

A Comparative Study of Topical 5% 5-Fluorouracil with Needling versus 30% Trichloroacetic Acid with Needling in the Treatment of Plantar Warts

Abstract

Background: Warts are benign proliferations of keratinocytes caused by Human Papilloma Virus (HPV). Plantar warts are caused by HPV types 1, 2, 4, 27 and 57. It is challenging to treat them due to frequent recurrences. **Aim:** To compare the efficacy and safety of topical 5% 5-Fluorouracil (5-FU) with needling versus 30% Trichloroacetic acid (TCA) with needling in the treatment of plantar warts. **Materials and Methods:** Sixty consecutive patients of plantar warts were randomly allocated into two groups of 30 each and treated with either 30% TCA with needling or 5% 5-FU with needling once in four weeks, until complete clearance of warts or for a maximum of three sessions. Baseline clinical photographs were taken and subjective response at the end of treatment was recorded. Objective assessment at 4, 8, and 12 weeks was carried out and outcome was evaluated by reduction in number and size of warts. Adverse effects of each group were noted and compared. Follow-up of patients was done at 6 months for clinical assessment of results and to study recurrence. **Results:** Out of 30 patients in 30% TCA group, 28 patients (93.33%) had complete response and 02 patients (6.66%) had partial response at the end of 12 weeks. In 5-FU group, 26 patients (86.66%) showed complete response, 02 patients (6.66%) had partial response, and 02 patients (6.66%) had no response to treatment. The mean reduction in size and number of warts was better in the TCA group and was significant at 4th week of follow up while at the end of 8th week and 12th week, the response was identical. There was no recurrence of warts in the complete responders at the end of 6 months. The main adverse effect seen in both groups was pain at the needling site. **Conclusion:** Needling with both topical 5% 5-FU and 30% TCA are highly effective in clearing plantar warts. However, 30% TCA has the advantage of early action and complete clearance of plantar warts with fewer adverse effects.

Keywords: 5% 5-Fluorouracil, 30% Trichloroacetic acid, needling, plantar warts

Introduction

Warts are benign proliferations of keratinocytes caused by Human papilloma virus (HPV). Plantar warts are commonly caused by HPV type 1 and less frequently by HPV types 2, 4, 27, and 57 and are notorious for being recurrent. They present with a rough keratotic surface on the soles. Epidermal abrasion and a transiently impaired immune system are required to inoculate the virus into keratinocytes in this condition.^[1]

Several accepted treatment modalities for cutaneous warts include simple occlusion, curettage, cautery, diathermy, TCA, cryotherapy, radiofrequency ablation, electrofulguration, laser ablation, hypnosis, podophyllin, keratolytics, antiproliferative agents, and immunotherapy.^[2] Even though all of these methods have been shown

to give a significant clearance rate, they also have a disappointing and apparently inexplicable recurrence or failure rate.

Trichloroacetic acid is a caustic and hemostatic agent which works by hydrolysis of cellular proteins leading to cell death and tissue destruction.^[3]

5-FU is an antimetabolite drug that inhibits nucleic acid synthesis, thereby arresting cell proliferation. It was first used by Goldman *et al.* in 1962^[4] and later studied in mosaic plantar warts by Bunny in 1973.^[5] "Needling" was first described by Falknor in 1969 as a form of physical trauma without the use of chemicals in verrucae causing destruction of HPV infected keratinocytes in addition to inducing an enhanced immune response.^[6]

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In this study, we compared the efficacy of topical 5% 5-fluorouracil with needling versus 30% trichloroacetic acid with needling in the treatment of plantar warts and observed the additive effects of combining topical treatment with needling.

Materials and Methods

This was a prospective, single center, interventional, parallel group, randomized study conducted over a period of one and a half years in a tertiary care hospital. All treatment naïve patients of plantar warts aged more than 18 years who attended Dermatology OPD and were willing to comply with the protocol were included in the study. Before initiating the study, due approval was taken from the institutional ethical committee. Pregnant and lactating women, those with other types of warts and co-morbid conditions like diabetes or immunosuppression were excluded from the study.

All patients were enrolled after taking written informed consent. They underwent a detailed clinical history, general physical, systemic and dermatological examination including recording of size (measured using vernier caliper) and number of lesions documented by a single examiner. Baseline clinical photographs were taken. The patients were randomly divided into two groups and treated either with 30% TCA or 5% 5-FU followed by needling using 26-gauge needle once every 4 weeks on OPD basis until complete clearance of warts or a maximum period of three sessions.

