A Study to Evaluate the Role of Intradermal and Intralesional Measles, Mumps, Rubella (MMR) Vaccine in Treatment of Common Warts

Abstract

Background: Warts are common cutaneous viral infection with a wide range of therapeutic modalities. Various agents have been tried for immunotherapy in warts. Objectives: Determine the role of intralesional and intradermal measles, mumps, rubella (MMR) vaccine in the treatment of common warts; to compare the efficacy of intraleral versus intradermal MMR vaccine.

Methods and Materials: Patients diagnosed with verruca vulgaris were divided into two groups. In study group A, the individuals were injected with an intralesional MMR vaccine of 0.3 mL in the representative wart (largest) once in 3 weeks till there is complete clearance or maximum of four injections whichever is earlier, while in study group B, the individuals were injected with an intradermal MMR vaccine of 0.3 mL over the unilateral deltoid muscle area at similar intervals.

Results: There were 33 patients in each group. In group A, 10 (30.3%) patients showed complete, 9 (27.3%) marked, 6 (18.2%) moderate, 3 (9.1%) mild, and 5 (15.2%) no response. In group B, seven (21.2%) patients showed complete, one (3.0%) marked, one (3.0%) moderate, four (12.1%) mild, and 20 (60.6%) no response. There were minimal side effects in the form of pain, erythema, itching at the injection site in a few patients, only one patient had syncope. Conclusion: We conclude that the MMR vaccine is an effective and safe modality of treatment for verruca vulgaris without any serious adverse effects. Also, the intraleral route showed better results in comparison to the intradermal route when we consider the treatment of a representative wart.

Keywords: Immunotherapy, intradermal, intralesional, MMR vaccine, wart

Introduction

Warts are common cutaneous viral infections involving skin and mucous membranes characterized by benign proliferative hyperkeratotic lesions caused by human papillomavirus (HPV).[1,2] Spontaneous resolution occurs in 65–70% of warts within 2 years. About one-third or more do not resolve and become highly recalcitrant to treatment with different modalities, including the most aggressive therapies.[1] Poor prognostic indicators include warts in adults, long duration, the involvement of palms, soles, and numerous warts; such cases are frequently resistant to therapy and persist for a long time.[3]

Though apparently benign, they create a profound impact on a patient’s quality of life. Moderate to extreme discomfort is reported in 51.7% of patients, and social or leisure activities are affected to a moderate to an extreme degree in 38.8%.[4] Most patients seek treatment because of their unsightly appearance and often painful or tender nature.[3]

Although a wide spectrum of therapeutic modalities has been used for the management of warts, none has yielded consistently effective results or succeeded in preventing recurrence of warts. Destructive modalities act blindly on the HPVs present in keratinocytes of macroscopic lesions sparing the viruses present in other keratinocytes.[5,6] Moreover, in patients with numerous lesions, most of the time they do not have any effect on the distant lesions other than the treated ones, resulting in repeated and long-drawn treatment sessions.

Various systemic immunotherapies including contact sensitizers such as squaric acid dibutyl ester and diphenycryprole; proinflammatory cytokines such as interferons; immunomodulatory agents such as imiquimod; and immune enhancers such as imiquimod, interferons, and immuno-modulators.

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as oral levamisole, zinc sulfate have been attempted to stimulate the host immune response.\(^{[7]}\)

Intralosomal injections of vaccines and organic antigens have also been studied extensively with a variable degree of success. Antigens studied include *Candida albicans*\(^{[8]}\); measles, mumps, rubella (MMR)\(^{[1]}\); Trichophyton\(^{[9]}\); tuberculin antigens such as purified protein derivative (PPD)\(^{[10]}\); Mycobacterium w vaccine\(^{[3]}\) and Bacillus Calmette-Guerin (BCG) vaccine.\(^{[11]}\)

Immunotherapy is relatively inexpensive and can potentially lead to considerable improvement in warts, including widespread warts.

