

Efficacy of Intralesional 5-Fluorouracil in Treatment of Palmo-Plantar Warts

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ABSTRACT

Background: Palmo-plantar warts are difficult to treat and currently no single treatment is effective in all the patients. The present study to evaluate the efficacy and safety of intralesional 5-fluorouracil in the treatment of palmo-plantar warts in Indian patients.

Materials and Methods: This placebo-controlled study with multiple palmo-plantar, categorized in groups A and B of 25 patients each. Alternate patients were included in groups A and B and treated respectively with intralesional 5-fluorouracil solution and normal saline as placebo, fortnightly for maximum up to two injections. Patients were followed up fortnightly up to 12 weeks, and then quarterly for 1 year. If warts persisted after 12 weeks of starting treatment, it was considered a failure. Statistical analysis was done by the chi-square test using M-stat software.

Results: Group A and B patients were having 65 warts and 60 warts, respectively. The cure rate in group A and B patients was 95.38% and 13.33%, respectively, after one or two injections within 12 weeks. The difference in the cure rate between two groups was statistically highly significant ($p < 0.001$). In group A patients, a haemorrhagic eschar was formed which gradually healed in without atrophy or

pigmentation; this phenomenon was not seen in group B. Only moderate pain was observed by most of the patients during injection in both groups.

Conclusion: The intralesional injection of 5-fluorouracil is highly effective and safe in palmo-plantar warts.

KEYWORDS: 5-fluorouracil, Intralesional injection, Palmo-plantar.

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INTRODUCTION

Warts or verrucae are benign proliferations of skin and mucosa caused by infection with human papilloma virus.¹ Clinical appearance of warts is variable and depends to some extent on the type of HPV involved and the site of infection.² The commonly used treatment modalities for warts involve destruction of the epidermis infected with virus. These include topical preparation or surgical approaches. The commonly used treatment modalities for warts involve topical application of salicylic acid,³ glutaraldehyde,⁴ formaldehyde,³ and retinoic acid⁵ but they require months of treatment. Electrocoagulation,⁶ cryotherapy,⁷ CO₂ laser,⁸ pulse dye laser,⁸ photodynamic therapy,⁹ and radiofrequency¹⁰ have also been used. Pain related to treatment, side effects and cost can be determining factors in choosing a therapy.¹¹ 5-Fluorouracil is an antimetabolite that suppresses cell division and causes cell cycle arrest.¹² Topical 5-fluorouracil is used in the treatment of warts but is not very effective.¹³ Intralesional injection of 5-fluorouracil permits higher drug concentrations throughout the lesion and previous study has shown its effectiveness in treatment of warts.¹⁴

MATERIALS AND METHODS

The present clinical trial was conducted between December 2013 and August 2014 in the Department of Dermatology. A written

informed consent was taken from all the patients and ethical clearance was obtained from appropriate authorities of the college. Fifty patients with 1-5 palmo-plantar, without any history of previous treatment, whose age ranged from 15 to 50 years, were included in the present study. Patients with more than 5 warts were excluded to prevent untoward side effects as safety profile of the drug was also being evaluated. Pregnant women and patients with a history of Raynaud's disease or any other systemic illness were also excluded from the study. Diagnosis was made on the basis of history and typical clinical features. Patients were categorized into two groups (groups A and B) of 25 each. Alternate patients were included in groups A and B which were treated with intralesional 5-fluorouracil and normal saline (placebo), respectively.

A solution was created containing 4 mL of 50 mg/mL 5-fluorouracil and 1 mL of a mixture of 20 mg/mL (2%) lidocaine and 0.0125 mg/mL epinephrine. Each wart and the adjacent skin were cleansed with isopropyl alcohol. The fresh solution was injected strictly intralesionally till blanching of the lesion occurred.

After 2 weeks of 5-fluorouracil injection, a black, ecchymosed eschar developed which was pared, and residual warts if present were injected a second time. In the controlled group, normal saline was injected in a similar manner as the 5-fluorouracil solution.

After each injection antibiotics and anti-inflammatory agents were prescribed for 5 days to prevent secondary infection and post injection pain. The patients were followed fortnightly up to 3 months and then quarterly up to 1 year. Results were evaluated on the basis of clinical improvement. Patient was considered as cured if there was complete absence of

clinically apparent wart. Persistence of wart after 3 months of last injection was taken as failure of treatment. A chi-square test was applied for statistical analysis using M-stat software. Routine haemogram, liver function tests, renal function tests and X-ray of the chest were done before and after 3 months of treatment.



Figure 1a: Wart present on left palm & index finger



Figure 1b: Warts regressed without any scarring or pigmentation

Site	Group A		Group B	
	Cured after 1 injection	Cured after 1 or 2 injections	Cured after 1 injection	Cured after 1 or 2 injections
Palmar	18 (81.82%)	21 (95.45%)	2 (10.53%)	3 (15.79%)
Plantar	36 (83.72%)	41 (95.35%)	3 (7.32%)	5 (12.2%)
Total	54 (83.08%)	62 (95.38%)	5 (8.33%)	8 (13.33%)

Table 1: Distribution of Number of warts according to site

Site	Group A	Group B	Total
Palmar	22 (33.85%)	19 (31.67%)	41 (32.8%)
Plantar	43 (66.15%)	41 (68.33%)	84 (67.2%)
Total	65 (100%)	60 (100%)	125 (100%)

