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Original Article

Comparative study on the effectiveness of intralesional Measles, Mumps, and Rubella vaccine and intralesional vitamin D3 injection in the treatment of verruca

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ABSTRACT

Background: Human papillomavirus (HPV) is the causative agent of verruca and is contagious, recurrent, and recalcitrant due to defects in cell-mediated immunity. No single mode of treatment is completely effective. The most commonly used treatment options are destructive and lead to scarring. The emerging new modality of treatment is immunotherapy, which acts by enhancing cell-mediated immunity (CMI) against HPV to clear treated as well as remote warts. **Objectives**: The objective was to compare the efficacy of intralesional Measles, Mumps, and Rubella (MMR) vaccine and intralesional vitamin D_3 in cutaneous warts. **Materials and Methods**: A randomized, hospital-based, single-blind study on forty patients divided into two groups (groups A and B), comprising twenty patients each, was conducted. In group A, intralesional MMR vaccine 0.5 mL was injected into the base of warts. In group B, intralesional vitamin D_3 0.5 mL was injected into the base of warts after achieving local anesthesia. Sessions were performed in two-week intervals for a maximum number of five sessions. The patients were followed for sixteen weeks. **Results**: In group A (MMR vaccine), a complete response was seen in 75% (15/20) of the patients, a moderate response in 15% (3/20), a partial response in 5% (1/20), and no response in 5% (1/20). In group B (vitamin D_3), a complete response was seen in 65% (13/20) of the patients, a moderate response in 15% (3/20), a partial response in 10% (2/20), and no response in 10% (2/20). No recurrence was noticed after follow-up in either of the two groups. **Conclusion**: Immunotherapy is an option that is easy, safe, cost-effective, and well-tolerated with minimal side effects.

Key words: Verruca; Intralesional MMR; Intralesional vitamin D_3; Immunotherapy

INTRODUCTION

Verrucae, or warts, are the benign epidermal growths of skin or mucosae caused by HPV with no envelope, containing double-stranded DNA (ds-DNA) [1].

HPVs are divided into various genotypes. Different HPV types infect either the cornified squamous epithelium of the skin or the non-cornified mucosa [2]. Some warts remit spontaneously, while others remain and may spread to other parts of the body [3]. Not all warts need treatment as many give little inconvenience and resolve spontaneously.

The available treatment options include topical salicylic acid, glutaraldehyde, formalin, imiquimod, 5-flurouracil, cantharidin, podophyllotoxin, and vitamin D analogs [4]. The systemic treatments include oral H2-receptor antagonists, oral zinc, oral retinoids, and IV cidofovir. The different agents employed in immunotherapy are *Candida* antigen, *Trichophyton* antigen, BCG vaccine, PPD, MMR vaccine, vitamin

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D_3, bleomycin, and interferons. Destructive procedures such as cryotherapy, electrosurgery, and laser lead to destructive scarring or dyspigmentation [5]. No single treatment is considered completely efficient.

A major role is played by cell-mediated immunity (CMI) in the clearance of warts. The principle of immunotherapy is by enhancing CMI, thereby clearing warts. Nowadays, immunotherapy is the preferred treatment option as it is safe and overcomes other complications. Its mechanism of action is by mounting a type IV hypersensitivity reaction and the production of Th1 cytokines, which activate cytotoxic and natural killer cells, thus eliminating the infection. Because of sensitization, we have an added benefit in the clearance of remote warts along with treated warts [6].

MATERIALS AND METHODS

This hospital-based, prospective, comparative, interventional study was conducted at the Department of DVL of Kamineni Academy of Medical Sciences and Research Centre in Hyderabad, India, after obtaining ethics committee approval on a total of forty patients. The patients were randomly divided into two groups (groups A and B) comprising twenty patients each. Group A was given intralesional MMR, whereas group B was given intralesional vitamin D_3.

Inclusion Criteria

Included were patients of both sexes suffering from verruca, aged between 12 and 70 years, consenting, and not having taken any treatment for their verruca in the past three months.

Exclusion Criteria

Excluded were patients not consenting, younger than twelve years or older than seventy years, pregnant and lactating females, patients with immunosuppression such as HIV and chronic renal, hepatic, and cardiovascular disorders, patients on immunomodulatory drugs, patients allergic to MMR vaccine, patients with a history of keloidal, hypertrophic scar tendency, and patients who had taken treatment in the past three months.

Methods

After detailed history taking and clinical examination, the patients were divided into two groups, twenty patients each.

In group A, under aseptic conditions, after reconstitution with distilled water, 0.5 mL of MMR vaccine was given with an insulin syringe to the base of the largest warts to a maximum of five warts in each session.

