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Efficacy of intralesional MMR vaccine for the management of cutaneous warts in adults

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Abstract
Background: No single treatment for warts has proven 100% efficacy and most therapeutic modalities remain unsatisfactory. Immunotherapy with Measles-Mumps-Rubella (MMR) vaccine remains a key treatment of interest.
The study done from August 2020 to March 2021 in the department of Dermatology, KIMS hospital, Narketpally. Telangana state.
Objective: To evaluate the efficacy of intralesional MMR vaccine in the treatment of cutaneous warts in adults.
Patients and Methods: Fifty patients (34 men and 16 women) aged 18–61 (mean ± standard deviation = 34.58 ± 11.74) years with common warts received 0.25 ml of MMR vaccine injected intralesionally in the largest wart. The dose was repeated at 2-week interval until complete clearance or for a maximum of 5 doses. Thereafter, they were followed up once a month for 24-week study period. The response was evaluated as complete clearance (complete disappearance of the wart(s) including distant ones and appearance of normal skin), partial clearance (≤99% reduction in size and number including distant ones and few residual warts still visible), good response (some reduction in size only including that of distant ones but no decrease in number of warts), or poor response (no change in size and number).
Results: 50 patients completed the study and 29 (58%) of them had complete clearance of warts, 14 (28%) showed partial clearance and 5 (10%) patients showed good response. Complete clearance of warts occurred after five doses in 19 (38%) patients and after 4 doses in 9 (18%) patients.
Conclusion: MMR vaccine is a promising treatment modality for common warts, particularly the multiple and recalcitrant ones. It seems to be inexpensive, effective and safe option that has the potential advantages of widespread and sustained effects against HPV. Intralesional MMR also appears to be much less painful and safe than traditional destructive methods for wart treatment, and thus seems to be better tolerated.

Keywords: MMR vaccine, 100% efficacy, KIMS hospital

Introduction
Cutaneous warts or verruca vulgaris are hyperkeratotic papillomas due to human papilloma virus (HPV) infection. They frequently occur over hands of children and young adults but may be located on any cutaneous or mucosal surface. Although spontaneous recovery occurs, it usually takes a long time and even years.
Treatment of warts becomes a challenge when they are numerous or present over inaccessible areas. There are many ablative modalities of therapy such as electrocautery, chemical cautery, cryotherapy, laser surgery, curettage and topical keratolytics. Most of these take months and many of them may result in pain, scarring, and recurrences [1]. Ablative therapies are also limited by the fact that they only remove visible lesions; non-visible infected tissues are not targeted, resulting in a high chance of recurrence [2]. The other type of therapy is immunotherapy which is based on the activation of the immune system to deal with the virus and suppress its activity. Such therapy may be applied either topically or through intralesional injection or through systemic administration [3].
In this study we treated patients with intralesional immunotherapy with MMR vaccine. It has the potential advantages of clearance of both treated and untreated distant warts without scarring, a presumed low rate of recurrence, and a high safety profile. Although the mechanism of effectiveness of intralesional injection of MMR vaccine and antigens has not yet been known, it seems that nonspecific inflammatory response to the antigens is the major mechanism of immunotherapy [4].

Patients and Methods

The study enrolled 50 adults diagnosed with common warts for the study after informed written consent. Demographic and clinical details for number and size of warts and sites involved were recorded. Photographic records were made prior to treatment (at baseline) and at each subsequent visit. Immunocompromised, pregnant and lactating mothers and patients below 18 years of age were excluded.

All enrolled patients were given freeze-dried MMR vaccine. The vaccine was reconstituted with 0.5 mL of provided diluent (distilled water) immediately before intralesional use. All enrolled patients received intralesional injection of 0.25 mL of reconstituted MMR vaccine in largest wart with 30G insulin syringe (one dose). The dose was repeated at every 2-week interval in a similar fashion until complete clearance or for a maximum of five doses. Thereafter, they were followed up once a month for 24-week study period

Out of 50 patients only few patients followed the stipulated schedule; most of the patients came one or three days after the scheduled period. Few patients came after complete clearing of the lesions.