Although the mechanism is not entirely understood, these vaccines are thought to work by inducing a systemic T-cell-mediated response. Cytokines released from Th1 cells such as interleukin-2, 4, 5, 8 and interferon-gamma are predominantly increased in response to the injection of the vaccine. These cytokines activate cytotoxic and natural killer cells to eradicate HPV infection which clears not only local warts but also distant warts unlike traditional wart therapies. The intralosomal injection might also play a role in concentrating the local immune response; however, some argue that the trauma of injection alone may be enough to induce a sufficient immune response in immunocompetent patients.\(^{[1,12]}\)

This study was designed to explore the effectiveness, tolerability, and practicality of the MMR vaccine [Figure 1] used intralasionally and intradermally (deltoid area) to treat cutaneous warts. This method can be used in larger populations because of vaccine availability and safety. Also, the method of immunotherapy is less painful and cosmetically better tolerated than most of the destructive methods which are painful and leave scars.

### Aims and Objectives of the Study

To determine the role of intradermal and intralosomal MMR vaccine in the treatment of common warts.

To compare the efficacy of intradermal versus intralosomal MMR vaccine.

### Methods

#### Materials and Methods

#### Study setting

Patients of either sex having multiple common warts (verruca vulgaris) (>5) attending the outpatients' department (OPD) were screened and recruited in the study after satisfying the subject selection criteria.

#### Subject selection criteria

Patients attending the dermatology OPD were recruited if they satisfied the following criteria.

Inclusion criteria: Patients willing to consent, having multiple common warts (verruca vulgaris) (>5) at various sites of the body of the age group 12–40 years.

Exclusion criteria: Pregnant females, lactating mothers, children under 12 years, immunosuppressed individuals, patients having any chronic systemic illness, genital and perianal warts, ulcerated or inflamed warts, and patients with hypersensitivity to antigens.

#### Study design

The study was designed as an open-label, quasi-randomized, controlled, parallel-group trial of intralosomal versus intradermal MMR vaccine and was carried out at a single center.

#### Sampling technique

Consequent, convenient sampling.

### Methodology

Patients were selected and enrolled in the study after they met the subject selection criteria and gave written informed consent. Detailed history including name, age, sex, address, marital status, occupation, history of medication was noted along with their contact number. Selected patients were thoroughly examined and the number of lesions, size, site, duration of warts, type of warts, any previous treatment was recorded. Patients were divided into two groups, A and B on an alternate basis of presenting to the OPD.

In study group A, the patients were injected with an intralosomal MMR vaccine (0.3 mL) in the representative (largest) wart with an insulin syringe once in 3 weeks till there was complete clearance or a maximum of four injections (3 months) whichever was earlier [Figure 2a].

In study group B, the patients were injected with an intradermal MMR vaccine (0.3 mL) once in 3 weeks till there was complete clearance or a maximum of four injections (3 months) whichever was earlier [Figure 2b].

The site chosen for this intradermal injection was unilateral

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**Figure 1:** Measles, mumps, rubella (MMR) vaccine with diluent and insulin syringe
deltoid muscle area to study the effect of the vaccine if given at a distant site.

On each follow-up, patients were examined for evidence of partial or complete regression of their lesions by measuring the size of the wart, the appearance of any new lesions, to record any adverse effects and to ensure that the patients were not using any other treatment. Photographic documentation was done before the procedure and then periodically on follow-up.

Results were assessed at the end of 3 months. The primary outcome measure was the complete disappearance of all the lesions without residual scarring. Complete disappearance was said to have happened when the thickening, hyperkeratosis was no more evident and the normal skin markings return.

The results were assessed as:

Complete response: Disappearance of the wart(s) and appearance of normal skin.

Marked response: Partial responders who show a 75–99% outcome.

Moderate response: Partial responders who show a 50–75% outcome.

Mild response: Partial responders who show a 25–50% outcome.

No response: Those who show less than 25% outcome.

**Results**

The treatment groups were comparable at baseline regarding age, sex, education, occupation, and sites of warts. The study showed an urban dominant population with most patients in the mid-20s. There was no gender predominance. Most of the patients were students (57.6%) indicating an increased concern among this population to seek treatment of warts [Table 1].

Eight patients had a history of warts previously that resolved spontaneously or by various treatments.