In group B, under aseptic conditions, under local anesthesia with 2% lignocaine, 0.5 mL of vitamin D_3 (600,000 IU) was given to the base of the largest warts with an insulin syringe to a maximum of five warts in each session.

The procedure was repeated every other week for a maximum number of five sessions. In each session, the response was noted (size, number, new lesions). Follow-up was performed up to sixteen weeks.

Treatment responses were classified as complete, moderate, partial, and no response (Table 1).

Ethics Statement

An institutional ethical committee certificate was taken.

RESULTS

All forty patients completed the study and their clinical and demographic data was recorded (Table 2).

In group A, the mean age was 24.4 years, ranging from 12 to 33 years. In group B, the mean age was

Table 1: Response grading.

Response	Definition
Complete response	100% clearance (of local and distant warts)
Moderate response	> 50% clearance
Partial response	< 50% clearance
No response	No clearance

Table 2: Demographic data of the patients in the two groups.

Data	Group A	Group B
Age range	12–33	14–52
Mean	24.4	29.6
Sex ratio (M:F)	4:1	4:1
Type of warts		
Verruca vulgaris	8	10
Palmo-plantar warts	8	6
Periungual warts	4	4
Number of warts		
Mean	5.4	6.4
Range	1–10	1–15
Duration of warts		
Mean	17.6 months	16.6 months
Range	6–36 months	5–35 months
Number of sessions		
Mean	4	3.2
Range	3–5	2–5

29.6 years, ranging from 14 to 52 years. The sex ratio (male-to-female) in both groups was 4:1. In group A, verruca vulgaris and palmoplantar warts were the most common types (40%), with periungual warts being 20%. In group B, the most common type was verruca vulgaris (50%), with palmoplantar and periungual warts being 30% and 20%, respectively.

In group A, the mean duration of warts was 17.6 months, ranging from 6 to 36 months. In group B, the mean duration of warts was 16.6 months, ranging from 5 to 35 months. In group A, the mean number of sessions performed was four, ranging from three to five. In group B, the mean number of sessions performed was 3.2, ranging from two to five.

In group A, a complete response was seen in 75% (15/20) of the patients, a moderate response in 15% (3/20), a partial response in 5% (1/20), and no response in 5% (1/20) (Fig. 1).

In group A, 25% (5/20) of the patients achieved a complete response in three sessions, 30% (6/20) achieved a complete response in four sessions, and 20% (4/20) achieved a complete response in five sessions.

In group A, the side effects observed were pain during the injection of MMR vaccine. No new lesions were noted in the follow-up period.

In group B, a complete response was seen in 65% (13/20) of the patients, a moderate response in 15% (3/20), a partial response in 10% (2/20), and no response in 10% (2/20) (Fig. 2).

In group B, 25% (5/20) of the patients achieved a complete response in two sessions, 25% (5/20) achieved a complete response in three sessions, and 15% (3/20) achieved a complete response in four sessions (Figs. 3 and 4).

In group B, the side effects observed were pain during injection and erythema on the injection site present for one week, which resolved spontaneously. No new lesions were noted in the follow-up period.

Figs. 5 and 6 show photographs of the improvements. Table 3 shows improvements in both groups.

DISCUSSION

Immunotherapy is the preferred option nowadays as it acts on cell-mediated immunity in the individual

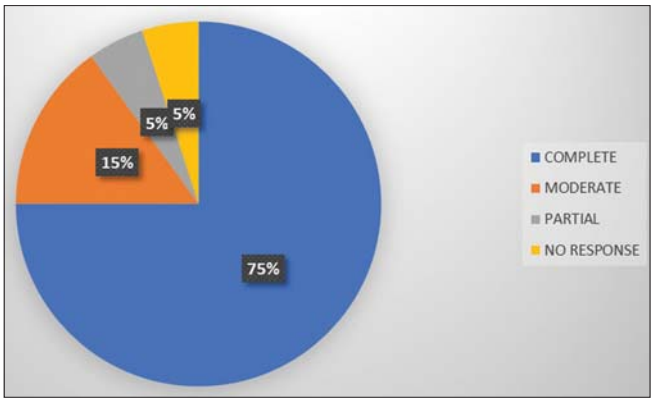

Figure 1: Pie diagram showing response rates in group A.

