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Role of autoinoculation in the management of cutaneous warts: a comparison study with 100% tricholoroacetic acid application

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ABSTRACT

Background: Persistent and recurrent warts pose a challenge to physicians despite the availability of multiple treatment options. Autoinoculation exposes HPV antigens to the dermis and vasculature thereby activating a delayed hypersensitivity response, facilitating clearance of both local and distant warts. The aim of this study was to assess the efficacy of autoinoculation and compare it with chemical cautery using 100% trichloroacetic acid.

Methods: A non-blinded interventional study was conducted at Goa Medical College, a tertiary care centre. Non-immunocompromised patients with 5 or more non-genital warts were included. Group 1: a wart was removed by punch biopsy, minced and implanted in the dermis. The procedure was repeated at 4 and 8 weeks. Group 2: weekly trichloroacetic acid (100%) application. Response was assessed at 4, 8 and 12 weeks in terms of percentage reduction in the number of warts. Statistical correlation with respect to age, sex, duration, number and type of warts was assessed using Welch ANOVA.

Results: In group 1, 63 patients and in group 2, 54 patients completed the study. Post autoinoculation, complete clearance was seen in 46.0% and 3.2% had partial clearance. With TCA application, 33.3% patients had complete and 13% had partial clearance. Response differed with the type of warts. Palmoplantar, periungual warts and verruca vulgaris showed better response to autoinoculation. Filiform and plane warts showed better response to TCA.

Conclusions: Autoinoculation is an efficacious treatment modality which can be performed routinely especially for palmoplantar and periungual warts which are particularly challenging to treat with other modalities.

Keywords: Autoinoculation, Cutaneous wart, Tricholoroacetic acid

INTRODUCTION

Warts are caused by human papilloma virus infection of the epidermis. They can spread to contiguous sites as well as to contacts. They can cause pruritus and be painful (especially on soles), causing considerable morbidity.

Extensive, refractory and relapsing cases are challenging. Ideally, treatment should remove all warts in one to three sessions, while avoiding aggressive (potentially scarring) procedures and induce life-long immunity to human

papillomaviruses (HPV), thereby preventing recurrences. The majority of available treatment modalities are destructive, requiring multiple sittings, and are limited by potential scarring and recurrence. A variety of immunotherapeutic agents have been tried with variable benefit. Immunotherapy can overcome the limitations of conventional ablative therapy by resolving lesions distant from the site of administration as well as sub clinically infected virus tissue thereby making it a preferable choice for patients with multiple warts and those with warts at difficult to treat sites (subungual, periungual, eyelids).

We therefore thought it worthwhile to evaluate the role of autoinoculation as an immunotherapeutic modality in the management of cutaneous warts.

Autoinoculation therapy is a simple, minimally invasive, inexpensive technique wherein the patient's wart is excised, minced and implanted into a dermal pocket. Exposing HPV antigens to the dermis and the cutaneous vasculature can activate a delayed hypersensitivity response, facilitating clearance of both local and distant warts. This therapy was shown to be associated with an increase in Th1 cytokines - TNF-α and IL-1, which downregulate transcription of HPV genes whereas IFN-γ and IL-2 stimulate cytotoxic T cells and natural killer cells to eradicate HPV-infected cells.²

METHODS

An open non-randomized comparison study was conducted from October 2017 to March 2018 in the skin and V.D. Department of Goa Medical College, a tertiary care centre in Goa. After Institutional Ethics Committee approval, patients aged 12 and above, with five or more non-genital warts were included in the study. Exclusion criteria were: patients less than 12 years, mucosal warts, history of keloids or hypertrophic scars, pregnant and lactating women, diabetes, immunocompromised patients and inability to follow up monthly (group 1) and weekly (group 2).

History of onset and progress of lesions, family history of similar complaints, treatment taken in past and response to treatment, site, type, and number of warts were recorded. Based on the previous treatment history and patient consent, patients were allocated to group 1 (autoinoculation) or group 2 (TCA).

In group 1, a well-formed wart was selected as the donor. After disinfection and local anaesthesia, the donor wart was removed using a punch biopsy (4mm) going up to the mid dermis. For palmo-plantar and periungual warts epidermal scrapping with a 15-scalpel blade were obtained till pinpoint bleeding occurred, to avoid scarring on palms and soles. The epidermal portion was minced on a sterile glass slide with a surgical blade into fine bits (increase surface area of antigen exposure). Volar aspect of the non-dominant forearm was used as the recipient site. After disinfection and local anaesthesia, a dermal pocket was created using 20G sterile needle. Minced bits of donor wart were introduced into this pocket using tip of the same needle. The nick was sutured using a nonabsorbable suture. Immediate adverse effects like anaphylaxis, syncope, and pain were looked out for. Both donor and recipient sites were dressed with sterile medicated gauze and micropore. Oral and topical antibiotic were given for 5 days. Patient was advised not to wet or remove the plaster for 5 days.

