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Effectiveness of autoinoculation therapy in cutaneous warts: A double - blind, randomized, placebo - controlled study

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Abstract:

Background: Viral warts persist and recur in spite of the availability of multiple treatment options, causing frustration to patients and physicians. **Aims:** To study the effectiveness of autoinoculation as a treatment modality in cutaneous warts. **Methods:** A double-blind, placebo controlled study was carried out. In the treatment group, full thickness warty tissue was excised, minced and implanted in a small dermal pocket. In the control group, warty tissue was only excised and not implanted, though a dermal pocket was made. Patients were evaluated every four weeks with lesion counts .Response was assessed at each visit and at 12 weeks. **Results:** Forty patients with cutaneous warts (male: female = 25:15) were randomized into autoinoculation and control groups. The number of warts at baseline was comparable in both groups (P = 0.293). Reduction in the number of warts was significantly more in the autoinoculation group (8.50 ± 13.88) than in the control group (10.04 ± 5.80) from 8 weeks onwards (P = 0.010). Complete resolution occurred only in the autoinoculation group, in 68.5% of cases. Adverse effects were seen in 9 patients, including infection of the donor site (5 cases), keloid formation (2) and hypopigmentation (2). **Conclusion:** Autoinoculation may be an effective therapeutic modality for cutaneous warts.

Key words: Condom, Abstinence, Molluscum Contagiosum, Genital and Perianal warts

Introduction:

Viral warts are papillomas caused by the human papilloma virus (HPV) and can grow anywhere on the body, commonly on the hands and feet. Most require treatment but some warts regress spontaneously [1]. Management is difficult because of recalcitrance to standard therapy and recurrence. Currently available options like cryosurgery, laser, electrosurgery, curettage, and topical keratolytics are generally painful and limited by recurrences[2].The need for immunotherapy is felt by all practicing dermatologists, especially in cases of multiple warts and warts at inaccessible sites. Diphenylcyclopropenone (DCP), squaric acid dibutylester (SADBE), imiquimod, tuberculin jelly, Candida antigen and autologous vaccines have all been tried for immunotherapy but none has been consistently effective [2]. Also DCP and SABDE can cause allergic contact dermatitis, urticarial lesions, and pigmentary disturbances, while autologous vaccines might have oncogenic potential [3]. Autoinoculation of warts seems to be a cost-effective treatment modality. We therefore did a study to find the effectiveness of autoinoculation as an immunotherapeutic modality to warts.

Materials and Methods

The study was designed as a double-blind, randomized placebo controlled trial and carried out between June 2014 and May 2015 at a tertiary care hospital in southern India. Clearance from the institutional ethics committee was obtained before starting the study. All patients of either sex with more than four clinically diagnosed cutaneous warts attending the dermatology out patient department were included. Our exclusion criteria were: pregnancy and lactation, immunosuppression, renal failure, liver failure, inability to come for monthly follow-ups, alcohol or other substance abuse, and those with mucosal warts. All patients included were tested for HIV infection and found negative. At the screening visit, patients were enrolled based on inclusion and exclusion criteria. Written informed consent was obtained from the patient.

Patients were randomized equally into two groups. A thorough clinical examination was done in all patients and the numbers of warts were recorded. Complete blood count, random blood glucose, renal function and liver function tests were done. The first session of autoinoculation was then carried out. Patients were given intramuscular tetanus toxoid (0.5 ml) at the baseline visit.

Three follow-up visits were scheduled at intervals of 4 weeks each. At each follow-up visit, effectiveness of treatment and adverse events were assessed. The primary effectiveness parameter was reduction in the number of warts on the skin. Wart to be removed for autoinoculation was not counted. The secondary effectiveness parameter was the percentage reduction in the number of warts.

Adverse events were recorded at each visit. Baseline laboratory tests done at the screening visit were repeated at the third follow-up visit.

Autoinoculation procedure

The procedure was performed in the dermatology procedure room under strict aseptic precautions. The Shivakumar *et al*. technique with modifications was used [4]. A wart of adequate volume was chosen and anesthetized by 2% lignocaine infiltration. It was then excised using a number 11 scalpel blade. Hemostasis was achieved with a radio- frequency ablator. The tissue thus obtained was minced into tiny bits. Using a 20 gauge needle, a dermal pocket extending up to the subcutis was created over the volar aspect of the left forearm, 5 cm below the anterior cubital crease with prior infiltration anesthesia. The minced bits of the donor wart were introduced into this pocket using the tip of the same needle. Both donor and recipient sites were dressed with sterile medicated gauze and adhesive plaster. Oral cephalexin and topical mupirocin were prescribed for 7 days. Patients were advised not to wet or remove the plaster for 24 hours after the procedure.

Blinding

Patients were unaware of which group they were allocated to, and wart tissue was taken from patients in both the groups. While autoinoculation was done in the treatment group, a sham inoculation procedure was carried out in the control group, where only a dermal pocket was created but no wart tissue was inoculated. Dressings of the donor and recipient sites as well as antibiotics given were similar in both the groups. The dermatologist who noted the number of warts and adverse events at each visit was also unaware of the treatment received.