TCA 30% solution was obtained by dissolving 30g of TCA crystals in distilled water making up to a volume of 100 ml. 5% 5-FU solution was readily available in ampoules meant for injection. The treatment area was first cleansed with povidone-iodine solution. Local anesthetic (Inj 2% lignocaine) was infiltrated and any overlying callus was removed using surgical blade number 15. This was followed by application of 5% 5-FU or 30% TCA solution over the lesion. A 26-gauge needle was then used to puncture through the solution into the lesion up to the subcutaneous tissue. Each puncture produced pin-point bleeding in the 5-FU group and was continued till the entire lesion was beefy red in color [Figure 1a]. But in the TCA group, there was no bleeding because of coagulation of proteins by TCA and hence needling was continued until there was no more resistance felt [Figure 1b]. The patients were observed for 15 minutes post procedure for any side effects. The total number of punctures varied according to the size of the lesion. Pressure was then applied to the wound with sterile gauze and then dressed with a non-adherent sterile dressing. All the warts in a patient were treated in the same sitting. This procedure was repeated every 4 weeks for 3 sessions or till the clearance of warts, whichever was earlier. Patients were advised to avoid NSAIDs for a period of one week post needling.



Figure 1: (a) Pinpoint bleeding after needling with 5% 5-FU (b) Frosting after needling with 30% TCA due to coagulation of proteins

The patients were followed up at 4 weeks, 8 weeks, and 12 weeks to assess the response to treatment. The size and number of lesions were measured at each visit and photographs were taken.

After completion of the protocol, patient's subjective response was assessed using patient satisfaction score which was graded as excellent, good, satisfactory and poor.

Objective assessment was determined by the mean percentage reduction of number and size of warts in both groups at the end of 4, 8, and 12 weeks from the initial visit.

Those patients with total clearance of warts in terms of size and number after treatment were considered to be complete responders whereas, those patients with only reduction in size and/or number of warts were considered as partial responders. Non responders had neither reduction in size nor number of warts.

Adverse effects in the form of pain, burning sensation or bleeding were noted. Follow-up was done at six months to detect any recurrence in complete responders. The mean percentage reduction of size and number of lesions were compared between the two groups at every visit and were statistically analyzed using Mann Whitney U test. The subjective response of the two groups was statistically analyzed using Chi square test.

Results

A total of 132 patients were assessed for the study over a period of 18 months, out of which 58 patients were excluded based on exclusion criteria and 14 were lost to follow-up [Figure 2] due to official transfers. Sixty patients completed the study, of which 30 were treated with 5% 5-FU and rest with 30% TCA. The mean age of subjects in 5-FU and 30% TCA groups were 23.43 ± 8.08 years and 22.3 ± 4.09 years, respectively. The 5-FU group had 30 males and no females, whereas 30% TCA group had 27 males and 3 females.

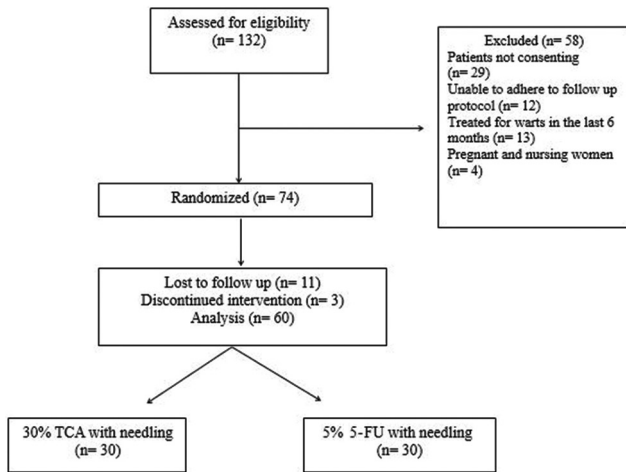


Figure 2: Flow chart of the study

No. of warts	5% 5 - FU	30% TCA	P
1-3	16	19	0.642
3-6	10	8	
6-9	2	0	
Multiple	2	3	
Total	30	30	

The number of warts in both the groups was comparable as shown in Table 1. Mean size of plantar warts in subjects in 5-FU and 30% TCA groups were 5 ± 1.08 mm and 4.90 ± 0.99 mm respectively. Mann Whitney U test was applied and *P* value of 0.7565 was obtained. Therefore, there was no statistically significant difference between the groups with respect to the size of warts.

