A Comparative Analysis of Efficacy of Intraleisonal Mumps-Measles-Rubella Vaccine Versus 5-Fluorouracil in the Treatment of Palmoplantar Warts

Abstract
Background: Palmoplantar warts are quite resistant to treatment, so treating them is a challenge as ablative modalities lead to pain, temporary immobility, secondary infections, and scarring. The treatment of warts using immunotherapeutic methods and cytotoxic methods is being increasingly used to overcome drawbacks in the treatment of warts. Aim: To evaluate the efficacy and safety of intraleisonal mumps-measles-rubella (MMR) vaccine versus 5-fluorouracil (5-FU) in the treatment of palmoplantar warts. Materials and Methods: A total of 36 patients were divided into two groups of 18 each, MMR and 5-FU groups, respectively. The patients in the MMR group were given 0.1 ml - 0.5 ml of intraleisonal MMR vaccine in each lesion depending on the dimensions of the lesion and was repeated at 2 weekly intervals until complete clearance or a maximum of six doses. The patients in the 5-FU group were given 0.1 ml - 0.5 ml of intraleisonal injection of a solution containing 4 mL of 250 mg/mL of 5-FU and 1 mL of a mixture of 20 mg/mL (2%) lidocaine and 0.0125 mg/mL of epinephrine, which was given at 2 weekly intervals until complete clearance or maximum six doses. Results: In our study, warts had resolved in all 18 (100%) patients belonging to the MMR group by the 12th week, whereas 11 (61.11%) patients still had warts among the patients belonging to the 5-FU group (i.e., warts had resolved only in 7 (38.89%) patients at the end of 12th week), which was found to be statistically significant (P-value < 0.05). Limitation: Smaller sample size and lack of follow-up to evaluate for possible recurrence. Conclusion: MMR vaccine is a safe and effective treatment modality for palmoplantar warts compared to 5-FU.

Keywords: 5-FU, MMR, warts

Introduction
Viral warts are cutaneous and sometimes mucosal lesions caused by various strains of human papilloma viruses. Palmoplantar warts are quite resistant to treatment because of their endophytic growth pattern and very thick cornified layer. It has been found that cell-mediated immunity (CMI) plays a major role in wart resolution, which highlights the need for immune protection against human papilloma virus (HPV) infection and has directed attention towards the stimulation of the patient’s immune system, particularly CMI to eradicate viruses. Both intraleisonal mumps-measles-rubella (MMR) vaccine and intraleisonal 5-fluorouracil (5-FU) have been used previously for the treatment of warts. But there is no comparative evaluation done so far between 5-FU and MMR in the treatment of warts. So, we intended to evaluate which modality is more efficacious and faster in terms of resolution.

Materials and Methods
The present study was a prospective comparative interventional study carried out from January 2020 to December 2020 in the outpatient department of dermatology in a tertiary care center after approval from the institutional ethics committee. The study included 36 patients clinically diagnosed as having palmoplantar warts. The patients were assigned randomly into two groups of 18 each, using a randomization table derived from R software. Exclusion criteria were age less than 12 years, pregnant and lactating females, any evidence of immunosuppression, any systemic/local infection, and hypersensitivity to 5-FU, lignocaine, or MMR.

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Informed consent was obtained from each patient who participated in our study. Age, sex, duration of warts, site of warts, number of warts, and prior treatment history were recorded. At each visit, the lesions were photographed and were measured using a Vernier caliper.

In the MMR group, the patients were injected at the base of each wart with 0.1ml - 0.5ml of freeze-dried MMR vaccine after reconstitution with 0.5 mL of the provided diluent. In the 5-FU group, the patients were injected with a solution containing 4 mL of 250 mg/mL of 5-FU and 1 mL of a mixture of 20 mg/mL (2%) lidocaine and 0.0125 mg/mL of epinephrine, 0.1ml - 0.5ml to the base of each wart.[4,5] The injections were repeated every 2 weeks for a maximum of six doses or until complete clearance, whichever was earlier.[4,5]

The possible clinical outcomes were analyzed by taking photographs and measuring warts at each visit using a Vernier caliper and assigning a Visual Analogue Scale (VAS)[6,7] score [Table 1].

**Statistical analysis**

The statistical analysis was done by R software version 4.0.4 and Excel. To compare the age, gender, type of warts, duration of warts, adverse effects, and clearance of warts according to VAS score, Chi-square test was used. The mean age and mean duration of warts between the two groups were compared using a t-test. The number of warts between the two groups was compared using Mann–Whitney test. The VAS score between two groups at different time points was compared using Friedman’s test. A P value less than or equal to 0.05 was considered statistically significant.