Statistical analysis

The target sample size was 40, with 20 evaluable subjects in each group. Continuous variables were compared between groups by the independent samples t-test. Categorical data were compared between groups by a Chi-square test. Analysis of co- variance (ANCOVA) was done where the baseline was a co- variate. MedCalc version 11.6 and Graph Pad Prism version 5 software were used for statistical analysis. Effectiveness analysis was done on subjects reporting at follow-up visit.

Results

Forty patients were randomized equally into two groups. None was lost to follow-up and all patients returned for follow-ups as advised.

Males outnumbered females and patients were mostly in their mid-twenties. Patients in the autoinoculation group were younger on average than those in the control group. There were no pediatric patients.

There was a significant reduction in the number of warts in the autoinoculation group from the first follow-up itself .The difference in reduction in the number of warts was independent of age, sex of the study participant or the number of lesions on performing ANCOVA.

All participants had multiple warts on their trunk and extremities; a few had plamoplantar warts and periungual warts. Significant reduction started from the second follow-up in the autoinoculation group. Complete resolution occurred only in the autoinoculation group in 68.5% of cases. The earliest response noted was at the 4th week (in 3 patients) after the first autoinoculation session.

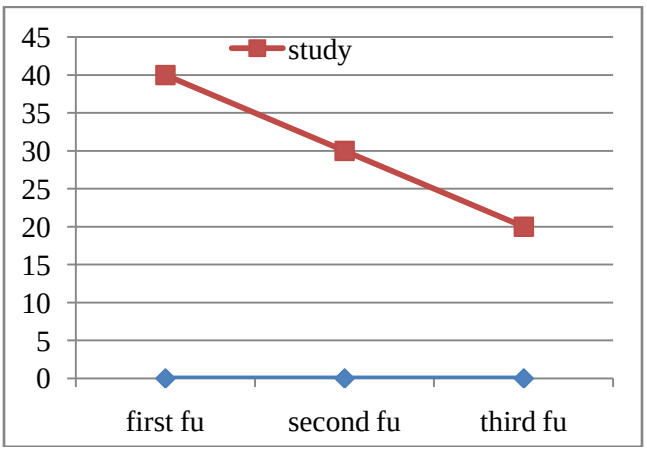

Figure 1:

Table 1: Comparison of the mean percentage reduction in the number of warts in the two study groups

Visit	Autoinoculation group (*n*=24)	Control group (*n*=24)	*P* value
Baseline (mean±SD)	15..88±12.61	10.04±5.80	0.023
1st follow-up (mean±SD)	12.25±13.20	10.04±5.80	0.490
2nd follow-up (mean±SD)	9.50±13.88*	10.04±5.80	0.010
3rd follow-up (mean±SD)	5.54±14.26*	10.04±5.80	<0.001

Adverse events were observed in 10 patients, with infection of the donor site in 9 patients in the control group, while 2 patients each in the autoinoculation group developed keloids and hypopigmentation. Laboratory parameters were within normal limits and comparable between the groups.

Discussion

Study shows the patient's cell mediated immunity plays an important role in the treatment of warts [5]. Recent literature suggested intralesional antigen immunotherapy (Candida, mumps skin test antigen, MMR vaccine) as the first line for treatment of numerous (>5) warts, large (>1 cm) warts, warts associated with distant lesions, periungual warts and as the second line of management in recalcitrant warts that have failed to clear with destructive therapies[7] .

Autoinoculation work by activating a delayed hypersensitivity response to the wart tissue antigens that helps in clearance of warts. This therapy was shown to be associated with the production of Th1 cytokines [6] . Th1 cytokines like IL-1 and TNF alpha down regulate the transcription of HPV genes whereas IFN gamma and IL-2 stimulate cytotoxic T cells and natural killer cells to eradicate HPV infected cells [5].

Three open labelled studies reported response to autoinoculation therapy in 66- 74% of patients [4,8,9] . The psychological effects of undergoing a procedure may be therefore be important as hypnotherapy can regress warts [9]. To exclude this possibility a sham inoculation procedure as placebo in the control group. Resolution was achieved in 68.5% of patients in the treatment group and those cured, only one showed recurrence within three months of the study period. Local adverse events were mild. Other forms of immunotherapy like Candida, mumps, trichophytin antigens [3] shows systemic symptoms (fever, myalgia, and arthralgia) or local pain, erythema and itching which were not observed in our patients. A double bind study done showed reduction about 68 % in autoinoculation groups [10].

Longstanding warts as well as peri and subungual warts responded well to autoinoculation in our study .It also proved autoinoculation is very effective in treating warts.

Limitations of our study were inability to identify HPV types , ILs and extension of follow up period.

Conclusion

Our study indicates that autoinoculation therapy is an easy cost-effective procedure in treatment of warts.

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