In group 2, patients received weekly trichloroacetic acid (100%) topical application. For both groups, changes in

the lesions were recorded at the end of 1, 2 and 3 months after initiating treatment in terms of: appearance of new lesions, size of lesions (decrease/increase in diameter or thickness), percentage reduction in number of lesions = (number of lesions at baseline excluding those removed for the procedure) - (actual number of lesions)/(number of lesions at baseline excluding those removed for the procedure) and other signs of response: itching, blackening, shriveling and dehiscence. Delayed adverse effects such as infection at site of implantation, new lesion at site of implantation and post inflammatory hypo or hyperpigmentation were looked for.

Response of patients was assessed as percentage of warts showing clearance. Those having 100% resolution were categorized as complete clearance, while those having less than 50% reduction in the number of warts or worsening were categorized as failure. Those showing 50.01-99.99% reduction was categorized as partial clearance. Those showing failure or partial response were re-inoculated at follow up visit.

Statistical analysis

The efficacy of therapy was calculated in terms of percentage of patients showing response. Independent t-test was used to check for statistically significant difference between the two groups with respect to the age, duration and number of warts. Regression rates were analysed with respect to age, sex, duration, number and type of warts using Welch ANOVA to look for statistical correlation.

RESULTS

Clinico-demographic data of study participants are highlighted in (Table 1). Males outnumbered females and majority of patients were between 20 and 30 years of age. Response seen at each follow up is documented in (Table 2). Three months post autoinoculation, 49.2% patients showed response. Complete clearance was seen in 46.0%. At the end of 3 months of TCA application, a greater proportion of patients (61.1%) showed more than 25% improvement. However, complete clearance was seen in only 33.3%.

Subgroup analysis (Table 3) within the autoinoculation group showed no statistically significant difference with respect to age or sex and response to therapy. Patients who failed to respond had greater mean number and duration of warts compared to those who responded, but the difference was not statistically significant. Response differed with the type of warts. With autoinoculation therapy, best response was seen in cases of palmoplantar warts wherein clearance was seen in 88.2% cases (complete clearance in 82.3%) and majority showed improvement at the first follow up visit. Among patients having verruca vulgaris, clearance was seen in 33.1% (complete clearance in 28.6%) and most of them improved after the second follow up visit. Improvement

in patients with planar and filiform warts was less impressive (0% and 25% complete clearance rates, respectively). With 100% TCA application, best response (66.6% complete clearance and 16.9% partial clearance) was seen in patients having filiform warts.

Adverse events following autoinoculation therapy have been shown in (Table 4). The commonest was post-inflammatory hyperpigmentation at the autoinoculation site, seen in 63.5% patients.

Table 1: Clinico-demographic profile.

Parameters	Autoinoculation group (n=63)	TCA group (n=54)	P value
Age (years) mean±SD	25.03±10.27	25.87±9.95	0.701
Sex (male: female)	50:13	41:13	0.656
Duration of illness (months)	13.62±19.73	12.39±20.88	0.744
<3	11 (17.46)	16 (29.63)	
3-6	14 (22.22)	12 (22.22)	
6-12	23 (36.51)	16 (29.63)	
>12	15 (23.81)	10 (18.52)	
Type of warts			NA*
Verruca vulgaris	21 (33.33)	15 (27.78)	
Palmo-plantar	17 (26.98)	13 (24.07)	
Periungual	2 (3.18)	1 (1.85)	
Planar	2 (3.18)	5 (9.26)	
Filiform	4 (6.35)	6 (11.11)	
Combination of different type of warts	17 (26.98)	14 (25.93)	
Number of warts: (mean ±SD)	27.62±20.52	20.26±18.36	0.045
<10	13 (20.63)	22 (40.74)	
11-20	16 (25.40)	13 (24.07)	
>20	34 (53.97)	19 (35.19)	
Treatment history			NA*
None	27	37	
TCA	8	0	
SA and LA	23	9	
Electrocautery	12	7	
Cryotherapy	4	3	
Alternative medicine	5	5	
Self-removal	8	2	

^{*}Not applicable.

Table 2: Response following therapy.

Follow up visit	Autoinoculation group number of patients	TCA group (n=54) number of patients
	N (%)	N (%)
End of 1 month		
Complete clearance	6 (10.20)	7 (12.96)
Partial clearance	8 (13.60)	7 (12.96)
Failure	45 (76.30)	40 (74.07)
End of 2 months		
Complete clearance	17 (27.0)	17 (31.48)
Partial clearance	8 (12.70)	7 (12.96)
Failure	38 (60.30)	30 (55.56)
End of 3 months		
Complete clearance	29 (46.0)	18 (33.33)
Partial clearance	2 (3.20)	7 (12.96)
Failure	32 (50.80)	29 (53.70)

Table 3: Subgroup analysis within each group.