The mean percentage reduction in number and size of plantar warts at 4th week, 8th week, and 12th week in 5-FU group and 30% TCA group are as shown in Table 2. Mann-Whitney U test was applied and *P* value was obtained. At 4th week the difference between the two groups was statistically significant with respect to response to treatment (*P* value <0.05). Hence, the results show that 30% TCA has better effect (in terms of reduction in number and size of plantar warts) as compared to 5-FU at the end of 4 weeks, however, there was no statistically significant difference between the groups at the end of 12 weeks.

Out of 30 patients in 30% TCA group, 28 patients (93.33%) had complete response and 02 patients (6.66%) had partial response at the end of 12 weeks [Figure 3a-c]. In 5-FU group, 26 patients (86.66%) showed complete response, 02 patients (6.66%) had partial response and 02 patients (6.66%) had no response to treatment [Figure 4a and b].

Patient satisfaction score was noted in both groups as depicted in Table 3. Chi square test was applied and

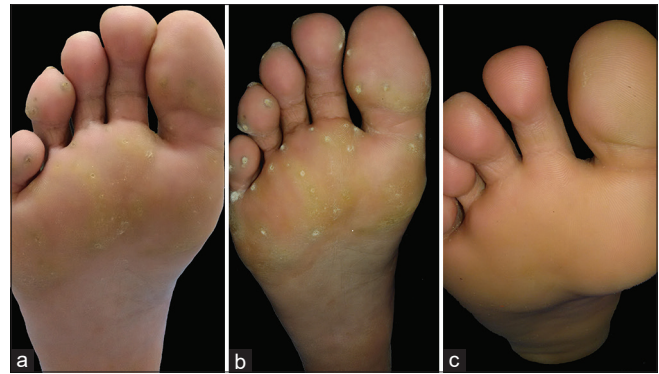


Figure 3: Needling with 30% TCA (a) Multiple endophytic papules with loss of dermatoglyphics before the procedure (b) Frosting seen immediately after needling (c) Resolution of warts after 4 weeks

P value was found to be 0.008, which shows statistically significant difference between the groups.

Pain at the treatment site was the main adverse effect observed in both the groups as depicted in Table 4. Chi square test was applied and *P* value of 0.134 was obtained. Therefore, there was no statistically significant difference between the groups with respect to adverse effects of treatment.

In the present study, follow up at six months did not reveal any recurrence of warts after treatment with both topical 5% 5-FU and 30% TCA followed by needling.

Discussion

Plantar warts are quite common and at times can be incapacitating due to pain while walking. Treatment of common warts is often frustrating for both the dermatologists and patients because optimal treatment with high efficacy and low recurrence has not been established till date.

A multitude of therapeutic options are available for the treatment of warts^[7] and the clearance rate varies between 60% to 70% with commonly used modalities.^[8] According to British Association of Dermatologists’ guidelines for the management of cutaneous warts 2014, salicylic acid has the highest strength of recommendation A whereas for cryotherapy, it is B and for laser, contact immunotherapy and 5-FU strength of recommendation is C and for TCA and phenol it is D.^[2] Despite the availability of a wide range of therapeutic options, none is absolutely efficacious. Persistence and recurrence have been the major problems with all of these modalities. There are few studies which have investigated the efficacy of topical 5-fluorouracil and other topical destructive or caustic agents which are safer, inexpensive, and easy to use in the treatment of plantar warts.

TCA is a caustic, hemostatic agent which causes cell necrosis. To study the exact mechanism of action Zhu *et al.* applied 40% TCA *in vitro* to excised genital warts and

Table 2: Mean percentage reduction in number and size of plantar warts

Time since treatment	Mean percentage reduction in number of plantar warts			Mean percentage reduction in size of plantar warts		
	Mean (SD)			Mean (SD)		
	5% 5 - FU with needling	30% TCA with needling	P	5% 5 - FU with needling	30% TCA with needling	P
At 4 th week	53.17 (3.71)	78.00 (3.75)	0.01016	63.17 (2.97)	81.67 (3.36)	0.0096
At 8 th week	83.17 (2.91)	86.00 (3.25)	0.50286	85.50 (2.54)	87.33 (3.02)	0.4902
At 12 th week	95.33 (1.77)	88.67 (2.99)	0.63836	95.67 (1.65)	89.33 (2.87)	0.6455

Table 3: Subjective response

Subjective response	5% 5 - FU with needling	30% TCA with needling	P
Excellent	7	17	0.008
Good	14	7	
Satisfactory	8	2	
Poor	1	4	
Total	30	30	

