

## Original Research Article

# Treatment of periungual warts: comparison of topical 5% 5-fluorouracil and intralesional purified protein derivative in a South Indian teaching hospital

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### ABSTRACT

**Background:** Verrucae or warts are common skin lesions caused by the human papilloma virus. Treatment of warts, particularly those in the periungual region is usually difficult, exhibiting resistance. Available conventional treatment modalities offer little hope in curing periungual warts. Thus, there is a need for a simple, reliable, non-expensive treatment for periungual warts. Aim was to determine and compare the efficacy of intralesional immunotherapy using purified protein derivative (PPD) and topical 5-fluorouracil (5-FU) under tape occlusion for the treatment of periungual warts.

**Methods:** In this prospective comparative study, Group 1 (PPD) patients, intralesional injection of PPD is given in a randomly selected lesion every 3 weeks for a maximum of six sittings. For Group 2 (topical 5% 5-FU under tape occlusion), patients are advised to apply 5% 5-FU under occlusion on the lesion(s) selected for study during the night and left for 12 hours. This is done for 3 months. After completion of the treatment and after the declaration of the cure – follow-up is done for the next three months to look for recurrence.

**Results:** Intralesional PPD had a significantly higher cure rate (88%) than that of topical 5-fluorouracil under occlusion (20%). The mean time taken for the resolution of the periungual warts was 6.6 weeks for intralesional PPD compared to 9.8 weeks for topical 5-fu under tape occlusion.

**Conclusions:** The cure rate of intralesional PPD group (88%) was much higher than that of topical 5% 5-fluorouracil under tape occlusion group (20%). In the PPD group, the younger patients responded well and faster. There was no difference in cure rate among age groups in 5 FU group.

**Keywords:** Periungual warts, Purified protein derivative, 5 fluorouracil, Resistant warts, Immunotherapy

### INTRODUCTION

Verrucae or warts, caused by human papilloma virus, are acquired by direct or indirect contact from the clinical or subclinical case or the virions present in the environment. Periungual Warts are found in those who bite, pick and tear their nails, presenting as ugly, unnatural growth surrounding the nail folds causing benign fissures, loss of

cuticle, pain, and Paronychia, disturbing nail growth. In severe cases, there may be onycholysis or permanent deformity of the nails. There is always the chance of spreading the virus to other parts of the body. Diagnosis is clinical and can be confirmed by histopathological examination. None of the many treatment options have been proved to be 100% effective.<sup>1</sup> Periungual warts are difficult to treat/cure because of the involvement of the

nail and/or nail bed leading to the possibility of deforming or damaging the nail apparatus including nail bed and matrix. Recurrence is commonly observed.<sup>2</sup> Most treatment options for warts involve the physical destruction of the infected cells, i.e., they are not virucidal. Occlusion Therapy involves the application of antiseptics, steroids, etc., under either wet or dry wrap dressings. It cools the skin, enhances hydration, increases topical agents' penetration and acts as a barrier to external antigens and trauma. It probably acts by enhancing the immune response by local irritation.<sup>3</sup> It is postulated that the sweat and the water released in the area accumulates inside the occluded space, increasing its humidity, producing maceration and damaging the epidermal barrier. The macerating and keratolytic response helps in more efficient penetration of the drug, causing quicker regression of the lesion.<sup>4</sup> Occlusion is less costly than most therapies; particularly useful in the pediatric age group compared to the more painful procedures such as cryotherapy. 5-fluorouracil (5-FU) is an antimetabolite, a pyrimidine analog. 5% ointment is used for the topical treatment of warts. 5FU may be combined with 10% salicylic acid under occlusion. Erosion, erythema, hyperpigmentation, onycholysis are the adverse effects.<sup>5</sup> Intralesional injections have been used in many dermatological disorders like acne cysts, keloids, etc., it uses the ability of the body to mount an immune response- a delayed-type (type IV) hypersensitivity to several antigens and also the wart tissues. This treatment modality is associated with the production of Th1 cytokines which in turn activate the natural killer and cytotoxic cells to eradicate the human papilloma virus.<sup>6</sup> A unique feature of this mode of treatment is that it clears not only the local wart lesions but also distant warts, unlike other traditional warts therapies.<sup>6</sup> It has been found that the responders to this type of treatment have a significant peripheral mononuclear cell proliferation compared to those who do not respond to therapy. Immunotherapy with intralesional injection is particularly useful in the pediatric population in whom the traditional methods like cryotherapy induced pain and other adverse effects preclude proper and complete treatment course. The most common adverse events are injection site reactions and flu-like symptoms, probably due to inadvertent injection of the antigen into the circulation with the resultant elaboration of the cytokines. They respond well to non-steroidal anti-inflammatory drugs. Rare events include painful purple digits; post immunotherapy revealed cicatrix (PIRC).<sup>6</sup> Tuberculin or the purified protein derivative (PPD) is a glycerol extract of the tubercle bacillus. For intralesional immunotherapy of warts, 1 TU strength is used.

