

Study of Homologous Autoimplantation Therapy for Treatment of Multiple Warts in Patients Attending the Dermatology Out Patient Department

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Abstract

Introduction: Warts are benign tumours that commonly involve skin and other epithelial tissues. There is no single treatment modality that is 100% effective. In multiple warts, especially on face, palms, and soles destructive procedure are inappropriate and impractical. Homologous autoimplantation is a simple technique, which helps in inducing cell mediated response, causing clearance of warts. **Aims and objectives:** To evaluate the effect of homologous autoimplantation therapy in treatment of multiple warts. To study the untoward effects of this treatment. **Material and methods:** A total of 49 patients of viral warts were included in study. Homologous autoimplantation of wart was done and regular follow up was done to see the result. **Results:** Out of 49 patients, in 24 patients there was good response, 14 showed moderate response, 5 showed poor response and in 6 patients there was no response. **Conclusion:** Homologous autoimplantation is an easy, minimally invasive technique which clears multiple, recurrent and recalcitrant warts.

Keywords: Homologous Autoimplantation, Warts

1. Introduction

Warts are benign tumours that commonly involve the skin and other epithelial tissues like oral and anogenital mucosae. The etiologic agents for these infections are a class of double stranded DNA viruses called papillomaviruses¹.

Various clinical types are verruca vulgaris, verruca plana, verruca palmaris and plantaris and anogenital warts².

Common warts have been a frustration for both patients and clinicians since early Greek and Roman times. They can greatly affect a patient's quality of life by causing embarrassment, fear of negative appraisal by others and frustration caused by persistence and/or recurrence³.

There is no single treatment that is 100% effective. Hence, multiple modalities like hypnosis/suggestive therapy, cytotoxic treatments like electrocauterization, radiocauterization, chemical cauterization, cryotherapy, CO₂ laser ablation, virucidal therapies like topical glutaraldehyde, formaldehyde and cidofovir, antimetabolic therapies like bleomycin, retinoids, podophyllin and podophyllotoxin, immunotherapies such as oral zinc sulfate, cimetidine, levamisole, topical dinitrochlorobenzene, diphencyprone, squaric acid dibutyl ester, intralesional interferon, imiquimod, BCG vaccine and HPV vaccines all have been tried. These treatment modalities have an average of 60-70% clearance of warts in 3 months⁴. Pain related to treatment, side effects and costs can be determining factors in choosing a therapy. With all the treatments recurrences are frequent.

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Children with common warts may not require treatment as spontaneous regression is common⁵.

Significant alterations occur in the immune status of patients during spontaneous wart regression or following successful wart therapy⁶. The most striking feature is the increase in viral-specific antibodies (both IgM and gG type). Delayed hypersensitivity to HPV antigen also increases in regressing warts.

The ideal aims of the treatment of warts should be to remove the wart without recurrence, avoid aggressive procedures, and to assist the immune system in dealing more effectively with the virus and inducing life-long immunity to human papilloma viruses (HPVs)⁴. In multiple warts,

The ideal aims of the treatment of warts should be to remove the wart without recurrence, avoid aggressive procedures, and to assist the immune system in dealing more effectively with the virus and inducing life-long immunity to human papilloma viruses (HPVs)⁴. In multiple warts, especially of face, alms and soles, destructive procedures are inappropriate and impractical. Homologous autoimplantation is a simple technique, which helps in inducing a good cell-mediated immune response, essential for clearance of warts⁶. The stimulation of the immune system by exposing the virus to immune mediators forms an ideal modality of treatment due to spontaneous regression of the wart with long-lasting immunity. As it is an autograft technique, it is more likely that immunity against the same serotype is elicited (in contrast to the HPV vaccine where immunity is developed only against HPV types 6, 11, 16 and 18)⁸.

2. Aims and Objectives

- To evaluate the effect of homologous autoimplantation therapy in the treatment of multiple warts.
- To study the untowardly effects (if any) of the foresaid treatment modality.
- To provide recommendations based on this study.

