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Efficacy and safety of intralesional measles, mumps, and rubella vaccine versus topical salicylic acid therapy for common warts: A comparative study

Seema Sitaula[1*], Aarif M Syed[2], Suraj Shrestha[3], Elisha Poddar[3], Rajesh Bhurtel[4]

[1]Department of Dermatology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal.
[2]Department of Medicine, Chand Memorial Hospital, Bihar, India.
[3]Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal.
[4]Metro Kathmandu Hospital, Kathmandu, Nepal.

*Corresponding author: Dr. Seema Sitaula, seema.sitoula@gmail.com

ABSTRACT

Background: Treating warts endures a therapeutic challenge for dermatologists. No single therapy has been proven universally effective in achieving complete remission for all patients. However, the use of intralesional immunotherapy with various antigens including MMR vaccine has shown promising results in the treatment of different types of warts.

Objectives: This study aimed to determine the effectiveness and safety of the MMR vaccine in the treatment of warts and compare its efficacy over the traditional topical keratolytic therapy.

Methods: A hospital-based, prospective randomized study was conducted with 131 patients diagnosed with common warts over various parts of the body. The patients were randomly assigned into two groups. Group A included 67 patients who received intralesional MMR vaccine in every two weeks, and Group B included 64 patients in whom topical Salicylic acid was applied to the warts daily. The response to treatment was assessed at 2 weeks and after 12 weeks.

Results: The MMR group showed significantly better results, with 85.5% showing complete clearing, and only 4.8% of patients exhibiting no improvement. In contrast, 55.8% of patients in the SA group showed 100% clinical response, and 11.5% showed partial clearing ($P<0.001$). Both the MMR group and the salicylic acid group had similar side effect profiles.

Conclusion: Intralesional immunotherapy with MMR vaccine is safe, practicable, and cost-effective with minimal side effects and local complications than traditional salicylic acid therapy.

Keywords: Common warts, Immunotherapy, MMR, Salicylic acid

1. Introduction

Verruca vulgaris (common warts) are benign verrucous proliferative lesions of skin caused by human papillomavirus (HPV) [1, 2]. No single therapy has been proven universally effective in achieving complete remission for all patients. Many treatment approaches have been studied, using single or multiple remedies in combination for the most desirable outcome [2-4].

Salicylic acid (SA) requires prolonged treatment and is associated with side effects, which often lead to poor patient satisfaction. In contrast, immunotherapy stimulates an immune response that targets and removes cutaneous warts across the body, thereby eliminating the need for cumbersome topical treatments for each individual wart. This approach includes the use of the intralesional mumps, measles, and rubella (MMR) vaccine. Immunotherapy, such as the MMR vaccine, works by harnessing the body's immune system to recognize and destroy the virus responsible for wart formation. This method has shown promise due to its ability to treat multiple warts simultaneously, making it a more efficient option compared to traditional topical therapies.

The MMR vaccine is safe, cost-effective, and practical for the treatment of widespread or numerous warts [5-7]. Key findings from previous studies supported the use of the MMR vaccine as an effective treatment option for warts, highlighting its immunological mechanisms that result in significant clinical improvement. These studies demonstrated that immunotherapy may be superior to topical treatments in both efficacy and patient satisfaction. Therefore, this study aimed to evaluate the effectiveness and safety of the MMR vaccine in the treatment of warts and compares its efficacy to traditional topical keratolytic therapies.

2. Methods

2.1 Study Area

Tribhuvan University Teaching Hospital (TUTH) is a premier government tertiary care centre that caters to patients from across the country. The outpatient settings of the department of Dermatology and Venereology at TUTH provided access to a diverse patient population presenting with various dermatological conditions, including arts, ensuring comprehensive data collection and follow-up.

2.2 Study Design

This study was a hospital-based, prospective, open-label randomized study carried out in the outpatient clinic of the Department of

Dermatology and Venereology, Tribhuvan University Teaching Hospital (TUTH), Kathmandu over one year, between July 2015 and July 2016. Patients who presented to the outpatient department and were diagnosed with a cutaneous wart clinically at different sites of the body and consented to participate in the study were included in the study. Patients were excluded from the study if they had any of the following conditions: History of atopy, known allergic reaction to MMR vaccine, pregnancy, lactating patients, children less than 12 years of age, acute febrile illness, and immunosuppression due to disease or drugs; HIV infection, and patients who lost to follow-up.