Parameter	Complete clearance	Partial clearance	Failure	P value
Age (mean±SD)		·		-
Autoinoculation group	23.55±8.06	22.50±7.78	26.53±12.07	0.503
TCA group	24.17±9.25	31.16±9.15	25.34±10.51	0.336
Sex				
Autoinoculation group (M: F)	26:6	1:1	23:6	NA
TCA group	16:1	5:1	18:11	NA
Duration of illness	•			
Autoinoculation group	10.38±17.19	5±1.41	17.09±22.01	0.346
TCA group	6.29±4.58	6.58±8.64	17.15±27.21	0.161
Baseline number of warts				
Autoinoculation group	23.07±16.32	12±5.66	32.72±23.20	0.056
TCA group	10.82±6.96	22.33±10.39	24.10±21.86	0.01
Type of warts	N (%)	N (%)	N (%)	Total (%)
Autoinoculation group				
Verruca vulgaris	6 (28.6)	1 (4.7)	14 (66.7)	21 (100)
Palmoplantar	14 (82.3)	1 (5.9)	2 (11.8)	17 (100)
Periungual	1 (50.0)	0 (0)	1 (50.0)*	2 (100)
Planar	0 (0)	0 (0)	2 (100)	2 (100)
Filiform	1 (25)	0 (0)	3 (75)	4 (100)
Combination of warts	7 (41.2)	0 (0)	10 (58.8)	17 (100)
TCA group				
Verruca vulgaris	3 (20.0)	3 (20.0)	9 (60)	15 (100)
Palmoplantar	5 (38.5)	0 (0)	8 (61.5)	13 (100)
Periungual	0 (0)	0 (0)	1 (100)	1 (100)
Planar	1 (20)	1 (20)	3 (60)	5 (100)
Filiform	4 (66.6)	1 (16.7)	1 (16.7)	6 (100)
Combination of warts	5 (35.7)	2 (14.3)	7 (50.0)	14 (100)

^{*}Complete clearance occurred at 4 months post autoinoculation.

Table 4: Adverse events following autoinoculation therapy (n=63).

Variables		Number of patients
Immediate side effects	Pain	3
	Anaphylaxis	0
	Excessive bleeding	1
	Pre syncope	2
	Syncope	0
Delayed side effects - at autoinoculation site	Secondary infection	2
	Contact dermatitis	1
	Persistent pain without discharge (>1 week)	1
	Persistent erythema without pain (>1 week)	2
	New wart at site of autoinoculation	1
	Hypopigmentation	3
	Hyperpigmentation	40
Delayed side effects - at donor site	Secondary infection	0
Delayed side effects - at site of warts	Hypopigmentation	4
	Hyperpigmentation	0
	Post immunotherapy revealed cicatrix	1

DISCUSSION

At the end of 3 months, complete clearance was seen in 46.0% post autoinoculation as compared to 33.3%

following weekly TCA application. Complete clearance has been reported as 20-74.1% in various studies on autoinoculation.²⁻¹¹ We found improvement with autoinoculation therapy as early as 2 weeks. Other

workers have reported improvement occurring earliest at 3 weeks and 4 weeks.^{3,4} Partial clearance in the autoinoculation and TCA groups was seen in 3.2% and 13% patients, respectively. The findings of our autoinoculation group are similar to that of Nischal et al.4 Several studies have reported higher partial clearance rates (22.64-53.06%), while others have not reported partial clearance.^{2,3,5-8} Infection with antigenically heterogeneous HPV types in some cases, could account for partial clearance, and it is possible that complete rather than partial clearance was seen in our study because we re-inoculated patients at follow ups. An unusual finding in our study was that both patients showing partial clearance had only a single wart remaining which persisted after a further 2 months of observation in both the patients without appearance of new lesions. Similar finding has been reported by Nischal et al.4

Our study found no correlation between age or sex and response to autoinoculation or TCA. We found that response differed with the type of warts. Similar to our study, Shivakumar et al have reported 80% response rate in palmoplantar warts.3 In contrast, Biberstein and Cormia et al found poor response in patients with periungual and palmoplantar warts.^{9,10} Das et al also reported poor response of palmoplantar warts (16% had complete response).6 Cormia et al reported complete cure in only 20% of their cases using auto lysate therapy for verruca vulgaris. 10 This was similar to our study wherein 28.6% of patients with verruca vulgaris showed complete clearance. Ghosh and Maplestone reported that none of the patients with verruca vulgaris showed response to auto lysate. 11 However, Shivkumar et al have reported 70% clearance for verruca vulgaris which contrasts the findings of our study.³

In our study, none of the patients with plane warts responded to auto inoculation. Gugle et al reported least response in plane warts (34.49% reduction in mean number of warts). In contrast to our findings, Ghosh and Maplestone reported cure in 9 of 12 patients with plane warts and significant improvement in those who were not cured. Gugle et al reported maximum response in filiform warts (93.28% reduction in mean number) which contrasts the findings of our study (13.11% reduction in the mean number). However, percentage of patients showing complete, partial and failure to respond for each type of wart was not reported.