3. Material and Methods

The present study was carried out in the department of Dermatology, Venereology and Leprology of a tertiary health care institute attached to a medical college. Approval of institutional ethical committee was taken. A total of 55 patients of viral warts were included in the study, who visited the hospital from the period between Jan 2011 to June 2012. A written informed consent of each patient was taken.

3.1 Patient Selection

3.1.1 Inclusion Criteria

- Patients with multiple (>5) verrucae vulgaris,
- Filiform warts, verruca plana and/or palmo-plantar warts.
- Patients willing to participate in the study and ready to sign the informed consent form.

3.1.2 Exclusion Criteria

- Pregnant and lactating mothers
- Patients less than 18 years of age.
- Immunosuppressed patients and those with a history of intake of immunomodulatory/ immunosuppressive drugs and/or systemic corticosteroids.
- Patients having anogenital warts.
- Patients not willing to participate in the study.

3.2 Treatment Modality

- Homologous autoimplantation of warts.

3.2.1 Method

On Visit 1

After eliciting a detailed history and examining the patients, relevant investigations were carried out. These included a complete blood count, bleeding time, clotting time, prothrombin time, random blood sugar levels, urine pregnancy test and an HIV-tridot test. The patients who qualified as per the inclusion criteria were selected.

All selected patients were evaluated for baseline lesion count and measurement of diameter of the lesions.

- Lesion Count - Lesion count was done by the same physician on every visit.
- Measurement of diameter of lesions – Largest diameter of the individual warts was measured in millimetres (mm) on a standard scale and average diameter was counted by calculating the mean diameter of the lesions. A well developed warty lesion was chosen. After cleaning the site with spirit followed by liquid povidone iodine followed again by spirit to achieve asepsis, local anesthesia in the form of 2% lignocaine was given into the lesion site with the help of an insulin syringe. A chunk of wart tissue was removed with the help of a scalpel blade (11 no. straight surgical blade) and placed on a sterile swab (Figure 1 and 2). This tissue was then transferred to a new glass slide cleaned with spirit and the wart tissue was cut into small pieces with the same surgical blade.

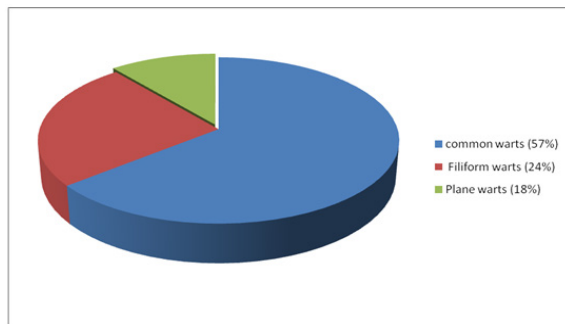


Figure 1. Pie diagram of the distribution of study sample according to type of warts.



Figure 2. Before treatment.



Figure 3. After treatment.

An area approximately 2 inches below the antecubital crease, on the flexor aspect of the forearm of the non-dominant side was chosen as the recipient site. Under local anesthesia and strict aseptic precautions, a small nick was made on the skin up to the level of subcutis using scalpel blade (Figure 3). Pieces of the harvested tissue were introduced into this breach and was pushed upto subcutaneous level with the help of plain forceps. The wound was secured with a 4-0 ethilone suture to make sure the wart tissue was not extruded out. The donor area was dressed with a band-aid plaster. The recipient area

was cleaned with liquid povidone iodine followed by spirit after which povidone iodine ointment was applied at the recipient site and the area dressed with a gauze piece and sticking tape. Tablet Cefadroxil (500mg) twice daily for 5 days was prescribed along with Tablet Brufen (400mg) as and when required for pain. Patients were called for follow up after 7 days.

On Visit 2 (7 Days after the 1st Visit)

The patients were inquired about any fresh complaints. The donor site and the recipient site were examined. In case of a healthy recipient site the suture was removed and the site cleaned with povidone iodine and spirit. The patients were then prescribed povidone iodine ointment to be applied on the recipient site twice daily for the next 5 days. Again a lesion count and the average diameter of the lesions were recorded. The patients were called for a follow up every 15 days for the first month and monthly once thereafter for the subsequent visits to complete a period of 5 months.