Patients were randomly assigned into two groups; Group A and Group B. Group A included patients receiving the intralesional MMR vaccine and Group B included patients receiving topical salicylic acid. Written informed consent was obtained from all the participants or parents/guardians in cases of minors (patients <18 years of age) and baseline characteristics of warts were recorded at the start of the study.

2.3 Sample size and sampling

The sample size for this study was calculated with 95% power and a 5% significance level, yielding a requirement of 63 patients in each group, totalling 126 participants. A total of 131 patients were enrolled, with 67 in the MMR group and 64 in the salicylic acid group. Patients were randomly assigned to either group based on inclusion criteria**.** Randomization was performed using a computer-generated random number sequence, and group allocation was concealed with sealed opaque envelopes to ensure proper randomization and representative sampling of the study population.

2.4 Data Collection

Upon obtaining written informed consent, all patients of diverse ages and genders, presenting with warts at various body locations, in differing quantities, sizes, and durations whether newly developed or previously treated were thoroughly examined. Photographic documentation was also conducted, and data were recorded separately using a pre-designed proforma. The total sample size was then randomly divided into two groups based on the patients' age and gender, ensuring a randomized categorization into two groups.

The data was collected using a validated proforma and entered Microsoft Excel. The

patients were given call backs for follow-up sessions.

Group A

Before administration of the MMR vaccine intralesional, sensitivity testing was done using a dose of 0.1 mL via intradermal injection into the volar aspect of the left forearm. The injected site was examined after two weeks to assess for an immune response in the form of erythema or nodule formation. All patients demonstrated existing immunity with a positive skin test. In sensitized patients, 0.5mL of MMR vaccine after reconstitution with distilled water was injected intradermally into their single wart or the largest wart in patients with multiple warts. Intralesional MMR vaccine was administered every two weeks to the same wart until the disappearance of the wart(s) or a maximum of three doses.

Group B

This group included patients who were randomized to self-treatment with SA (single brand) and were instructed on how to apply the treatment. Varying concentrations of SA were used for several sites depending on the thickness of the stratum corneum (hands and feet: 40%; face: 10%; any other sites: 20%). The patients were instructed to apply SA daily after gently pumicing or filing off the dead tissue of the verruca for a maximum duration of twelve weeks.

In both groups, outcome evaluations were done every two weeks for a total period of twelve weeks from the onset of treatment. The response to treatment was assessed by an apparent decrease in the size or number of wart(s) on each follow-up visit. “Complete clearing" was defined as the total resolution of all warts present at the beginning of the study (100%). “Partial clearing” was defined as a reduction in the number and/or apparent size (50-99%). “No improvement” was defined as a 50% reduction in the number, apparent size, or appearance of new lesion(s) (<50%) [8].

To ensure proper adherence to the treatment protocol, patients were likely reminded during follow-up visits to follow these steps, although specific adherence monitoring methods (e.g., self-reports or compliance logs) were not explicitly mentioned.

For both groups, monitoring and recording of side effects were integral to the study. Group A, which received intralesional MMR vaccine, was observed for potential side effects such as erythema or nodule formation at the injection site during sensitivity testing and throughout the treatment course. In

Group B, patients were likely assessed for local irritation, skin peeling, or other adverse reactions associated with SA application. Side effects were monitored at each follow-up visit, conducted every two weeks for twelve weeks, and systematically recorded to ensure safety and comprehensive evaluation of treatment responses.

2.5 Data Analysis

Categorical variables were presented as frequency, and continuous data were presented as mean and standard deviation. For the comparison of categorical data between groups, a chi-square test was used. Statistical analysis was performed on SPSS Statistics version 20.0. For all statistical analyses, significance was accepted at $P < 0.05$.

2.6 Ethical Clearance

Ethical clearance and clinical practice guidelines were obtained from the Institutional Ethics Committee of Tribhuvan University Teaching Hospital [(Ref No. 20 (6-11-E)2/072/073)].