**Results**

All 36 patients completed the study. The age of the subjects ranged from 14 to 56 years with a mean age of 26.38 ± 9.47 years. Only patients with palmoplantar warts were included. The most common type of wart was the endophytic variant, followed by subungual warts and mosaic warts. The mean number of warts in the 5-FU group was 2.44 ± 2.55, with a minimum of 1 wart and a maximum of 11 warts. The mean number of warts in the MMR group was 3.17 ± 2.96, with a minimum of 1 wart and a maximum of 13 warts. The mean duration of warts in the 5-FU group was 7.44 ± 5.93 months, with a minimum duration of 1 month and a maximum duration of 24 months. The mean duration of warts in the MMR group was 7.17 ± 6.96 months, with a minimum duration of 1 month and a maximum duration of 26 months [Table 2].

In the MMR group, the complete clearance of warts was seen in 100% (18) patients by the end of the study period (12 weeks, 6 doses of injection). By the 4th week (that is, after evaluating the outcome of previous 2 injections), seven (38.89%) patients had complete clearance of warts. By the 6th week (i.e. after evaluating the outcome of previous 3 injections), six more patients (7 + 6), that is a total of 13 (72.22%) patients had complete clearance of warts, and a VAS score of 75%–99% was seen in three (16.67%) patients [Figure 1a, 1b]. By the 8th week (i.e. after evaluating the outcome of previous 4 injections), 18 (100%) patients had complete clearance of warts [Figure 2a, 2b]. By the end of 8 weeks itself, none of the patients in the MMR group had residual warts [Table 3].

In the 5-FU group, out of 18 patients, only 7 (38.89%) patients had complete resolution of warts by the end of 12 weeks of intervention (i.e., a total of six injections). By week 6, one (5.56%) patient had complete clearance of warts. By week 8, four more patients, (4 + 1), that is a total of five (27.78%) patients had complete clearance of warts, and a VAS score of 75%–99% was seen in one (5.56%) patient [Figure 3a, 3b]. By the end of 12 weeks (i.e. 6 injections), 11 (61.11%) patients had residual warts [Figure 4a, 4b]. [Table 3].

In our study, from the VAS score, we have observed that warts had resolved in all patients (100%) belonging to the MMR group by the 12th week, whereas 61.11% still had warts among the patients belonging to the 5-FU group (i.e., warts had resolved only in 38.89% patients at the end of 12th week), which was found to be statistically significant (P-value < 0.05) [Table 4].

| Table 1: Visual Analogue Scale (VAS) score |
|------------------------------------------|
| VAS Score | Description                              |
|-----------|------------------------------------------|
| VAS 100%  | Complete disappearance of lesions and appearance of normal skin. |
| VAS 75%–99% | Partial clearance i.e. reduction in number and size of warts, few residual warts are still visible. |
| VAS 50%–75% | Some reduction in size, but no decrease in the number of warts. |
| VAS less than 50% | No change in the number and size of warts. |

| Table 2: Clinico-demographic data of the subjects |
|-----------------------------------------------|
| Parameters | MMR Group | 5-FU group |
|------------|-----------|------------|
| Age        | Number of patients | Number of patients |
| less than 20 years | 9 (50%) | 3 (16.67%) |
| 20-30 years | 6 (33.33%) | 10 (55.56%) |
| 30-40 years | 2 (11.11%) | 3 (16.67%) |
| 40-50 years | 0 | 1 (5.56%) |
| 50-60 years | 1 (5.56%) | 1 (5.56%) |
| Sex        | Number of patients | Number of patients |
| Female     | 6 (33.33%) | 6 (33.33%) |
| Male       | 12 (66.67%) | 12 (66.67%) |
| Duration of warts | Number of patients | Number of patients |
| Less than 6 months | 13 (72.22%) | 9 (50%) |
| 6-12 months | 3 (16.67%) | 8 (44.44%) |
| More than 12 months | 2 (11.11%) | 1 (5.56%) |
| Type of wart | Number of patients | Number of patients |
| Palmar warts | 7 (38.89%) | 11 (61.11%) |
| Plantar    | 10 (55.56%) | 7 (38.89%) |
| Palmar and plantar | 1 (5.56%) | 0 |
In our study (n = 36), 100% of the patients in both MMR and 5-FU groups complained of pain during injection. Hyperpigmentation around the injected site was noted in four (11.11%) cases in the 5-FU arm [Table 4].