On Visit 3 (after 15 days), Visit 4 (after 1 month), Visit 5 (after 2 months), Visit 6 (after 3 months), Visit 7 (after 4 months) and Visit 8 (after 5 months):

The patients were inquired about any fresh complaints. Lesion count and average diameter of the lesions were recorded.

If oozing from the recipient site or signs of frank infection were noticed in any of the follow up visits, a course of Tablet Azithromycin (500mg) orally once daily was prescribed for 3 days.

3.3 Statistical Analysis

Data was collected and statistically evaluated by using 'Z test' to find the significance of the treatment modality. The Z test was performed in the software Microsoft Excel 2008.

4. Results

Table 1. Age and sex wise distribution of the study sample

Age	Sex		Total
	Male	Female	
16-25	13(26.53%)	3(6.12%)	16(32.65%)
26-35	18(36.73%)	3(6.12%)	21(42.85%)
36-45	9(18.37%)	1(2.04%)	10(20.41%)
46-55	2(4.08%)	0(0%)	2(4.08%)
Total	42(85.71%)	7(14.28%)	49

Table 2. Distribution of study sample according to percentage reduction in number of warts on final visit

Percentage Reduction In Number of Warts	Number of Patients		Total
	Males	Females	
0%	4(8.16%)	1(2.04%)	5(10.20%)
>0% To <25%	1(2.04%)	0(0%)	1(2.04%)
<25% To <50%	2(4.08%)	3(6.12%)	5(10.20%)
<50% To <75%	13(26.53%)	1(2.04%)	14(28.57%)
<75% To <100%	7(14.28%)	0(0%)	7(14.28%)
100%	15(30.61%)	2(4.08%)	17(34.69%)

Table 3. Distribution of study sample according to percentage reduction in size of warts on final visit

Percentage Reduction In Size of Warts	Number of Patients		Total
	Males	Females	
0%	12(24.49%)	4(8.16%)	16(32.65%)
>0% To <50%	11(22.44%)	0(0%)	11(22.44%)
<50% To <100%	4(8.16%)	1(2.04%)	5(10.20%)
100%	15(30.16%)	2(4.08%)	17(34.69%)

Table 4. Efficacy of homologous autoimplantation therapy in reducing number of warts

Visit No	Mean No	Standard Deviation	Z-Value	P-Value	Percentage Reduction
1	14.88	13.11	N/A	N/A	0
2	14.88	13.11	0.0009	>0.05	-0.27
3	14.92	13.13	-0.01	>0.05	-0.27
4	13.84	13.42	0.39	>0.05	7.51
5	11.71	11.35	1.28	>0.05	21.30
6	5.55	6.66	4.44	<0.05	62.70
7	4.77	6.09	4.89	<0.05	67.94
8	4.80	6.09	4.88	<0.05	67.74

The following graph shows the mean number of warts on different visits, where the curve is the steepest between in the fifth and the sixth visit, which corresponds to the third (Graph 1 & 2) & Table 5.

Month after the autoimplantation has been performed

The average size of warts drooped from 3.10 mm on the first visit to 1.59mm on the eighth visit. Hence, a 48.71% reduction in the mean size of warts was observed on the final visit (Table 1 - 4).

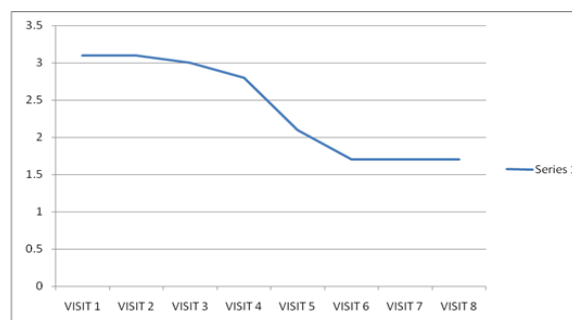


Graph 1. Mean reduction in the number of warts at different visits(x- axis: visits, Y- axis: mean number of warts).