3. Results

During the study period, a total of 131 patients who presented to the outpatient clinic of TUTH with common warts were randomly assigned to two groups: 67 patients in the MMR group (group A) and 64 patients in the SA group (Group B). Five patients in group A and eight patients in group B lost their second follow-up. Additionally, four patients missed their third follow-up in Group B. Therefore, a total of 114 patients, with 62 (54.38%) patients in the MMR group and 52 (45.6%) patients in the SA group were studied (Figure 1).

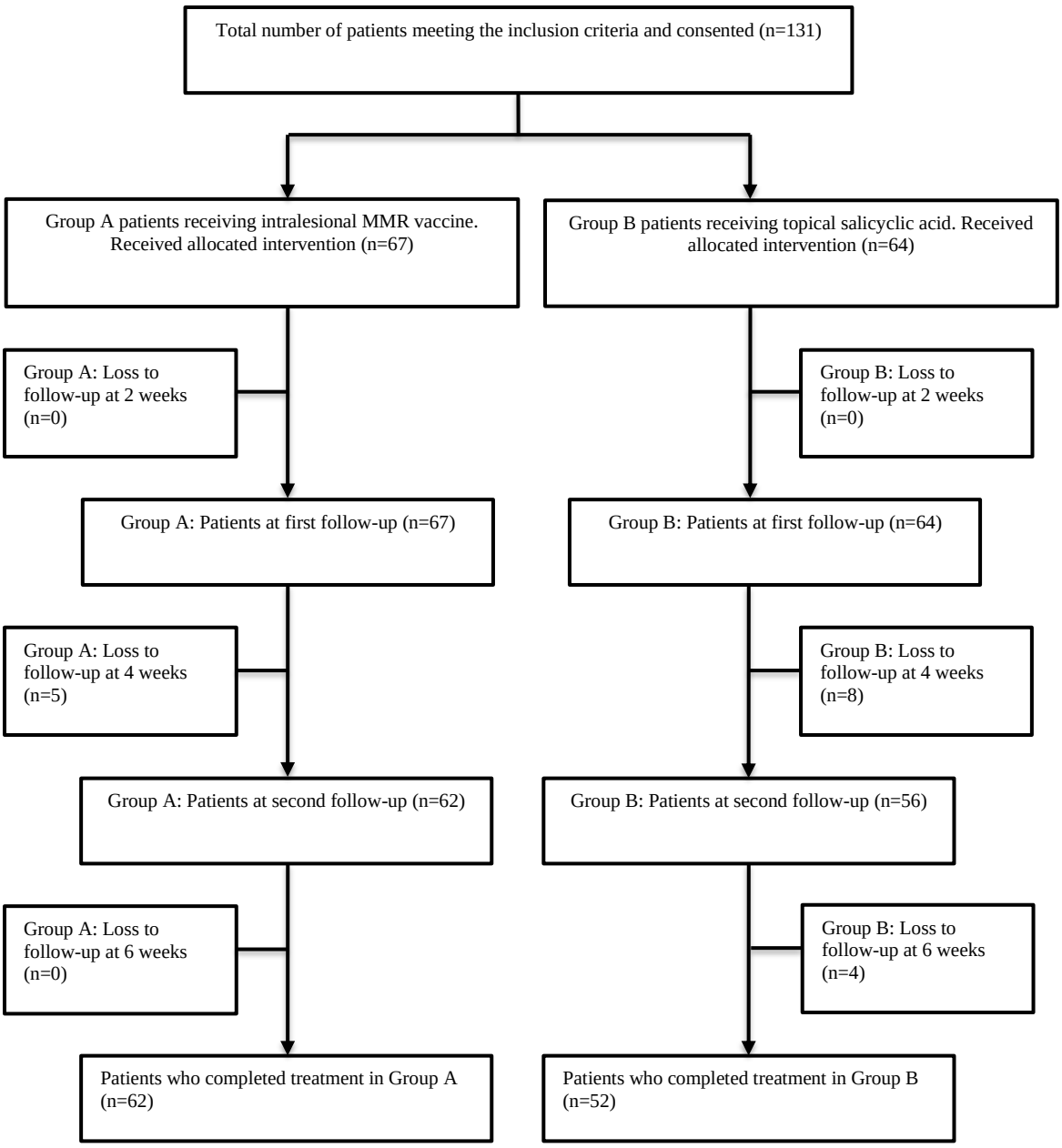

Figure 1: Flow diagram of patient selection

Characteristics of warts

The characteristics of warts of all the patients included in the study revealed that most of the patients presented with localized warts; 89.6% were in the MMR group, and 90.6% were in the SA group. The most frequent sites of warts in the MMR group were the dorsum of the hand in 35.8%, followed by the face (17.9%), palm (14.9%), and soles (14.9%), legs (9%), forearm (4.5%), dorsum of the foot

(1.5%), and periungual (1.5%). In contrast, most patients in the SA presented warts in the soles (20.3%), followed by the dorsum of the hand (18.8%) and palm (17.2%). In both groups, hyperkeratotic papules were the most common clinical findings and most warts in both groups were <5mm (Table 1).

Table 1: General characteristics of caregiver' elderly (n=107)

Variables	MMR group (n = 67) n (%)	SA group (n = 64) n (%)
Gender		
Male	36 (53.7)	29 (45.3)
Female	31 (46.3)	35 (54.7)
Age (years)		
Mean ± SD	26.7 ± 8.9	29.3 ± 11.3
Duration of warts (range) (months)	1-36	2-24
Number of warts	1-15	1-12
Localized warts	60 (89.6)	58 (90.6)
Localized and distant warts	7 (10.4)	6 (9.4)
Involved sites		
Dorsum of hand	24 (35.9)	12 (18.8)