**Discussion**

It has been found that CMI plays a major role in wart resolution, which highlights the need for immune protection against human papilloma virus (HPV) infection and has directed attention towards the stimulation of the patient’s immune system, particularly CMI to eradicate viruses. So, immunotherapeutic modalities are being increasingly used to treat warts.[4]

5-FU is an antimetabolite drug that inhibits DNA and RNA synthesis and may also function as an immunomodulatory drug. 5-FU suppresses cell division and causes cell cycle arrest.[5] 5-FU is a fluorinated pyrimidine antimetabolite that inhibits DNA synthesis as well as RNA processing.
and thus causes cell cycle arrest and decreases epidermal proliferation, thus helping in decreasing the proliferation of wart tissue. It is a nucleic acid synthesis inhibitor. It inhibits the nucleotide synthetic enzyme, thymidylate synthetase thereby blocking the synthesis of pyrimidine thymidine, which is a nucleoside required for DNA replication.\(^\text{[5]}\) This mechanism of action allows intralesional 5-FU to be utilized in the treatment of viral warts caused by human papilloma virus (HPV).\(^\text{[5]}\) Intralesional injection of 5-FU permits higher drug concentrations throughout the lesion.\(^\text{[5]}\)

Intralesional MMR vaccine immunotherapy employs the ability of the immune system to recognize viral antigens that induce a delayed-type hypersensitivity reaction not only to the antigen but also against the human papilloma virus, thereby increasing the ability of the immune system to recognize and clear HPV. Consequent to this, the stimulated immune response clears all the lesions on other body sites along with locally treated lesions.\(^\text{[4]}\)

When comparing immunotherapeutic methods with cytodestructive methods, it is found that scarring is seen in 30%\(^\text{[1]}\) subjects, recurrence of warts in 30%,\(^\text{[3]}\) and pain leading to morbidity is seen in 64%\(^\text{[1]}\) patients while using ablative methods to treat warts, whereas these adverse effects are not seen while using immunotherapy to treat warts.

Compared to other studies like the studies done by Chauhan et al.\(^\text{[6]}\) and Jartarkar et al.,\(^\text{[7]}\) our study had a longer period of intervention. In our study, the period of intervention and the total period of the study was the same, that is 12 weeks and no follow up was done afterward, whereas in Chauhan et al.\(^\text{[6]}\) study, the total period of intervention was 8 weeks followed by which the patients were followed up every 4 weeks for another 8 weeks. In the study done by Jartarkar et al.,\(^\text{[7]}\) the period of intervention was 6 weeks, and the patients were followed up for 3 months.

In the study done by Chauhan et al.\(^\text{[6]}\) in the treatment of common warts with intralesional MMR, 51/110 completed the study. Overall, 42 (82.4%) subjects showed complete resolution of warts by the end of the 16 weeks, i.e., 8 weeks of intervention (5 doses of injection), followed by which patients were followed up every 4 weeks for another 8 weeks. Nine (17.6%) patients showed partial clearance of warts. In the study done by Jartarkar et al.,\(^\text{[7]}\) in the treatment of recurrent warts with intralesional MMR, in the MMR group, \(n = 33\), complete clearance of warts was seen in 23 (70%) patients at the end of 6 weeks of intervention and 3 months of follow up. Good response was seen in two (6.1%) patients, and a minimal response was seen in one (3.1%) patient. In our study, we observed that warts had resolved in all patients (100%) belonging to the MMR group \(n = 18\) by the 12th week. We postulate that the differences in the sample size and period of intervention from the above studies could be one of the reasons for variation in the observations encountered in our study in the form of 100% resolution of warts in the MMR group in our study versus resolution rates of 82.4% and 69.7% in the studies by Chauhan et al.\(^\text{[6]}\) and Jartarkar et al.,\(^\text{[7]}\) respectively.

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Table 3: Distribution of VAS scores at different time points in both groups

| Groups         | VAS score                                      | Time Period   | P       |
|----------------|-----------------------------------------------|---------------|---------|
|                |      | Baseline  | Week 2  | Week 4  | Week 6  | Week 8  | Week 12 |        |
| 5-FU           | <50% (no change in number and size of warts)  | 18 (100%)    | 8 (44.44%) | 3 (16.67%) | 3 (16.67%) | 1 (5.56%) | 1 (5.56%) | <0.001* |
|                | 50%-75% (some reduction in size but no decrease in number of warts) | 0            | 10 (55.56%) | 15 (83.33%) | 14 (77.78%) | 11 (61.11%) | 7 (38.89%) |         |
|                | 75%-99% (Partial clearance)                   | 0            | 0       | 0       | 0       | 1 (5.56%) | 3 (16.67%) |         |
|                | 100% (complete disappearance of lesions and appearance of normal skin) | 0            | 0       | 0       | 0       | 1 (5.56%) | 5 (27.78%) | 7 (38.89%) |
| MMR            | <50% (no change in number and size of warts)  | 18 (100%)    | 7 (38.89%) | 0       | 0       | 0       | 0       | <0.001* |
|                | 50%-75% (some reduction in size, but no decrease in number of warts) | 0            | 11 (61.11%) | 9 (50%) | 2 (11.11%) | 0       | 0       |         |
|                | 75%-99% (Partial clearance)                   | 0            | 0       | 2 (11.11%) | 3 (16.67%) | 0       | 0       |         |
|                | 100% (complete disappearance of lesions and appearance of normal skin) | 0            | 7 (38.89%) | 13 (72.22%) | 18 (100%) | 18 (100%) |         |         |