### **Aim**

- To evaluate and compare the efficacy of intralesional immunotherapy using purified protein derivative (PPD) and topical 5-FU under tape occlusion for the treatment of periungual warts.

### **METHODS**

Open labelled prospective study with the prior approval of the Institutional Ethics Committee of Rajiv Gandhi Government General Hospital (RGGGH), Chennai was conducted from January 2012 to July 2012. Written informed consent was obtained from the patients/guardian.

Patients with periungual warts attending the Dermatology out Patient Department of RGGGH, Chennai. A total of fifty patients were included in the study.

#### ***Inclusion criteria***

Patients of all genders aged 12 years and above with periungual warts attending the dermatology OPD of Madras Medical College and RGGGH, Chennai. Patients who have warts in areas other than those in the periungual region are also included in the study.

#### ***Exclusion criteria***

Patients aged less than 12 years, pregnant/lactating women, HIV positive patients, patients with known immunoregulation disorders and/or those on steroids, cancer chemotherapeutic drugs or other immunosuppressive and immunomodulatory drugs were excluded. Patients with known allergy to purified protein derivative and/or 5-fluorouracil, those who had been treated earlier for periungual warts, and those with history of tuberculosis were excluded. Patients who were not willing to participate in the study and those who were lost to follow-up within 3 months of starting study/treatment were also excluded.

#### ***Treatment protocol and methodology***

Fifty patients with periungual warts were selected randomly. Diagnosis of periungual warts was clinical. After ascertaining the history of allergies to PPD and/or 5-fluorouracil they were randomly assigned into two groups: Group 1- intralesional immunotherapy with PPD; Group 2- topical 5% 5-fluorouracil under tape occlusion. For both groups, details like the location, numbers and dimension of the warts are recorded. The presence of other warts (other than the periungual warts) was also noted. The lesions are photographed. For Group 1 (PPD) patients, intralesional injection of PPD is given in a randomly selected lesion every 3 weeks for a maximum of six sittings. 27 gauge intradermal needles was used for the injection. The volume of the PPD to be injected was determined by the Mantoux reactivity (size of induration).

For Group 2 (topical 5% 5-FU under tape occlusion) patients, patients are advised to apply 5% 5-FU applied on the lesion(s) selected for study. It is applied under occlusion daily during the night and left for 12 hours.

This is done for a period of 3 months. Patients are advised to come for follow-up every 2 weeks.

**Table 1: Distribution of size of test reaction.**

Size of test reaction (mm)	Volume of PPD to be injected (ml)
5 – 20	0.3
21 -40	0.2
>40	0.1

For both groups - the complete disappearance of the lesion is taken as clearance. During every visit the size of the lesion is documented. Also, the status of the other warts is documented – other periungual warts for which the treatment is not applied and also the warts in other areas. After completion of the treatment, and after declaration of the cure– follow-up is done for the next three months to look for recurrence.

Data analysed using SPSS win 2 software, under a statistician's supervision. The statistical significance was set at a level of 0.05 and the confidence interval was set at 95%.

## RESULTS

The mean age in the intralesional purified protein derivative group was 22.68 years. The minimum age was 12 years and the maximum was 45 years. 14 out of the 25 in the PPD group were males.