All treated patients were evaluated by an independent blinded observer and by comparing clinical photographic records at each treatment session for decrease in size and number of warts and any immediate side effects, if any. Resolution of distant untreated warts was also assessed. The clinical improvement was rated by using Visual Analog Scale (VAS) score at each visit taking baseline clinical photograph as controls. The response was evaluated as complete clearance (VAS score 100, complete disappearance of the wart(s) including distant ones and appearance of normal skin), partial clearance (VAS score 75%–99%, ≤99% reduction in size and number including distant ones and few residual warts still visible), good response (VAS score 50%–75%), some reduction in size only including that of distant ones but no decrease in number of warts) or poor response (VAS score <50, no change in size and number.

Results

The study included 34 men and 16 women (M:F = 2.1:1) aged between 19 years to 61 years (mean ± standard deviation [SD] = 34.58 ± 11.74) years. The majority, 29 (58%) patients were aged between 21 and 40 years. The duration of warts was 1 month to 72 (mean ± SD = 15.52 ± 14.65) months and the number varied from a solitary in 2 patients to 42 warts in a single patient (mean ± SD = 11.8 ± 10.30) localized mainly over dorsal hands and feet, and soles (in 25 patients), periungual skin (in 2 patients), and multiple sites including hands and face in three patients. No patient had received any treatment for warts previously. Table No depicts therapeutic outcome; overall, in 50 patients who completed the study warts showed complete clearance in 29 (58%) and partial clearance occurred in 14 (28%) patients, good clearance was seen in 5 (10%) patients and poor response was seen in 2 (4%) patients during 9 months of study period. Complete clearance of warts occurred after five doses in 19 (38%) patients and after 4 doses in 9 (18%) patients. All patients experienced mild-to-moderate injection site pain at the time of MMR vaccine injection that did not warrant discontinuation of treatment. There were no systemic adverse effects, scarring, or residual pigmentation. MMR vaccine injection for periungual warts did not adversely affect nail growth or caused onycholysis or nail dystrophy. No recurrence of warts was noted among cured at the end of the study period. All cured patients were very much satisfied (score of 5 on Likert scale) from treatment.

Table 1: Gender distribution of patients in the study

Gender	Number of patients (n = 50)
Men	34
Women	16
Men:Women	2.1:1

Table 2: Age distribution of patients in the study

Age (years) range, mean ± SD	34.58 ± 11.74
<20	3
21-40	29
41-60	17
>60	1

Table 3: Number of warts

Range, mean ± SD	11.8 ± 10.30
1-10	28
11-20	13
21-30	5
31-40	3
>40	1

Table 4: Duration of warts in months

Range, mean ± SD	15.52 ± 14.65
1-12	18
13-24	23
25-36	4
37-48	2
49-60	2
>60	1

Table 5: Site of warts

Site of warts	Number of patients (n = 50)
Dorsum of Hand/Foot	25 (50%)
Palmoplantar	20 (40%)
Periungual skin	2 (4%)
Multiple sites	3 (6%)

Table 6: Grades of clinical improvement after intralesional MMR vaccine

Grade	Number of patients (n = 50)
Complete (VAS = 100%)	29 (58%)
Partial (VAS = 75%-99%)	14 (28%)
Good (VAS = 50%-75%)	5 (10%)
Poor (VAS < 50%)	2 (4%)

Discussion

The exact mechanism of effectiveness of intralesional injection of MMR vaccine or antigen in warts remains hypothetical. It is possible that it accelerates the clearance of virus and viral infected cells by stimulation of CMI and humoral immunity that is suggested to play a significant role in the pathogenesis and persistence of warts or perhaps the nonspecific inflammatory response to the antigens is the major mechanism of immunotherapy [4-7].

Nofal and Nofal [8] reported cure rates of 81.4% patients as compared with 27.5% in placebo group with intralesional MMR vaccine and antigens. Similar results were also reported by Mohamad *et al.* [9] and Zamanian *et al.*

[7] separately observing complete clearance in 82%, partial response in 6%, and no response in 12% patients of plantar warts, and complete cure of common warts in 75%, relative cure in 16.66% and no cure in 8.33% patients, respectively. Na *et al*. [4] also observed decrease in size of warts in 51% of 136 patients, while complete resolution occurred in 5.6% of patients. Intralesional immunotherapy with MMR was superior with clearance rates of 80% and 40% with MMR, 60% with purified protein derivative, and 0% with saline in 10 patients each and to cauterization with 100% TCA in two separate studies, respectively [10, 11].