Table 5. Efficacy of homologous autoimplantation therapy in reducing the size of warts

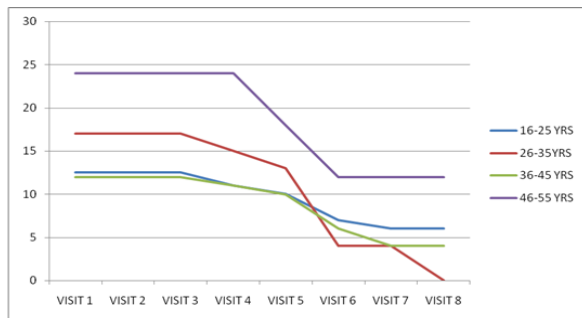
Visit No	Mean Size of Warts(Mm)	Standard Deviation	Z-Value	P Value	Percentage Reduction
1	3.10	1.45	N/A	N/A	N/A
2	3.08	1.43	-0.33	>0.05	0.64
3	3.06	1.45	-0.24	>0.05	1.29
4	2.82	1.55	0.70	>0.05	9.03
5	2.12	1.22	3.90	<0.05	31.61
6	1.65	1.36	5.58	<0.05	46.77
7	1.59	1.40	5.73	<0.05	48.71
8	1.59	1.40	5.73	<0.05	48.71

The following graph depicts the reduction in the mean size of warts on different visits.

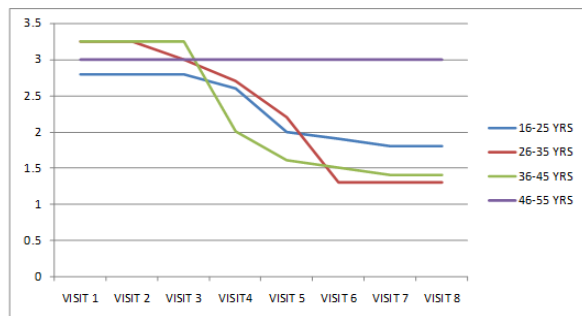


Graph 2. Reduction in the mean size of warts at different visits (X-axis: visits, Y-axis: Mean size of the warts in mm).

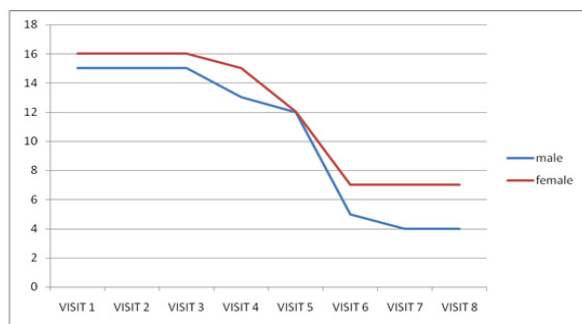
The success of the in different age groups (Table - 6, Graph : 3 - 8). The maximum response of homologous autoimplantation technique in reducing the number of warts was observed in the 26-35 years age group where the percentage reduction in the mean number of warts on final visit was 79.59%. Whereas the minimum response was observed in 46-55 years age group in which the patients showed a 52.08% reduction in the mean number of warts on the final visit.



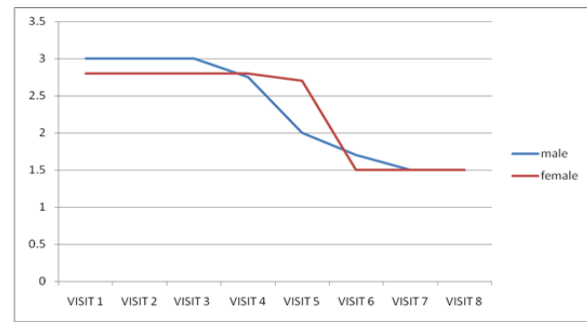
Graph 3. Comparison of reduction in number of warts between different age groups (X-axis: visits, Y-axis: mean number of warts).



Graph 4. Comparison of reduction in size of warts between different age groups (X-axis: visits, Y-axis: Mean size of warts in mm).



Graph 5. Reduction in number of warts in males and females (X-axis: visits, Y-axis: Mean number of warts).