Dorsum of foot	1 (1.5)	3 (4.7)
Forearm	3 (4.5)	4 (6.3)
Legs	6 (9)	8 (12.5)
Palm	10 (14.9)	11 (17.2)
Soles	10 (14.9)	13 (20.3)
Periungual	1 (1.5)	6 (9.3)
Face	12 (17.9)	7 (10.9)
Type of lesion		
Papules	54 (80.6)	35 (54.7)
Plaques	13 (19.4)	29 (45.3)
Size of warts		
<5mm	37 (55.3)	15 (23.4)
6-10mm	22 (32.8)	21 (32.8)
>10mm	8 (11.9)	28 (43.8)

Clinical response and grading of responses

Response to treatment at first follow-up

The response to the treatment on the first follow-up is summarized in Table 2. The MMR group had a better outcome, with 29% of patients showing complete clearance compared to only 5.8% in the SA group, which showed a statistically significant difference (P = 0.001). Partial clearing was observed in 46.2% of patients in the SA group as compared to 17.7% in the MMR group and showed statistical significance (P = 0.001).

Table 2: Response to treatment at first and second follow-up along with adverse effects observed in treatment groups

Follow-up	Clinical response	MMR (n = 62) n (%)	SA (n = 52) n (%)	P-value
	<50%	33 (53.2)	25 (48.1)	0.584
At 2 weeks	50-99%	11 (17.7)	24 (46.2)	0.001
	100%	18 (29)	3 (5.8)	0.001
Response to treatment at second follow-up				
	<50%	22 (35.5)	27 (51.9)	0.077
At 4 weeks	50-99%	13 (21)	11 (21.1)	0.981
	100%	27 (43.5)	14 (26.9)	0.065
Response to treatment at final follow-up				
At 6 weeks	<50%	3 (4.8)	6 (11.5)	0.186
	50-99%	6 (9.7)	17 (32.7)	0.002
	100%	53 (85.5)	29 (55.8)	<0.001
Adverse effects				
Pain		62 (100)	-	
Hyperpigmentation		20 (32.3)	13 (25)	
Erythema		-	12 (23.1)	
Blister		-	1 (1.9)	
Itching		2 (3.2)	4 (7.7)	
Maceration		-	11 (21.1)	

Response to treatment at second follow-up

On the second follow-up, complete clearance was observed in 43.5% and 26.9% of patients in group A and group B respectively (Table 2).