At present there is no consensus for a minimum dose of MMR vaccine, dosing frequency, and duration of therapy to treat warts [4, 7-17]. Invariably, three to six doses of 0.–0.5 mL administered at intervals of 2–3 weeks have been used with outcome as varied. For instance, three doses of 0.5 mL injected once in 3 weeks for up to three doses resulted in complete clearance in only 87% of plantar warts patients, whereas 5 intralesional doses of 0.3 mL given once in 2 weeks lead to complete resolution in only 63% of 65 patients in two separate studies [13, 14].

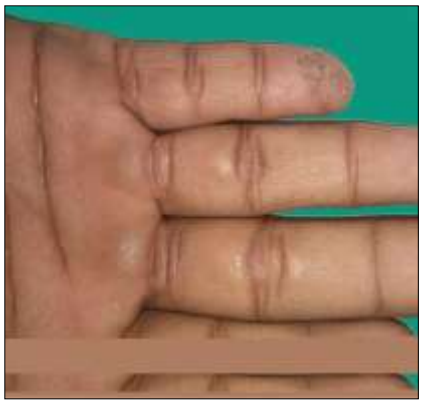
Conclusion

MMR vaccine is a promising treatment modality for common warts, particularly the multiple and recalcitrant ones. It seems to be inexpensive, effective and safe option that has the potential advantages of widespread and sustained effects against HPV. Intralesional MMR also appears to be much less painful and safe than traditional destructive methods for wart treatment, and thus seems to be better tolerated. Even though we were limited by sample size and lack of placebo or other therapeutic group for comparison, the results based on observation give us a potential idea about the effectiveness of this treatment modality.

Patient 1 (23 Years/M)
1st visit (Date: 08.04.2020)

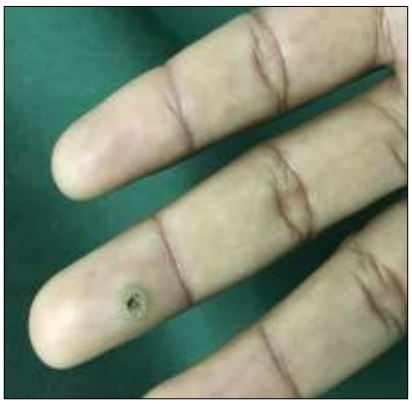
2nd visit (Date: 23.04.2020)

3rd visit (Date: 12.05.2020)

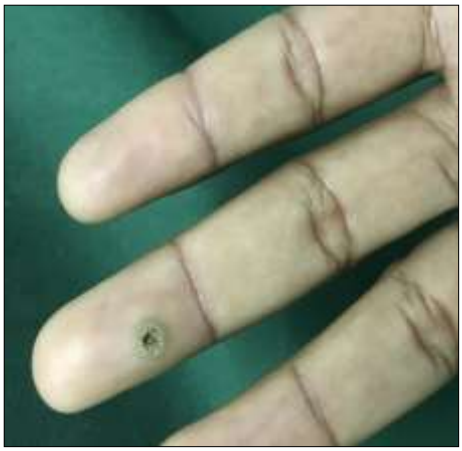


4th visit (Date: 26.0.2020)

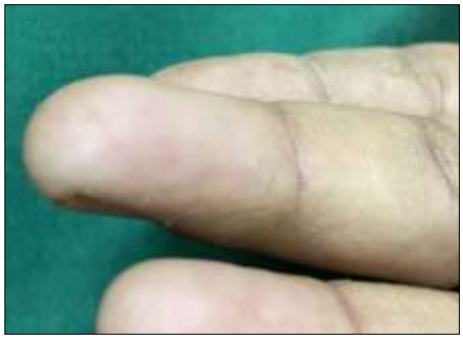
Patient 2 (20 Years / M)
1st Visit (Date: 02.06.2020)