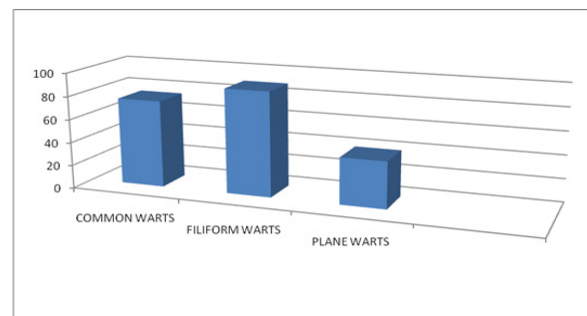


Graph 6. Comparison of reduction in mean size of warts in males and females (X-axis: visits, Y-axis: Mean size of warts in mm).

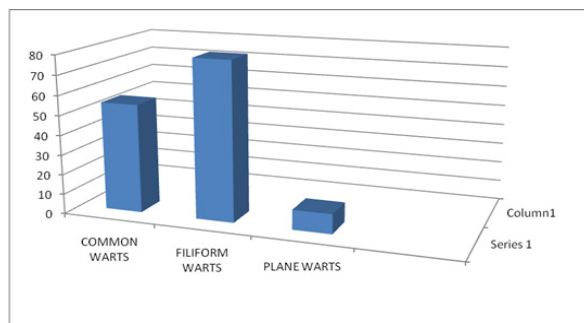
Table 6. Treatment response in different types of wart

Type Of Warts	Percentage Reduction In Mean Number Of Warts On Final Visit	Percentage Reduction In Mean Size Of Warts On Final Visit
Common Warts	69.41%	50.47%
Filiform Warts	93.28%	75%
Plane Warts	34.49%	5.55%

Most of the patients did not show any reaction at the autoimplantation site (recipient site). 3 patients showed frank infection with complaints of pain and pus discharge from the lesion. 2 patients showed oozing of clear fluid without any pain or discomfort, which subsided in 3-4 days. Nodule formation at the recipient site was seen in 8 patients at some point in the follow up visits. This phenomenon of nodule formation caused only a mild discomfort in the patients. None of the patients suffered from fever or other systemic complaints after undergoing the autoimplantation procedure.



Graph 7. Percentage reduction in mean number of warts on final visit (Y-axis: percentage reduction in mean number).



Graph 8. Percentage reduction in mean size of warts on final visit (Y-axis: Percentage reduction in mean size).

5. Discussion

Warts are benign tumours that commonly involve the skin and other epithelial tissues. They are caused by Human Papillomavirus infections. Warts can occur at any age. Clinically, warts can present with different morphological types like verrucae vulgaris (common warts), filiform warts, plane warts, palmoplantarwarts and condyloma acuminata. They can involve any area on the body covered by skin or mucous membrane ranging from palmo-plantar to anogenital areas. Although some warts regress spontaneously, they can persist for years causing physical discomfort and psychological trauma. No treatment till date has been validated to be 100% effective in clearing viral warts. Hence, multiple treatment modalities have been tried with an average of 60-70% clearance of warts in 3 months time⁶.

The ultimate wart treatment would resolve all or a great percentage of warts, be painless, need only one or a part of a wart treated, call for one to three treatments, create no scarring, offer HPV immunity for a lifetime and be available to all patients⁹. The presence of local as well as systemic immunity may be necessary to eradicate the clinical manifestations of HPV infection¹.

Specific immune stimulation against HPV has been tried by autoimplantation of the wart tissue in the uninvolved skin^{6,8}, injecting the suspension of the crushed wart into the muscle² or skin¹⁰ and by quadrivalent HPV vaccines^{8,11,12}.

Patients with regression of warts either spontaneously or following successful therapy or injection of antigens showed the development of cell-mediated immunity and appearance of virus-specific IgM and IgG antibodies^{10,13}. In the present study we used a pared stratum corneum tissue from the wart and cut it into smaller pieces before implanting it at a healthy site. The wart tissue was cut into smaller pieces in an attempt to increase the surface area of antigen exposure.

Shivakumar *et al.* in their study extracted a subcutis deep part of the wart using an eighteen gauge needle and implanted it into the skin elsewhere. This resulted in two wounds. Moreover,

HPV is an epidermal infection and there is no added advantage by extracting the donor tissue containing dermis and subcutis. In our study, we avoided wound at the donor site.