Response to treatment at final follow-up

At the final follow-up done at 6 weeks, the MMR group showed better results, with 85.5% (n = 53) showing complete clearing, 9.7% with partial clearing, and only 4.8% of patients exhibiting no improvement. In contrast, 55.8% (n = 29) of patients in the SA group showed 100% clinical response, followed by 32.7% and 11.5% showing partial clearing and no clearing, respectively. Better results were obtained in the MMR group, and the statistical difference was highly significant for 100% clinical response ($P < 0.001$) (Table 2). The photographic images of patients before and after treatment are shown in Figures 2-3.

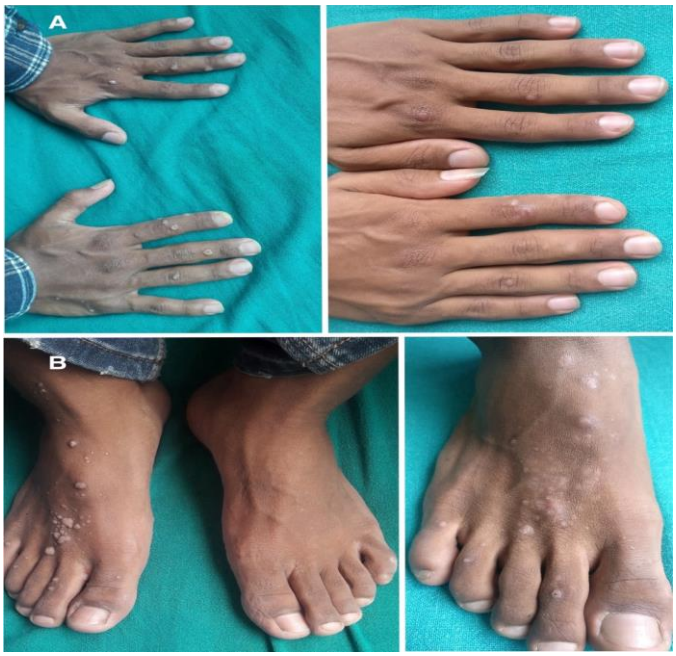

Figure 2: Multiple warts in palmar/plantar aspect (left) clearing after intralesional MMR injection (right)