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Table 4: Outcome of the study

| Treatment Groups | Therapeutic outcome   | Adverse effects |
|------------------|-----------------------|-----------------|
| MMR Group        | Eighteen (100%) patients had complete clearance of warts by the end of the study period. | nil |
| 5-FU Group       | Seven (38.89%) patients had complete clearance of warts, and 11 (61.11%) patients still had residual warts at the end of the study period. | Four (11.11%) patients had hyperpigmentation around the treated lesions. |

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Abbreviation: F-Friedman test, C-Chi square test, MC - Chi-square test with Monte Carlo simulation, *indicates statistical significance.
Yazdanfar et al. studied the use of intralesional 5-FU in the treatment of warts wherein only 34/40 subjects completed the study, and complete resolution of warts was seen in 22 (64.7%) patients at the end of 4 weeks of intervention and follow up at 1 month and 6 months. A partial resolution was seen in six (17.6%) patients, and no resolution of warts was seen in six (17.6%) patients at the end of the study period. Kamal T et al. (n = 40) employed a 2 weekly treatment regime with 5-FU, wherein a complete resolution of warts was seen in 30 (75%) patients after six doses of intralesional 5-FU. Three patients attained complete resolution of warts after the 3rd injection, 10 (25%) patients showed complete clearance of warts after the 4th injection, and 5 (12.5%) patients showed complete resolution after the 5th injection. However, in our study, only 38.89% (7) patients had complete clearance of warts in the 5-FU arm (n = 18), i.e., 61.11% (11) patients still had residual warts by the end of the study. This variation in our study could be attributable due to the type of lesions chosen by us i.e., palmpoplantar warts, which are endophytic, having a higher viral load along with thickened stratum corneum, which makes the penetration and delivery of 5-FU a little difficult. Also, some viral subtypes may respond differently to cytotoxic or immunotherapy.

In our study, pain while the injection was the only side effect seen in both MMR and 5-FU groups, and hyperpigmentation around the lesions was seen only in the 5-FU group.

5-FU is an antimetabolite drug that causes cell cycle arrest, whereas MMR is an immunotherapeutic drug that induces the body’s own immune response against HPV, thus helping in clearing the HPV laden cells. 5-FU has a very localized, cytotoxic effect on HPV-laden cells, whereas MMR vaccine induces a delayed type of hypersensitivity, which helps in clearing HPV-laden cells. We have postulated that because of this difference in mechanism of action, the MMR vaccine showed better efficacy than 5-FU in our study.

Variation in the rate of resolution in comparison to other studies could be because of the type of warts chosen to be treated by us, i.e., palmpoplantar warts which have an endophytic growth pattern along with high viral load and very thick cornified layer as compared to other types of warts.

Treating palmpoplantar warts with modalities that are cyto-destructive like electrocautery or cryotherapy can cause a lot of patient morbidity in terms of pain, secondary infections, and temporary functional impairment; hence, our study aims to emphasize the use of immunotherapeutic modalities to overcome this issue.

A review of the literature available so far shows no such studies which have compared the safety and efficacy of cytotoxic methods with immunotherapeutic methodologies; hence, our study is one such attempt to compare a cytotoxic (5-FU) modality with an immunotherapeutic (MMR) modality, thus bridging the gap in the current literature.

Limitation
The limitation of our study was that the sample size was small (n = 36) and follow up of the patients beyond 12 weeks of the study period was not done, so the rate of recurrence of warts in the MMR and 5-FU groups could not be compared and also, only palmpoplantar warts were included in our study, so the effects of these therapeutic options on other types of warts could not be evaluated. Hence, trials with a larger sample size and ones that include different variants of warts are required to further evaluate the effects of MMR vs 5-FU in the treatment of warts.

Conclusion
Though both MMR and 5-FU are effective nonablative methods available in the dermatologist’s armamentarium for the treatment of warts, from the observations made in our study, we can conclude that intralesional MMR vaccine is a more efficacious therapy than 5-FU in the treatment of palmpoplantar warts.

Declaration of patient consent
The authors certify that they have obtained all the appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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