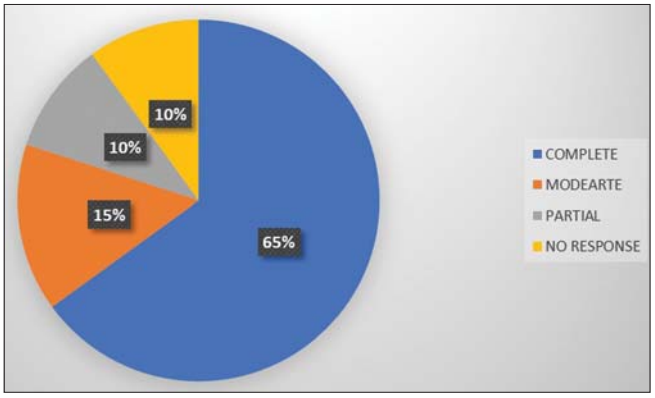

Figure 2: Pie diagram showing response rate in group B.

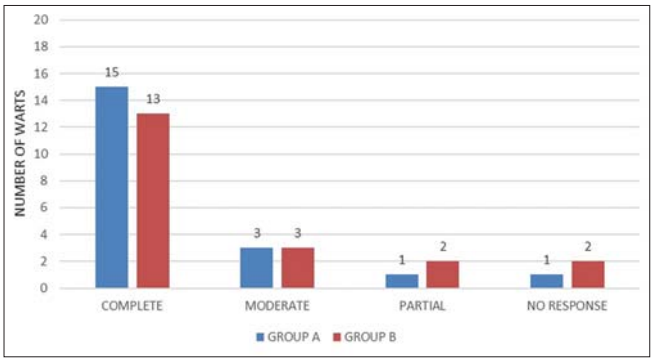

Figure 3: Graph showing clinical improvements in the two groups.

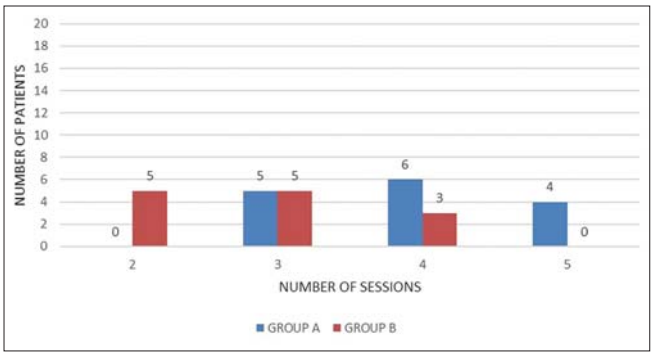

Figure 4: Graph showing patients achieving a complete response with respect to the number of sessions.

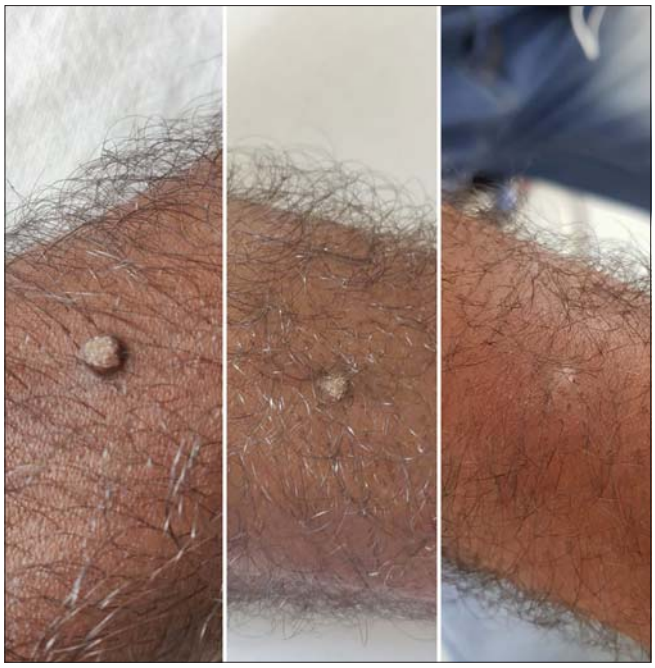

Figure 5: Before-and-after photographs of intralesional MMR vaccine.

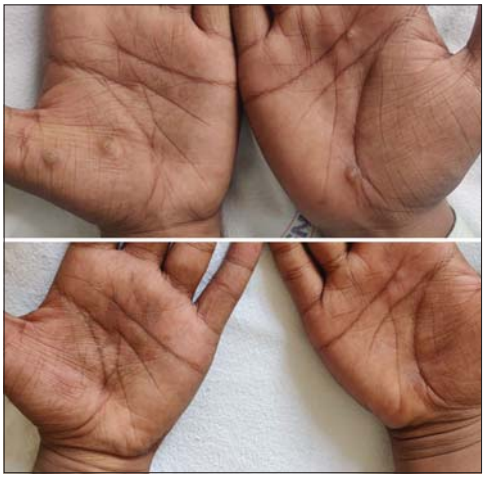

Figure 6: Before-and-after photographs of intralesional vitamin D_3.