**Table 1: Baseline and demographic characteristics of the subjects among the two groups**

|                          | Group A (n=33) | Group B (n=33) | p  
|--------------------------|---------------|---------------|---
| Age (years)              | 24.6±6.74     | 26.3±9.04     | 0.546
| Gender                   |               |               |   
| Male                     | 17 (51.5%)    | 20 (60.6%)    |   
| Female                   | 16 (48.5%)    | 13 (39.4%)    | 0.457
| Wart Site                |               |               |   
| Hands                    | 28 (59.6%)    | 19 (40.4%)    | 0.014
| Hands and feet           | 5 (26.3%)     | 14 (73.7%)    |   
| Wart duration (days)     | 858.3±860.04  | 1360±1556.93  | 0.221
| History of past wart     |               |               |   
| Yes                      | 4 (50%)       | 4 (50%)       | 1.00
| No                       | 29 (50%)      | 29 (50%)      |   
| History of MMR infection in past | | |  
| Yes                      | 8 (47.1%)     | 9 (52.9%)     | 0.778
| No                       | 25 (51%)      | 24 (49%)      |   
| Previous treatment       |               |               |   
| Yes                      | 15 (60%)      | 10 (40%)      | 0.205
| No                       | 18 (43.9%)    | 23 (56.1%)    |   
| Education                |               |               | 0.242
| Primary                  | 0 (0%)        | 4 (12.1%)     |   
| Middle                   | 2 (6.1%)      | 1 (3%)        |   
| High                     | 7 (21.2%)     | 9 (27.3%)     |   
| Senior Secondary         | 9 (27.3%)     | 5 (15.2%)     |   
| Graduate                 | 14 (42.4%)    | 14 (42.4%)    |   
| Post-graduate            | 1 (3%)        | 0 (0%)        |   
| Occupation               |               |               | 0.558
| Farmer                   | 3 (9.1%)      | 7 (21.2%)     |   
| Housewife                | 5 (15.2%)     | 4 (12.1%)     |   
| Laborer                  | 1 (3%)        | 1 (3%)        |   
| Student                  | 19 (57.6%)    | 19 (57.6%)    |   
| Shopkeeper               | 5 (15.2%)     | 2 (6.1%)      |   

SD: Standard deviation; MMR: Measles, mumps, rubella. *P value is from Mann-Whitney U test for age and wart duration (as they were not found to satisfy the criteria of normal distribution in the Shapiro-Walker test), Fisher’s exact test for the history of a wart; Chi-square test for gender, wart site, marital status, history of MMR, history of previous treatment

25 patients had a history of some form of treatment taken already for these warts with partial or no relief. Some of the patients had recurrence after chemical cautery and electrosurgery while others tried various home remedies or alternative medicines like homeopathy or Ayurveda without any obvious benefit. On the other hand, 41 patients did not seek any treatment previously and were subjected to the MMR vaccine as the primary treatment as a part of our study.

A statistically significant inverse correlation was found between the duration of warts and the degree of response (P = 0.008, Pearson correlation test) indicating that patients with shorter disease duration responded
better.\textsuperscript{[13]} Although, in our study, the duration of the wart did not vary significantly with the degree of treatment response ($P$ value = 0.118, ANOVA) [Tables 1 and 2].

There were 33 patients in each group. Six patients were lost to follow-up. In group A, 10 (30.3%) patients showed complete, 9 (27.3%) marked, 6 (18.2%) moderate, 3 (9.1%) mild, and 5 (15.2%) no response. In group B, seven (21.2%) patients showed complete, one (3.0%) marked, one (3.0%) moderate, four (12.1%) mild, and 20 (60.6%) no response [Tables 2-4 and Figure 3]. There were minimal side effects in the form of pain, erythema, itching at the injection site in a few patients, only one patient had syncope [Figure 4]. The decline in the size of the wart was found to be more in group A (92% reduction) as compared to group B (47.9% reduction) [Figure 5].