Srivastava *et al.* used distilled water extracted suspension of crushed wart and injected it intramuscularly². This method involved crushing the wart tissue and preparing a suspension, all under aseptic conditions which becomes a little tedious. Compared to this, our technique is less cumbersome involving just cutting the wart tissue into smaller pieces and directly implanting them into the recipient site.

Most of our patients were males with females constituting just 14.28% of the study sample. Majority patients belonged to the 26-35 years age group. A complete clearance of warts was observed in 34.69% patients in our study. Whereas, Shivakumar *et al.*, Srivastava *et al.* and Nischal *et al.* observed a complete clearance of warts in 73.3%, 66.03% and 74.1% respectively^{2,6,8}. However, a 67.74% reduction in the mean number of warts and a 48.71% reduction in the mean size of warts was observed in our study. 26(53.06%) patients showed a partial clearance of warts. This is higher than what was observed in other studies.

Srivastava *et al.* observed a partial clearance of 22.64% and a 3.7% partial clearance rate was observed by Nischal *et al.*^{2,8} Whereas Shivakumar *et al.* did not discuss about partial clearance in their study⁶.

In our study a good response (i.e. !75% reduction in number of warts) to treatment was observed in 48.97% patients, moderate response (i.e. !50% and <75% reduction in number of warts) in 28.57% and poor response (i.e. !25% and < 50%) in 10.20% patients. 12.24% patients who showed <25% reduction in the number of warts were considered as non-responders. one patient showed an increase in the number of warts after the treatment. We found a statistically significant reduction in the number of warts (p value < 0.05) only on and after the 6th follow up visit that is roughly after 3 months from the date of autoimplantation.

Whereas, statistically significant reduction in the mean size of warts was observed on the 5th follow up itself that is after 2 months from the auto implantation date. This shows that the reduction of warts was not by chance and e autoimplantation therapy definitely had influenced the disease course. These findings are consistent with the findings of Nischal *et al.* who also found maximum response within about 3 months time. Shivakumar *et al.*

on the other hand found maximum response within 2 months⁶. Srivastava *et al* also fixed complete resolution of warts after 2 months time period as a successful treatment outcome.

The maximum response was observed in the 26-35 years age group where the percentage reduction in the mean number of warts on final visit was 79.59%. Whereas the minimum response was observed in 46-55 years age group in which the patients showed a 52.08% reduction in the mean number of warts. Also, these patients did not show any reduction in the mean size of warts. This can be due to the fact that with increasing age, cell mediated immune response reduces. Also the finding could be a chance occurrence as there were only 2 patients in this age group causing a large difference in the two population groups. This difference in the response to treatment among different age groups has not been discussed in other studies.

As compared to females, males showed a fairly greater reduction in the mean number of warts. Again this difference cannot be considered significant because of the difference in the number of males and females in the study sample.

Patients having filiform warts showed the maximum response (93.28% reduction in mean number of warts) to the treatment while patients with plane warts showed the least response (34.49% reduction in mean number of warts). Total 13 (26.53%) patients showed some kind of reaction at the implantation site, out of which 3 patients had frank infection with complaints of pain and pus discharge from the wound and 2 showed oozing of clear fluid without any discomfort which subsided in 3-4 days. 8 (16.32%) patients showed nodule formation at the recipient site at some point of time in the follow up visits. This phenomenon of nodule formation caused only a mild discomfort to the patients and the nodule subsided after a 3 day course of oral Azithromycin (500 mg). Nischal *et al* also found similar nodule formation in 11.5% cases in their study as did Shivakumar *et al* in their study (number of patients not specified)^{6,8}. This nodule formation could be due to intense inflammation caused by implanted squames which act as a foreign body in the dermis and subcutis analogous to an inflammatory reaction which occurs in the case of a ruptured hair follicle⁸.

Homologous autoimplantation therapy has certain benefits over other treatment modalities.

- Unlike procedures such as electrocauterization, radio-cauterization, chemical cauterization, cryotherapy, etc all the warts need not be treated in homologous auto-implantation therapy. Only one or at the most a few warts need to be harvested.

