents another important advantage of auto-implantation over traditional treatments and may be attributed to the acquisition of a long-term HPV-directed immunity [4] . Although theoretically accepted, this advantage needs longer follow-up periods and more number of patients for further validation.

We used autologous wart for implantation. The major concern against auto-implantation was either its side effects or complication of procedure. No serious adverse effects were seen in study population. Nodule formation (4/100) and pustule development (6/100) at implantation site were main side effects. These side effects were managed easily with 5-7 days antibiotic course after auto-implantation. None of them required intensive care. Other side effects of auto-implantation like pruritus, keloid and scar was absent in our study patients. The side effect profile was similar to Lal NR et al [19] .Few warts resolved with post inflammatory hyper-pigmentation (PIHP).

Conclusion

Our preliminary experience with homologous implantation of wart suggests that this is a promising treatment modality for multiple and recurrent cutaneous warts. It is an inexpensive, safe and probably an effective option that has the potential advantage of widespread and sustained effects against HPV. By looking at the high proportion of patients who showed a positive response to homologous auto-implantation in this study, there seems to be a definite role of this in the treatment of multiple and recurrent cutaneous warts.

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Further studies on larger number of patients and randomized, double blind placebo controlled nature are needed to evaluate.

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