At the end of 3 weeks of the treatment, group A (intralesional) showed statistically more significant results as compared to group B (intradermal). After statistical analysis, we observed that as compared to intradermal group, intralesional group had 24 times higher chance

| Table 2: Comparison of the size of the wart in the two groups |
|-----------------|-----------------|-----------------|-----------------|
|                  | Group A ($n=33$) | Group B ($n=33$) | Mean difference |
| Baseline (mean±SD) |                  |                  |                |
| Length (cm)      | 1.18±0.635       | 0.99±0.600       | 0.19           | 0.165 |
| Breadth (cm)     | 1.28±0.588       | 0.99±0.571       | 0.29           | 0.020 |
| MMR1 (mean±SD)   |                  |                  |                |
| Length (cm)      | 1.07±0.631       | 0.94±0.623       | 0.13           | 0.282 |
| Breadth (cm)     | 1.12±0.544       | 0.93±0.596       | 0.19           | 0.092 |
| MMR2 (mean±SD)   |                  |                  |                |
| Length (cm)      | 0.91±0.568*      | 0.88±0.644       | 0.03           | 0.669 |
| Breadth (cm)     | 0.87±0.535*      | 0.87±0.622       | 0.00           | 0.831 |
| MMR3 (mean±SD)   |                  |                  |                |
| Length (cm)      | 0.68±0.553*      | 0.82±0.723       | −0.14          | 0.561 |
| Breadth (cm)     | 0.66±0.567*      | 0.78±0.697*      | −0.12          | 0.592 |
| MMR4 (mean±SD)   |                  |                  |                |
| Length (cm)      | 0.47±0.532*      | 0.75±0.709*      | −0.28          | 0.094 |
| Breadth (cm)     | 0.45±0.541*      | 0.75±0.701*      | −0.30          | 0.056 |
| Follow-up 1 (mean±SD) |              |                  |                |
| Length (cm)      | 0.43±0.557*      | 0.72±0.729*      | −0.29          | 0.071 |
| Breadth (cm)     | 0.37±0.555*      | 0.73±0.705*      | −0.36          | 0.018 |
| Follow-up 2 (mean±SD) |              |                  |                |
| Length (cm)      | 0.38±0.560*      | 0.72±0.729*      | −0.34          | 0.022 |
| Breadth (cm)     | 0.35±0.563*      | 0.72±0.707*      | −0.37          | 0.011 |
| Follow-up 3 (mean±SD) |              |                  |                |
| Length (cm)      | 0.37±0.562*      | 0.72±0.729*      | −0.35          | 0.020 |
| Breadth (cm)     | 0.34±0.564*      | 0.72±0.707*      | −0.38          | 0.009 |

$P$ value within groups $<0.001$ (for both, length and breadth) $<0.001$ (for both length and breadth)

$^aP$ value between groups determined by Mann-Whitney U test. $^bP$ value within groups determined by Friedman’s ANOVA followed by post hoc Dunn’s test in which the significance level was taken to be 0.00625 after applying the Bonferroni correction. *Significant reduction from baseline.
of getting moderate response, 36 times higher chance of getting marked response and 5.7 times higher chance of getting complete response [Figures 6-9].

Most (57.6%) of patients reported no adverse effect during the course of treatment or on follow-up. There were very few adverse effects in the form of pain at the injection site (45.5%) and itching (9.1%) which were more common in the intralesional group (group A) as compared to the intradermal group (group B) (6.1% and 0%, respectively). Erythema was more common in the intradermal (9.1% vs 3%) group. Though flu-like symptoms have been reported in the previous studies, they were seen in only three (4.5%) patients in our study. One patient had an episode of syncope immediately after giving intralesional injection on the second visit.

Our study clearly showed that injecting the MMR vaccine intralesionally (group A) was more efficient in decreasing the size of the representative wart as compared to the intradermal route (group B) given at a distant site. This can be due to the effect of the injection causing trauma at the given site leading to an inflammatory response at the site of wart causing a better response itself in addition to the inflammatory response against the vaccine antigens. Also, the response was evident much earlier in the case of intralesional (seen at the time of second injection average) as compared to the intradermal route (seen at the fourth injection on an average).

Almost 60.6% of group B patients showed no response at all while in group A only 15.2% of patients showed no clinical response. Earlier studies with MMR were concordant with our results in case of an intralesional vaccine showing optimum results.