Table 3: Percentages of responses in the two groups.

Response	Group A	Group B
Complete response	15 (75%)	13 (65%)
Moderate response	3 (15%)	3 (15%)
Partial response	1 (5%)	2 (10%)
No response	1 (5%)	2 (10%)

unlike other options, which usually concentrate on local clearance. Immunotherapy helps in the clearance of local and remote warts due to sensitization [7].

Various antigens are employed for immunotherapy, thus we chose two antigens in our study.

Injecting the MMR antigen causes the proliferation of peripheral blood mononuclear cells, stimulating a delayed, Th1-mediated hypersensitivity reaction and a release of interferon-gamma and interleukins 2 and 4. These cytokines activate cytotoxic T cells, which in turn stimulate tumor necrosis factor-alpha and IL1. This stimulation helps in the destruction of the HPV virus in both local and remote warts [8,9].

Vitamin D_3 regulates cell proliferation and the differentiation of keratinocytes, which inhibit hyperkeratosis by inhibiting cell replication. It also has immunoregulatory activity with the release of IL21, 42, IFN-γ, and TNF-α [10]. The mechanism of action of vitamin D_3 is by activating Toll-like receptors (TLRs) on macrophages, which stimulates the expression of vitamin D receptor (VDR) and vitamin D 1α hydroxylase leading to the activation of antimicrobial peptides. This activation contributes to the anti-inflammatory action of vitamin D_3 [11,12].

In our study, in group A (MMR vaccine), 75% showed a complete response, 15% showed a moderate response, 5% showed a partial response, and 5% showed no response. In a study by Hassan et al. [13], a complete response was seen in 80%, whereas a partial response, minimal response, and no response was seen in 6.67% each, which was in agreement with our study. Our study findings were also consistent with studies by Malhotra et al. [14] and Kadnur et al. [15], in which a complete response was noted in 76% and 70% of patients, respectively.

The mean number of sessions required in our study was four, with an average of two to five, which was consistent with other studies. There was no statistically significant relationship between age and sex with a treatment response as in other studies. Similarly to other studies, the most common complication noted in group A was pain on at the site of injection.

In our study, in group B (vitamin D_3), 65% showed a complete response, 15% showed a moderate response, 10% showed a partial response, and 10% showed no response. This was in agreement with a study by Hassan et al. [13], which showed a complete response in 66.7% of patients, a partial response in 6.67%, a minimal response in 20%, and no response in 6.67%. Our study findings were also consistent with studies conducted by Malhotra et al. [14] and Kadnur et al. [15], in which a complete response was noted in 60% and 52%, respectively.

The mean number of sessions required was 3.2, with an average of two to five, which was in agreement

Table 4: References with numbers of sessions and response rates.

Study	Vaccines	No. of Sessions	Response Rate
Hassan et al. [13]	MMR	6	80%
	vitamin D_3	6	66.7%
Bhadbhade et al. [16]	vitamin D_3	3	73.3%
	MR	5	66.7%
	PPD	5	30.7%
Kadnur et al. [15]	vitamin D_3	4	52%
	MMR	4	70%
Malhotra et al. [14]	MMR	3	76%
	vitamin D_3	3	60%
Our study	MMR	5	75%
	vitamin D_3	5	65%

with other studies. The most common complications noted were pain and persistent erythema, which faded spontaneously within a week, similarly to other studies [14-16].

Comparing intralesional MMR vaccine with intralesional vitamin D_3, no statistical significance was seen regarding the response. Yet, the number of sessions required was less in the case of vitamin D_3 when compared to MMR vaccine, which was consistent with a study by Hassan et al. [13]. Side effects were more pronounced in the case of vitamin D_3 when compared to MMR vaccine, which was in agreement with a study by Malhotra et al. [14].

Table 4 shows the various studies revealing comparative groups and treatment responses correlating with ours.

CONCLUSION

Immunotherapeutic treatment options are easy, safe, cost-effective, and well-tolerated with minimal side effects. The administration of vaccines in OPD itself is the advantage of immunotherapy. Both modalities of treatment are now preferred due to a decrease in recurrence, which is the significant problem with verruca.

The limitations of our study was a small sample size and a short follow-up period.

Statement of Human and Animal Rights

All the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 2008 revision of the Declaration of Helsinki of 1975.

Statement of Informed Consent

Informed consent for participation in this study was obtained from all patients.

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