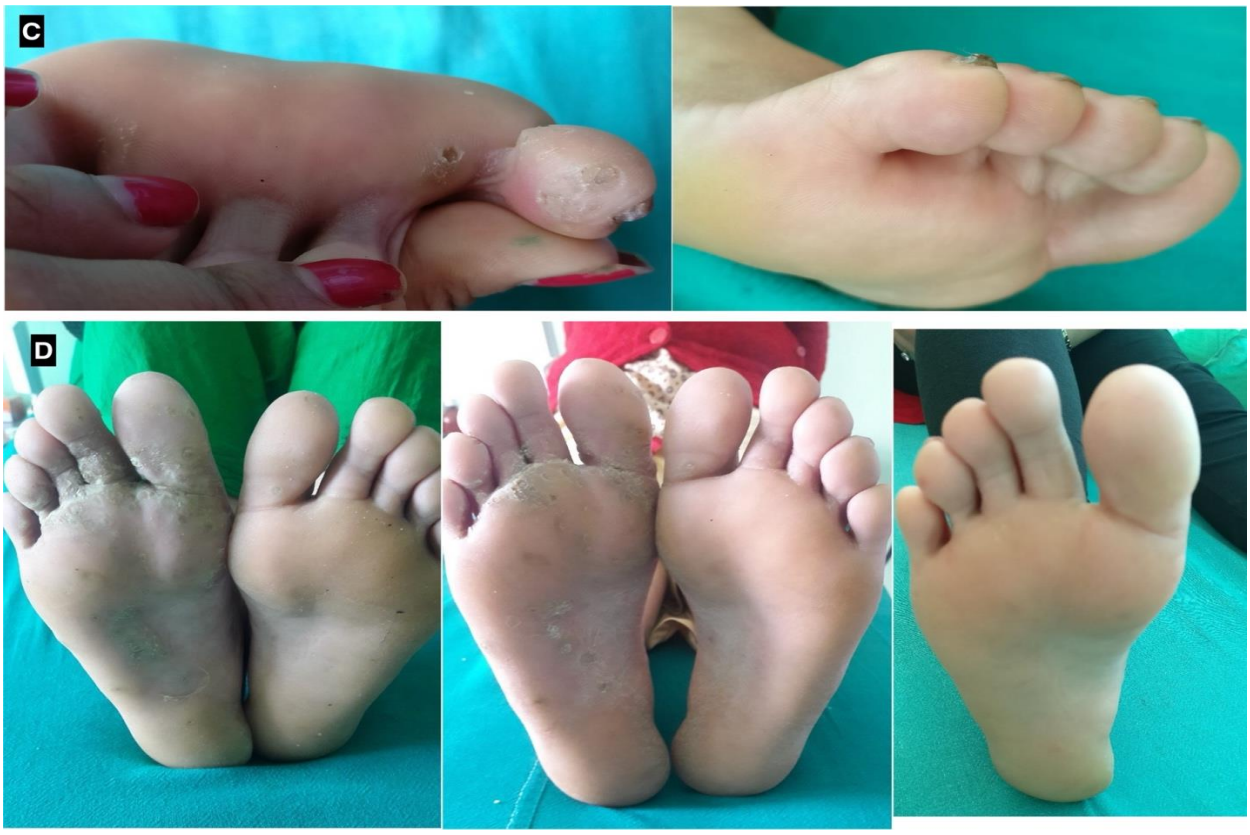

Figure 3: Multiple plantar warts clearing after MMR injection

Side effects

All patients in the MMR group who received intradermal injections experienced local pain at the volar aspect of the left forearm. This pain was described as mild to moderate in intensity and was generally transient, lasting for a maximum of 6 hour in a day.

In terms of other side effects, hyperpigmentation was observed in 32.3% of patients in the MMR group, while itching was reported in 3.2%. These side effects were comparable to the salicylic acid (SA) group, where 25% of patients experienced hyperpigmentation and 7.7% reported itching. Notably, no patients in the MMR group experienced erythema, blisters, or maceration.

In contrast, the SA group had a higher incidence of local irritation. Erythema was observed in 23.1% of patients, maceration in 21.1%, and one patient developed blister formation (Table 2).

4. Discussion

Although Verruca vulgaris is one of the most common skin conditions, treating verruca is still a therapeutic challenge for dermatologists. It is a complex process with the possibility of recurrences despite all treatment options currently available [2-4].

Spontaneous regression of warts is common and can occur at any time, from a few months to years. This has prompted researchers to explore the immune mechanisms associated with the clearance of the wart. *Lorizzo et al.* concluded more than 50% of warts may regress spontaneously within two years in adults, so providing no treatment would be a safe, cost-effective, and pain-free alternative [9]. However, cosmetic disfigurement and social embarrassment often lead the patient to seek medical attention.

Most of the current therapeutic options result in the clearance of warts within one to six months. However, 20%-30% of patients relapse, and new lesions erupt if the cellular immune system fails to recognize and eliminate the lesions [5].

Local tissue destruction using topical agents (salicylic acid, trichloroacetic acid), cryotherapy, thermocautery, lasers, and antiproliferative agents has remained the mainstay in the treatment of warts for a long time [2]. However, destructive procedures are painful, necessitate a longer duration of treatment in multiple sessions and individual treatment of each wart, and yield inconsistent results with variable efficacy, and notable side effects including hyperpigmentation and scarring [2-4]. On the other hand, the risk of

recurrence after treatment persists, making it a lesser preferred modality of treatment.

Immunotherapy has emerged as a promising treatment modality; its sustained and widespread action, high complete clearance, and low risk of recurrence for both previously treated as well as untreated multiple warts, distant warts, and facial warts make it a desirable therapeutic option [3, 4, 6, 8, 10, 11]. Intralesional antigen administration induces a strong nonspecific proinflammatory signal, attracts the antigen-presenting cells, and stimulates cellular immunity by inducing delayed hypersensitivity reactions against both the antigen as well as HPV-infected cells at the wart tissue. IL-2, IL-12, IFN-a, and TNF-a are the important cytokines that can potentiate the cytotoxicity of T-killer cells and natural killer cells implicated in HPV-infected cell clearance [5, 6, 8, 10]. This reaction accelerates the ability of the immune system to recognize and clearance of the wart virus not only at the site of injection but also across the body. Tuberculin, Bacilli Calmette-Guerin (BCG), mumps, candida, trichophyton, and MMR are amongst the antigens utilized in intralesional immunotherapies [1, 5, 6, 8, 10, 11].