Table 4: Adverse effects of treatment

Side effects	5% 5 - FU with needling	30% TCA with needling	P
Pain	17	18	0.134
Burning sensation	4	2	
Bleeding	8	0	

later amplified the DNA using a polymerase chain reaction and found out that HPV DNA was detected in 100% of untreated specimens, while it was amplified only in 7% of samples treated with TCA.^[9] Although TCA has been used traditionally for many years, studies on its efficacy in plantar warts are limited. Pezeshkpoor *et al.* studied the efficacy of 80% and 35% TCA solutions in common warts for a maximum of 6 sessions and found that 80% TCA solution was more efficacious, but advised the clinician to be very careful in its application.^[10] Cengiz *et al.* studied safety and efficacy of 40% TCA in plantar warts and found out that it is more effective for clearance of plantar warts with significantly improved long-term safety profile.^[11] Dailey *et al.* studied the histopathological changes in eyelid skin following the application of varying concentrations of TCA and found that 30% TCA produced least scarring and complications.^[12] Moreover, by combining two modalities a better response was obtained using a lower concentration of TCA, thereby avoiding the complications with higher concentration as observed in earlier studies.^[10]

5-FU is a fluorinated pyrimidine analogue which blocks DNA synthesis by inhibiting thymidylate synthetase and damages the dividing basal layer cells of the epidermis hindering proliferation of viral warts. This antimetabolite drug is most commonly used to treat a variety of skin neoplasms and precancerous lesions, such as actinic keratosis, keratoacanthomas, actinic cheilitis, Bowen's disease, superficial basal cell carcinomas and porokeratosis.^[13] Salk *et al.* studied efficacy of topical 5% 5-FU in plantar warts under occlusion and observed that 19 of 20 patients (95%)

**Figure 4: Needling with 5% 5-FU (a) Multiple verrucous papules with thrombosed capillaries before the procedure (b) Resolution of warts after 12 weeks**

had complete eradication of all plantar warts within 12 weeks of treatment.^[14] Dogra *et al.* compared topical 5% 5-FU with electrocautery in the treatment of warts and found that 100% of plantar warts showed good response with 5-FU while it was 80% with electrocautery.^[15]

Frazer opined that the localized immune response incited by verrucae is insufficient to trigger a systemic immune response as it is limited to the upper layers of the epidermis and hence an enhancement of immune response in the form of presentation of viral antigens using minor trauma is required for better clearance of warts.^[16] In 1969, Falknor described "Needling" as a form of physical trauma without the use of chemicals in verrucae which results in destruction of HPV infected keratinocytes besides inducing an improved systemic immune response by presenting the viral antigen to the host. He anesthetized the area and inserted a needle "in dart fashion, so as to penetrate the full depth of the verruca and exiting through the base of the capsule into the fat". Out of the 126 patients he treated, recurrence was noticed in only two of them.^[6]

This is the first study of its kind as per our knowledge, where we have combined topical medications with needling to explore their additive effects.

In the present study, the response of TCA group at four weeks was better than that of the 5-FU group but at the end of 12 weeks of follow up both the treatment modalities showed almost similar results. At 12 weeks, in TCA group 28 patients had complete response and 02 patients had partial response. In 5-FU group, 26 patients showed complete response while 02 patients had partial response and only 02 patients had no response. The response to treatment in this study was better than the earlier studies quoted above which had used TCA or 5-FU without needling. The main side effect noted was pain in both the groups even after local anesthesia which lasted for two to three days but did not interfere with their daily activities.

The absence or reduction of specific cellular response may explain the individual variation in response to treatment and it can be difficult even in immunocompetent individuals. Destruction of affected tissues either by a cytotoxic or physically ablative mode of action is the mechanism of most treatments which may not always produce the relevant cytokines to destroy latent virus in adjacent cells.^[6]

The ideal treatment modality for warts should be able to cause destruction of the present growth and provide long-lasting immunity against human papilloma virus, so that there is no recurrence. This can optimally be achieved by the stimulation of the immune system against the virus.^[17] In our study this was achieved by needling, which even if done for a solitary lesion produced a cascade effect whereby the remaining untreated and deeper lesions also resolved.

Limitations

Even though vernier caliper was used to measure the size of warts the depth of the warts could not be assessed, which was a major constraint.

Conclusion

30% TCA and 5% 5-FU are easily available and less expensive topical formulations, and when combined with needling offers around 90% clearance of plantar warts. Both topical 30% TCA and 5% 5-FU with needling can be considered as effective, safe and first line therapies for plantar warts in immunocompetent individuals, wherein clearance is faster with 30% TCA needling compared to 5% 5-FU needling.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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