**Table 2: Duration of warts in the PPD group (n=25).**

Duration	No. of patients	Percentage (%)
≤6 months	5	20
6 months to 1 year	10	40
1 to 2 years	8	32
2 to 3 years	1	4
≥3 years	1	4

Most of the patients had their lesions for less than 2 years, the majority of them within one year duration (Table 1). All the patients (n=25) in the intralesional PPD group had multiple warts. Only 3 patients had more than 10 warts. About 88% of the patients had less than 10 warts. A majority of the patients in the intralesional PPD group had warts in areas other than in the periungual areas. The volume of the PPD to be intralesionally injected into the warts was determined by the Mantoux reactivity done prior to the procedure. The mantoux reactivity is measured as the size of induration, (measured perpendicular to the long axis of the forearm) after 48 hours of PPD injection in the flexor aspect of the forearm.

The lesions are said to be cured if all of them disappear by the end of 6 sittings (i.e., 18 weeks – each sitting -

every 3 weeks) or during anytime before 18 weeks. 88% of the total number of patients (22 out of 25) selected for the intralesional PPD injection group were cleared of their periungual and other warts within 18 weeks i.e., within 6 sittings of injections. Out of the 25 patients in the study group, none of them – both those who were cured and those who were not - reported/had any adverse reactions/complications.

The age range of patients in the topical 5 FU group was between 15 years and 49 years. The mean age of this group was 29.68 years. Majority of the patients (84% of the total number) were below 40 years of age. 56% (n=14) were male. Most of the patients in this group had single periungual wart. Only 2 patients had more than one lesion. All the patients in the group did not have warts in any other area other than the periungual region. Regarding duration, 6 of the 25 had the lesions for less than 6 month, 9 had the wart for 6mo to 1 year, 9 had them for 1-2 years, and 1 had the wart for more than 2 years.

All patients in this group were advised daily application of 5% 5-fluorouracil cream under tape occlusion, to be left overnight. They were periodically reviewed fortnightly. At the end of three months of treatment, they were reviewed for clearance of the lesion. Only five of them had their lesions cleared. The cure rate of this group was only 20%. Only 5 out of the total of 25 patients had their lesions cleared. Of the total no. of 25 persons included in the study, 20 were not cleared of their lesions even after completion of therapy i.e., 3 months of daily occlusive application of 5% 5-fluorouracil. Only five persons had their lesions cleared. The time taken for clearance was uniformly distributed and it didn't show any pattern. Only 2 out of the 25 persons had complications. One of them had paronychia and the other had erythema, itching. Both of them were excluded from the study and referred for further management. There were no recurrences after 3 months of completion of treatment and declaration of clearance in all the five patients.

### **Comparison of the two groups – intralesional PPD vs topical 5% 5-fluorouracil under occlusion**

There were no major differences in the mean age and the gender ratio of both groups. In this study, Group 1 (intralesional PPD) gave a significantly higher cure rate (88%) than that of topical 5-fluorouracil under occlusion (20%) with a p value of 0.019 which is < 0.05, which is statistically significant.

The mean time taken for the resolution of the periungual warts was 6.6 weeks for group 1 (intralesional PPD) compared to 9.8 weeks for group 2 (topical 5-fu under tape occlusion). Group 1 thus had higher cure rate and also offered faster cure than that of Group 2.

**Table 3: Comparison of cure rates of intralesional PPD and topical 5% 5-fluorouracil under tape occlusion.**

Group	Cured	Not cured	P value
PPD group	22	3	<0.0001
	88%	12%	
5-FU group	5	20	
	20%	80%	

## DISCUSSION

Periungual warts are resistant to common treatment modalities. In our study, we compared the treatment of periungual warts with intralesional purified protein derivative— a novel modality and a conventional treatment modality - topical 5% 5-fluorouracil under tape occlusion.

The mean age in the intralesional PPD group is 22.68 years, and that of the 5-FU group was 29.68 years. Both groups had similar age groups. The mean age was also close, comparable to the mean age and the age range of the study done by Wananukul et al (mean age 20 years) using intralesional PPD and Ibraheem et al (mean age 20.35 years) with intralesional PPD.<sup>7,8</sup> In the PPD group, the cure rate was higher in younger patients - 90% of the patients who responded were less than 30 years old. This observation is consistent with that of Chandrasekar, who reports that older persons are less likely to respond to this treatment modality than younger persons probably because of the less robust immune responses with older age groups.<sup>6</sup> In contrast, there was no such difference in cure rate according to the age in the 5 FU group.

In both groups, males constituted the majority. The gender ratio of both groups was similar, i.e., male: female =14:11. There was no specific correlation between the gender and the response to treatment in both the groups.