In this study, the overall response to the MMR vaccine in the first follow-up was only 29%, which increased to 85.5% six weeks post initiation of treatment. In the SA group, at the first follow-up, the CC was seen at 5.8% and increased to 55.8% in the final follow-up. Our results are consistent with the response reported by *Nofal et al.,* conducted on 135 patients, 85 patients received the MMR vaccine and 50 received normal saline as a control. Their study reported a complete response in 81.4% of patients along with clearance of even untreated distant warts in the MMR group [7]. Likewise, in the study by *Naseem et al*, 81.3 percent of the 170 patients treated with intralesional MMR had a complete response [11]. Similarly, *Raju et al.,* observed complete clearance in 70.4% of patients treated with MMR [12]. The complete response rate achieved in the present study is comparable to that documented in the study by *Zamanian et al.*, a double-blind, randomized, controlled clinical trial comparing the efficacy of the MMR vaccine to a placebo (normal saline). Complete clearing was observed in 75 percent of those who received the MMR vaccine, compared to 25 percent in the control group [5].

A prospective study of 150 patients was concluded by *Saini et al.,* wherein a comparison was made between intralesional MMR and the topical keratolytic agent trichloroacetic acid (TCA). They reported a complete resolution in 6.44% of patients and > 75% improvement in 49.43% of patients who were treated with three doses of 0.3 mL intralesional given at a two-week interval. In contrast, in the TCA group, only 7.94% of patients had complete resolution, and 11.11 percent had >75% improvement. A highly significant difference was noted in response rates between the two groups (P<0.001) [13]. Furthermore, the relatively better response in our study with the use of MMR could be attributed to the usage of 0.5 mL of MMR vaccine instead of the 0.3 mL used by *Saini et al.,* as the increased dosage of MMR might have resulted in the prominent immune system stimulation.

The therapeutic response to the intralesional MMR vaccine observed in our study was significantly higher than that reported by *Kus et al.* (29.4%), *King et al.* (50%), and *Horn et al.* (53%), slightly higher than that reported by *Johnson and Horn* (70.9%), *Phillips et al.* (72%) and *Johnson et al.* (74%), and slightly lower than that reported by *Gupta et al.* (88.9%) [14-20]. Additionally, the side effects in Group A patients were mild and negligible in our study. All patients reported tolerable immediate pain at the injection site; this side effect has been observed in nearly all patients who received an intralesional injection [5, 8, 14, 21]. Hyperpigmentation at the site of injection was seen in 32%, which is higher different from similar studies [5, 8, 21]. In our study, 3.2 percent of participants complained of transient itching at the injection site. Other local reactions, such as erythema, oedema, maceration, secondary infection, scarring, and flu-like symptoms, which have been reported in similar studies, were not observed. This finding reinforces the safety profile of the MMR vaccine.

There are a few limitations to this study. The recurrence rates following MMR immunotherapy could not be recorded since the study was conducted over a short duration of time with a limited follow-up period. A larger sample size would have yielded much stronger evidence.

Intralesional immunotherapy with MMR vaccine is an emerging modality of treatment for common warts; it is an effective therapy that is less painful, cost-effective, offers lower recurrence rates, and without disfiguring scarring. Additionally, the MMR vaccine's ease of availability, cost-efficiency,

and needless treatment of each wart, makes this a near-ideal approach. Furthermore, most people in our country have been exposed to this vaccine in their infancy as part of the national immunization program. Hence, the possibility of adverse reactions is rare.

5. Conclusion

This study demonstrates that intralesional immunotherapy with the MMR vaccine is more effective than traditional salicylic acid therapy for treating common warts. The MMR vaccine shows higher efficacy, safety, and ease of application, with minimal side effects, making it a viable and cost-effective alternative. The self-limiting nature of warts did not affect the treatment outcomes in either group, suggesting MMR immunotherapy as a superior option for managing warts, with the potential to clear treated and distant warts without scarring or recurrence.

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