These differences could be due to variations in the duration of disease and type of warts in different groups. An immunofluorescence study by Shirodaria and Mathews showed that warts from sole, heel and toe had a much higher incidence of stainable virus antigen. ¹² This could account for the better response of palmoplantar warts seen in our study. The amount of inoculum used has not been standardized which could account for varying response rates in different studies.

In our study, patients with longer duration of warts showed decreasing response to autoinoculation therapy (56.25% clearance rate in patients with warts <1-year duration verses 26.67% in patients with warts of longer duration). However, the difference was not statistically significant. Similarly, in the TCA group, patients with warts of more than 1-year duration showed decreased response compared to those who had warts for lesser duration (48.84% vs. 28.57% clearance rate). We were unable to find any studies that compare response to TCA based on duration of warts. In most of the studies on auto implantation, autovaccination and auto wart injection there is no mention of response rates based on duration of warts. However, Malison et al reported that in all patients with condylomas accuminatum for up to 1 year, the cure rate with autogenous vaccine was 86% compared with 0% for those with disease more than a year. 13



Figure 1: (a) Patient 1 with multiple plantar warts pre autoinoculation and (b) showing complete clearance one-month post autoinoculation.

At the follow up visits, two (3.17%) patients had developed secondary infection at the autoinoculation site. Infection at the autoinoculation site has been reported in 2.4-6.12% cases in other studies.^{4,7,8} One patient complained of persistent pain at the autoinoculation site which subsided after 2-3 weeks. Two patients had persistent erythema without pain at the autoinoculation site which resolved after 5-6 weeks. These finding have been reported in previous not studies autoinoculation. 2-8,13 One (1.5%) of our patients developed a new wart at the site of autoinoculation. Hypopigmented macule at the autoinoculation site was seen in 4.5% patients and hyperpigmented macule or papule in 63.49% patients. In 6.35% patients, warts resolved leaving post inflammatory hypopigmentation.



Figure 2: (a) Patient 2 with multiple plantar warts pre autoinoculation and (b) complete clearance onemonth post autoinoculation.



Figure 3: (a and b) Patient 3 with multiple plantar and periungual warts pre autoinoculation, (c and d) partial clearance one-month post autoinoculation and (e and f) complete clearance two months post autoinoculation.

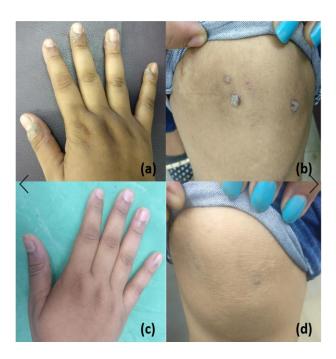


Figure 4: (a and b) Patient 4 with multiple verruca vulgaris and periungual warts pre autoinoculation and (c and d) complete clearance one month post auto inoculation.

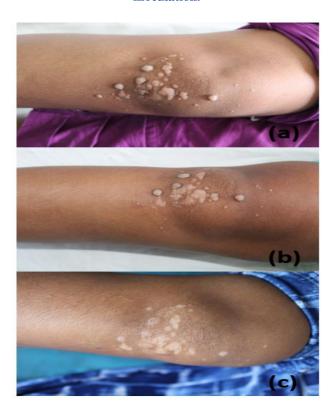


Figure 5: (a) Patient 5 with verruca vulgaris of >7 years duration pre autoinoculation, (b) flattening of warts 2 months post autoinoculation and (c) complete clearance at the end of 3 months post auto inoculation.



Figure 6: (a) Patients 6 with multiple verruca vulgaris pre autoinoculation and (b) complete clearance onemonth post auto inoculation.

Limitations

A limitation of our study was that patients who responded should be followed up for longer duration to assess recurrence.

CONCLUSION

In summary, one can say it was evident that autoinoculation method had the edge over TCA in palmoplantar and periungual warts, while TCA had the advantage in the filiform and plane variants. So, it makes sense to say that the ideal approach to wart treatment would depend on choosing a particular modality of treatment based on wart type like autoinoculation for palmoplantar type and TCA for filiform and plane types. On the other hand, in the case of verruca vulgaris either modality of treatment would yield similar cure rates. Moreover, for best outcomes the patients need to seek treatment within one year of having acquired the disease.

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