Duration of warts seemed to have little significance to the cure rate in both groups.

In 5 FU group, patients with the single or the minimal number of warts were preferred, since this treatment modality will cure only that lesion which is being treated. Out of 25 patients, 22 had the only single lesion. For PPD group, all had more than one lesion, since this is the only treatment modality that not only clears the local warts but also clears distant warts, unlike other therapies.

Around 50% of the patients had more than ten lesions in PPD Group. In a similar study done by Wananukul et al, more than 50% of patients had multiple lesions.<sup>7</sup> Another important aspect is that in our study under the PPD group, 84% of the patients had warts in other areas in addition periungual areas. In those patients, in addition to periungual warts, warts in other areas also cleared upon successful completion of treatment, emphasizing the fact

that for patients with multiple warts, intralesional immunotherapy using PPD offers better and wholesome treatment option compared to the conventional modalities. In the study done by Wananukul et al in patients with multiple warts, lesions that were not treated also disappeared in 87% of the patients.<sup>7</sup> In contrast, Chandrashekar reported clearance of 47% for warts injected directly and 34% cure rate for distant warts.<sup>6</sup>

Patients in Group 1 (PPD) had a cure rate of 88%. This is comparable to the cure rate of 93% reported by Wananukul et al and a cure rate of 94.1% reported by Ibraheem et al.<sup>7,8</sup>

Among the 25 patients in the 5 FU group, only 5 patients were cured of their lesions on their completion of treatment, i.e., at the end of the 3-month continuous application of 5-FU under tape occlusion. The cure rate was 20%. This is in contrast to the 44% cure rate reported by Dogra in a study involving the comparison of 5-FU with electrosurgery.<sup>9</sup> One possibility that should be considered is that despite periodical review once in every 2 weeks and proper periodic advice regarding the methods regarding this treatment modality, patients need to be highly motivated and strictly adherent to the regime without any skipping of the doses and proper application of the tapes, and the results largely depended upon the patients - this in contrast to those in the PPD group in whom the treatment part (injection) was exclusively carried out by the investigator, the patients attendance being the only requirement from the patient side. Thus while deciphering the lower rate of success in the 5-FU group the above said factors should be considered.<sup>10</sup>

In group 1 (PPD), there were no complications for all the patients, those who were cured and for also those who were not cured. In group 2 (5-FU) patients, two patients had complications. After almost two weeks of application, one had edema, pain, and erythema. Another patient had paronychia after 4 weeks of treatment. Treatment was stopped for those patients, released from this group, and referred for other treatment options.

In Group 1, around 73% of the patients had their lesions cleared within 6 weeks, i.e., 2 sittings of injections. All patients (22 out of 25) had their lesions cleared by the 12th week of therapy, i.e., 4 sittings (injections). Only 3 out of the 25 patients were not cleared of their lesions even after 6 sittings, i.e., 18 weeks – they were declared, “Not Cured.” There was no other correlation with regard to the duration of treatment required for the clearance of lesions like age, duration of lesions, etc., in Group 2 (5-FU), the duration of treatment required for the cure was not clustered as in group 1 but spread from 6 weeks to 12 weeks. One patient was cured by the 6th week. Two patients had to undergo 12 weeks of treatment for cure. There were no relations of the duration of treatment with the age of the patient, the duration of the lesions before starting treatment, etc.<sup>11</sup> In group 1 (PPD) and group 2 (5-

FU), none of those cured had recurrent lesions after 3 months of follow-up after having been declared cured.

## CONCLUSION

The cure rate of intralesional PPD group (88%) was much higher than that of topical 5% 5-fluorouracil under tape occlusion group (20%). In Group 1, the younger patients responded well and faster. There was no difference in cure rate among age groups in Group 2. For patients with multiple warts and those who had warts in areas other than in the periungual areas, intralesional PPD offered the better option as it helped to cure warts in other areas also in addition to those in the periungual region. In contrast, the 5-FU treatment group had been cleared only of those lesions for which the drug under occlusion was applied. Complications were not noted in Group 1 (intralesional PPD). The 5-FU group reported edema, erythema, pain, Paronychia. The complication rate was 8% for this group. In our study, both groups did not have recurrent lesions at 3 months follow up after the declaration of cure.

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