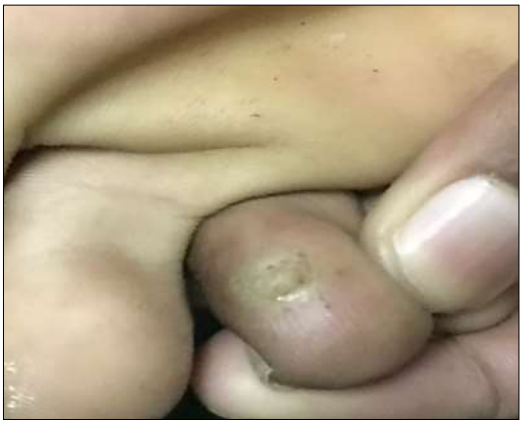
2nd Visit (Date: 29.06.2020)



3rd Visit (Date: 14.08.2020)



Same Patient as above
1st Visit (Date: 02.06.2019)



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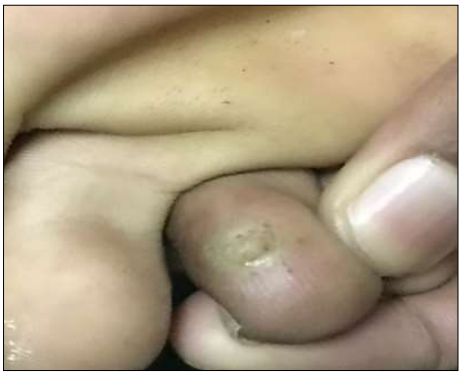

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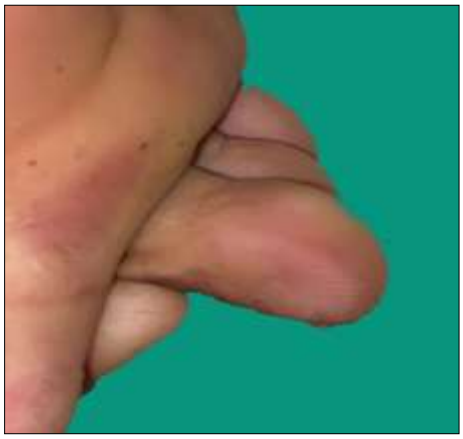
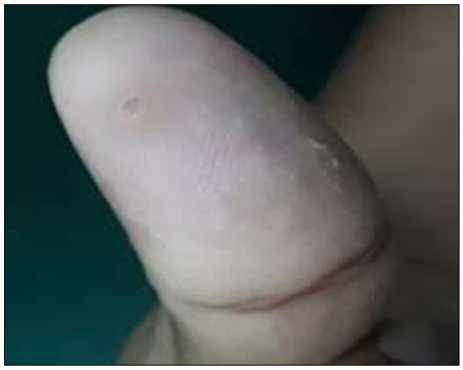


Patient - 3 (19 Years / F)
1st Visit (Date: 19.06.2020)



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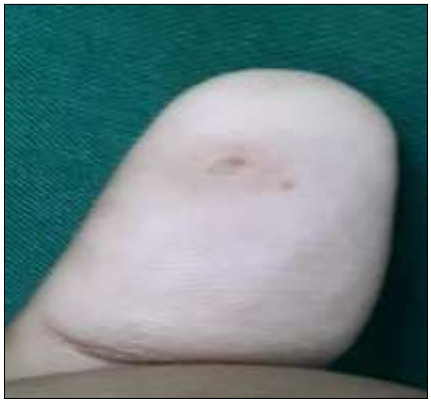

4th Visit (Date: 26.08.2020)

Patient 4 (25 Years / M)
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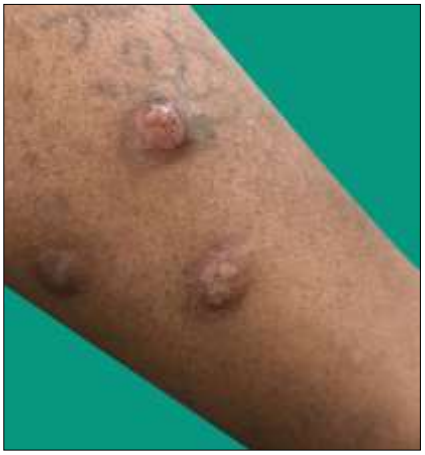