- Autoimplantation technique is minimally painful avoiding multiple painful sittings as is required with treatments like cryotherapy.
- Being a one time procedure, only requiring the patients to be followed up for suture removal, the patient compliance is better than the treatments like topical salicylic/lactic acid preparations, podophyllin application, DNCB, diphencyprone, etc which require application of chemicals or topical medications over the warts for days or months together.
- Autoimplantation technique can be carried out in an average out patient setup. The materials and instruments required for this technique are not costly and are easily accessible in contrast to treatments like CO₂ laser, radiocautery or cryotherapy which require costly equipments and chemicals not readily available in the market.
- Being a minimally invasive procedure it saves the patients from prolonged downtime required for healing after treatments like laser therapy.
- Scarring, hypo/depigmentation, blister formation, etc. at the treated sites seen with cytotoxic therapies and antimitotic therapies are avoided by the autoimplantation technique.
- Also, the treatment is free from unwanted effects like pigmentary alterations and scarring of the healthy skin surrounding the warts which is a problem with treatments like chemical cauterization and cryotherapy.
- Sites like eyelids and periungual areas where treatment with other modalities is difficult are effectively treated by autoimplantation therapy.
- Further, autoimplantation therapy may confer long lasting immunity by development of cell-mediated immunity and production of IgG antibodies against that specific type of HPV as shown by Viac J *et al.*¹⁰

Limitations of our study include a small sample size, lack of controls to assess spontaneous resolution of warts and lack of serotyping of warts or checking for serospecific HPV antibodies. Further, we were not able to procure patients with palmoplantar warts and hence the treatment response in such patients could not be assessed. The response to the treatment in different age groups also needs to be studied in depth with a fairly equal sample size in each age groups.

6. Summary and Conclusion

The aim of our study was to evaluate the effect of homologous autoimplantation therapy in treatment

of patients having multiple warts and to study any untowardly effects occurring in the patients thereby.

The study was conducted at a tertiary health care institute attached to a medical college and included 55 patients who had multiple, recurrent and/or recalcitrant viral warts. The patients either had common warts, filiform warts or plane warts. Single or a few warts were harvested from each patient and were implanted at a healthy site in the same patient at the level of subcutis and the recipient site was secured with a suture material. The patients were followed up for a total of 5 months period to assess the outcome of the treatment.

Out of 55 patients, 49 were available for complete follow up. An overall 67.74% clearance rate of warts was observed in our study, which is comparable to other documented successful treatment modalities for warts. A complete clearance of warts was observed in 34.69% patients. More than 75% clearance of warts was observed in 48.97% patients and 28.57% patients showed 50%-75% clearance of warts. Maximum response was observed in a 3 months time period. Out of the three types of warts, patients with filiform warts responded the best while those having plane warts showed the least response. One patient showed an increase in the number of warts after the treatment. None of the patients showed recurrence of warts in the subsequent follow up visits. Thirteen patients showed some kind of reaction at the autoimplantation site out of which 3 patients showed frank infection, 2 showed oozing of clear fluid and 8 patients showed nodule formation, which can be due to a reaction of the body to the implanted epidermal squames. Patients in the 26-35 years age group showed maximum response to the treatment while the patients more than 45 years age showed a less response to the treatment, though this could have been a chance occurrence as there was not an equal distribution of patients in all age groups.

To conclude, homologous autoimplantation is an easy, minimally invasive technique wherein autoimplantation of one or a few warts at a normal site clears multiple, recurrent and/or recalcitrant warts at distant sites in about 3 months time without causing scarring or other side effects at the site of warts and minimal, if at all any, untowardly effects at the site of autoimplantation.

It can be used to treat warts on difficult sites like eyelids and periungual skin. It may provide a life long immunity and protect against infection with human papillomavirus of that particular type.

There are no studies to sufficiently discuss all the facets of this treatment. A double-blind, randomized controlled

trial with a larger sample size involving patients of all ages in equal proportions with a longer follow-up period will help in determining the effectiveness of the treatment more accurately.

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