Table 2: Response of warts at different locations in Groups A and B after 12 weeks

RESULTS

One hundred and twenty-five warts (125) were present in 50 patients which were included in the present study. There were 29 males and 21 females whose mean age was 25.3 years and 26.7 years, respectively. Group A and B patients were having 65 and 60 warts, respectively [Table 1]. The baseline parameters (age, sex, sub-distribution of warts) between the two groups were

statistically comparable, and no significant statistical difference was observed. A total of 62 (95.38%) of the 65 warts treated with intralesional 5-fluorouracil in group A showed complete resolution after one or two injections within 12 weeks [Table 2]. A total of 8 of the 65 warts in group A required a second injection for cure. In all the patients, hemorrhagic eschar was taken as the primary outcome at the first visit. In group A, two warts recurred after initial

clearance during 1 year of follow-up. Of 60 warts treated with normal saline (group B), only 8 (13.33%) showed disappearance of the lesion within 3 months, but on further follow-up 15 (25%) warts disappeared at the end of 1 year. The difference in the resolution rate at the end of 12 weeks was statistically highly significant ($p < 0.001$) between groups A and B. The ecchymosed eschar did not develop in warts treated with normal saline. There was no change in haematological or biochemical investigation after 3 months of treatment in both groups. No side effects were observed in any of the patients in both the groups apart from pain at the site of injection which varied in intensity according to the perception of the patients from mild to severe and subsided with the use of anti-inflammatory agents. Warts regressed without any scarring or pigmentation [Figure 3a-b]. None of the patients experienced any systemic toxicity.

DISCUSSION

Warts at palmo-plantar site are difficult to treat and the search for effective treatment modalities has been going on since a long time. 5-Fluorouracil is an antimetabolite that suppresses cell division and causes cell cycle arrest.¹² As a treatment for warts, topical 5-fluorouracil is primarily of historical interest, with most of the trials carried out in the 1970s and 1980s. Evidence provided by these trials was limited by the heterogeneity of the methods and designs. Overall, this treatment was not considered to be very effective.¹³

Intralesional injection of 5-fluorouracil, lidocaine, and epinephrine (5-FU+LE) has several advantages over topical 5-fluorouracil cream or intralesional injection of 5-fluorouracil alone. Intralesional injection of 5-fluorouracil permits higher drug concentrations throughout the lesion. The addition of lidocaine makes the injection less painful. The usual dose of 5-fluorouracil for systemic chemotherapy of solid tumors is 300 to 1,000 mg/m² intravenously or continuous infusion.¹⁵ The mean administered dose of intralesional 5-fluorouracil for the treatment of warts is usually in the range of 2 to 6 mg, that is, less than 1/150th of the amount of systemic therapy. Therefore, the systemic adverse effects of 5-fluorouracil are eliminated.

Study by Yazdanfar et al¹⁶ showed a response rate of approximately 82.3% (64.7% complete response, 17.6% partial response) versus 55.9% in the placebo group in treatment of common warts. Swinehart et al¹⁷ and Kontochristopoulos et al¹⁸ used intralesional 5-fluorouracil for the treatment of condylomata acuminata and keloids. In the present study only palmo-plantar warts were included; hence the results are not comparable to these studies.

Iscimen et al¹⁴ carried out a study on use intralesional 5-fluorouracil in treatment of common, plantar and periungual warts in 2004. Seventy-six patients with a total 315 verrucae were randomized to receive either a 5-fluorouracil or normal saline injection into the paired verrucae in the same patient. The mixture of 5-fluorouracil (4 cm³, 50 mg/mL), lidocaine (1 cm³, 20 mg/mL) and epinephrine (0.0125 mg/mL) was injected into the wart using a mantoux needle. Each lesion was infiltrated once a week for up to a maximum of 4 weeks. Overall clearance rates of 88% (70% complete response and 18% partial response) were reported. Out of the total 57 plantar warts treated with intralesional 5-fluorouracil solution complete response was observed in 54% lesions and partial response in 28%. Pain and burning were noted by most

patients immediately after injection. The adverse effects observed in some cases were erythema, edema, hyperpigmentation, hypopigmentation, ulceration, necrosis, and scarring. These reactions subsided gradually and none of them were reported to cause significant cosmetic sequelae. In the present study, a total of 65 palmo-plantar warts were injected with 5-fluorouracil, lidocaine and epinephrine mixed in the same ratio as in the above mentioned study and intralesional injections were given every 2 weeks up to a maximum of two injections. The cure rate observed in present study was 95.38% which is quite high as compared to 54% complete cure rate in plantar warts reported in the previous study. Only side effect noted was pain at the site of injection. The difference in results and side effects may be due to the fact that injections were given at a gap of 2 weeks in the present study as opposed to weekly injections given by Iscimen et al¹⁴ which allowed the reaction of previous injection to settle down before the next injection was given. Also the black, ecchymosed eschar formed after each injection was pared before giving the next injection in the present study. Study by Iscimen et al¹⁴ showed complete clearance in 19% of the plantar warts treated with normal saline injection whereas in the current study 13.33% cure rate was observed in the normal saline group.

The results of the present study are limited by the low number of cases included in the study and further studies are required to ascertain the safety of injection 5-fluorouracil at higher doses in more number of warts. Also safety of the drug needs to be evaluated in the pediatric population.

CONCLUSION

Intralesional 5-fluorouracil is highly effective, safe and cheap alternative in the treatment of palmo-plantar warts.

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