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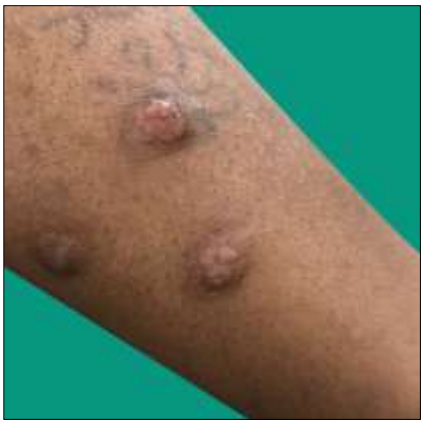

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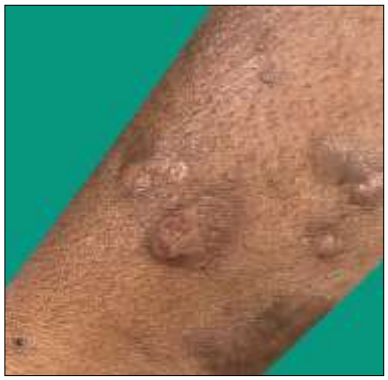
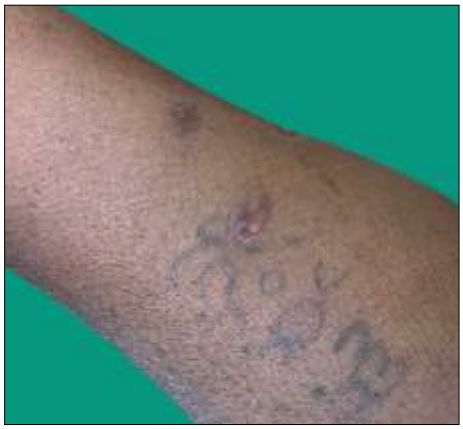
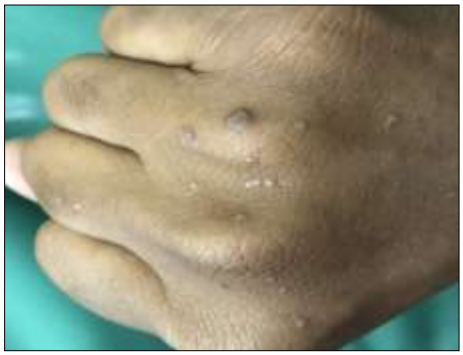


4th Visit (Date.29.10.2020)



Patient 5 (22 Years / M)
1st Visit (Date: 05.11.2021)



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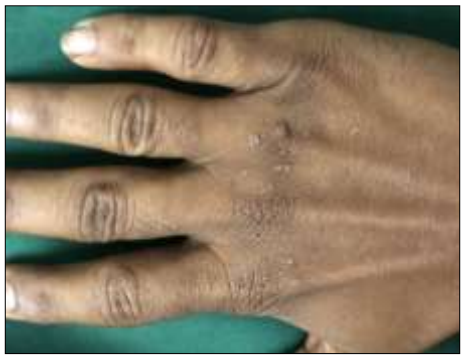
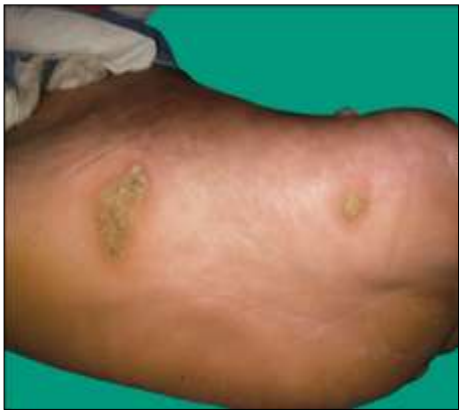


Patient 6 (25 Years / M)
1st Visit (Date: 05.01.2021)



2nd Visit (Date: 19.03.21)

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