### Table 3: Area of the representative wart in the two groups over the period of study at various points of assessment

| Area in cm² at | Group A | Group B |
|---------------|---------|---------|
| Baseline      | 1.51    | 0.98    |
| MMR1          | 1.19    | 0.87    |
| MMR2          | 0.79    | 0.76    |
| MMR3          | 0.44    | 0.63    |
| MMR4          | 0.21    | 0.56    |
| Follow-up 1   | 0.15    | 0.52    |
| Follow-up 2   | 0.13    | 0.56    |
| Follow-up 3   | 0.12    | 0.51    |

### Table 4: Comparison of responses in study group A (intralesional) and group B (intradermal) in 66 patients at the end of the study period

|                  | Group A (n, %) | Group B (n, %) |
|------------------|---------------|---------------|
| Complete         | 10, 30.3%     | 7, 21.2%      |
| Marked           | 9, 27.3%      | 1, 3%         |
| Moderate         | 6, 18.2%      | 1, 3%         |
| Mild             | 3, 9.1%       | 4, 12.1%      |
| No               | 5, 15.2%      | 20, 60.6%     |
| Total            | 33            | 33            |

Our study clearly showed that injecting the MMR vaccine intralesionally (group A) was more efficient in decreasing the size of the representative wart as compared to the intradermal route (group B) given at a distant site. This can be due to the effect of the injection causing trauma at the given site leading to an inflammatory response at the site of wart causing a better response itself in addition to the inflammatory response against the vaccine antigens. Also, the response was evident much earlier in the case of intralesional (seen at the time of second injection average) as compared to the intradermal route (seen at the fourth injection on an average).

### Discussion

Through ages numerous therapeutic strategies have been tried in the management of warts; ranging from hypnotherapy, acupuncture, alternative medicines, ablative therapies, and the newest addition to the list, immunotherapy. The range of therapeutic modalities speaks for itself that none of them is 100% effective and that’s the reason that the quest for newer and better therapeutic options continues.

The most intriguing factor in the management of warts is the high recurrence rate of at least 30% even after apparently successful treatment,[24] plausibly by the recrudescence of virus from the surrounding tissue reservoir. Immunotherapy for warts addresses the limitations of traditional ablative therapy by the fact that it enhances the cell-mediated immunity and enables the body’s own immune system to clear the virus-infected tissue irrespective of whether they are visible or not. In this sense, they can target lesions situated remotely from the site of immunotherapy; making it a preferred option in multiple warts, warts on inaccessible or difficult-to-treat sites (like sub- or peri-ungual region) or in cosmetically sensitive areas (facial warts).

From the patients attending our outpatient department, 72 patients having five or more lesions were diagnosed
Candida Our study observed which is found comparing observed that over half (51.5%) of patients Horn showed complete clearance in 40 (46.5%) of 86 patients with agents for the treatment of warts. Saini many open-labeled studies using other immunotherapeutic earlier in group A as mentioned earlier. There have been immunological response. As there has been previously stated that trauma can itself trauma causing more response in intralesional group. We were unable to find any previous study comparing the two routes of giving the MMR vaccine intradermally in the deltoid muscle area versus intralesionally in the wart. Our study was inspired by the study of Elela comparing the intraderal versus intralesional PPDs in the treatment of warts which showed comparable results in both groups.

Limitations
These results are only for common warts so we cannot generalize them for other types of warts (e.g., genital warts,
plantar warts, verruca plana, etc.). We have compared a single representative wart (largest wart) on both intralesional and intradermal groups without taking into consideration the effect on distant warts, relatively smaller sample size. We have limited our study to a maximum of four injections though few studies have used more than four injections with better outcomes.

**Conclusion**

- We conclude that the MMR vaccine is an effective and safe modality of treatment for verruca vulgaris without any serious adverse effects. Its added advantage over destructive therapies is that it does not cause any scarring or disfigurement. Also, the intralesional route showed better results in comparison to the intradermal route and it should be preferred over the latter when we consider the treatment of representative wart.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/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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