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Original Article

Dermatology Section

Intralesional Measles Mumps Rubella Vaccine versus Cryotherapy in Multiple Extragenital Warts: A Prospective Interventional Study

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ABSTRACT

Introduction: Verruca, commonly known as warts, is a common cutaneous infection caused by Human papillomavirus (HPV), often challenging to treat effectively. Traditional therapies like cryotherapy have limitations, prompting interest in immunotherapeutic alternatives, including intralesional Measles Mumps Rubella (MMR) vaccine.

Aim: To evaluate the clinical outcomes of cryotherapy vs intralesional MMR vaccine in patients with multiple extragenital warts.

Materials and Methods: The present prospective interventional study was conducted in the dermatology Outpatient Department (OPD) of Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India over a period of 18 months. A total of 50 patients diagnosed with multiple extragenital warts were enrolled, with 25 patients in each treatment group: Cryotherapy (CT) (Group CT) and intralesional Measles Mumps Rubella vaccine (Group MMR). The treatment outcomes were measured using a Visual Analogue Scale (VAS), percentage of clearance of the largest lesion and Likert's patient satisfaction scores. For continuous variables, comparisons between the two treatment groups were made using the independent t-test. For categorical variables, Chi-square test was used.

Results: Both groups had comparable wart characteristics, with verruca vulgaris being the most common type, with 10(40%) of patients in the MMR group and 11 (44%) of patients in CT group. Clinical improvement assessed using the VAS score showed better and faster clearance, predominantly in the early weeks of treatment (week 2 and week 4) in the MMR group. The assessment based on the size of the largest wart and patient satisfaction using the Likert score also demonstrated better clearance in Group MMR at two, four and six weeks. Blisters 10 (40%) and hypopigmentation 5 (20%) were exclusively observed in the CT group.

Conclusion: While response to both therapies were good and comparable, intralesional MMR can be considered as a superior alternative to cryotherapy because administration of MMR into a single large lesion showed significant clinical improvement of not just the lesion injected, but clearance of warts at distant sites as well which was in contrast to cryotherapy where each and every wart was to be treated.

Keywords: Cytodestructive, Human papilloma virus, Immunotherapy, Liquid nitrogen, Verruca vulgaris

INTRODUCTION

Verruca vulgaris commonly known as warts are benign, proliferative lesions caused by HPV [1]. They are a common dermatological condition with transmission occurring via direct or indirect contact [2]. While warts are generally asymptomatic, patients may present with symptoms such as itching, pain, and a feeling of pressure [2]. Morphologically, warts can appear as flat, dome-shaped, cauliflower-shaped, or pedunculated lesions affecting any site [3].

Treatment strategies for warts can be broadly categorised into immunological therapies and cytodestructive methods [1]. Immunotherapy aims to harness the body's immune response to target and eliminate warts, thereby reducing recurrence rates [4]. Common immunotherapeutic agents include the MMR vaccine, imiquimod, autoinoculation, and needling [5]. Cytodestructive therapies, on the other hand, focus on physically destroying the wart tissue and include cryotherapy, bleomycin, 5-fluorouracil, electrosurgery, scissors excision, curettage, laser treatment, photodynamic therapy, and carbon dioxide laser therapy [1,4-6].

The MMR vaccine, as an immunotherapeutic modality, has shown promise in the treatment of warts. Its mechanism of action involves stimulating both humoral and cell-mediated immune responses, which help in clearing the lesions and preventing recurrence [7]. While generally well-tolerated, the MMR vaccine can cause temporary side effects such as pain at the injection site and fever. It is contraindicated in pregnant or lactating women and in immunocompromised individuals [7].

Cryotherapy, a cytodestructive method, involves the application of extremely low temperatures (typically using liquid nitrogen at -196°C) to induce dermal and vascular damage, leading to epidermal and dermal necrosis [8]. Cryotherapy is simple to administer, cost-effective and safe for use during pregnancy. However, the need for repeated sessions and associated healthcare costs are notable disadvantages.

Despite the availability of numerous therapeutic options, there is no universally accepted standard treatment for warts. The choice of therapy depends on various factors, including the number, size, and location of warts, patient preferences, and the healthcare setting. Against this background, the objective of the present study was to evaluate the clinical outcomes of cryotherapy versus intralesional MMR vaccine in patients with multiple extragenital warts.

MATERIALS AND METHODS

The present prospective interventional study was conducted in the dermatology OPD of Sree Balaji Medical College and Hospital, Chennai, Tamil Nadu, India, from March 2023 to September 2024. The study received approval from the Institutional Human

Ethics Committee (IHEC) with reference number 002/SBMCH/IHEC/2023/1915 dated 17/03/2023.

Patients clinically diagnosed with warts (verrucous lesions) present in sites other than the genitalia, who met the following criteria, were recruited for the study.

Inclusion criteria:

- Patients of more than 18 years of age;
- Patients with extragenital warts more than three in number;
- Patients with a treatment free period of at least four weeks.

Exclusion criteria:

- Known allergy to liquid nitrogen and/or measles, mumps, and rubella vaccine;
- Pregnant women;
- Lactating women;
- Patients on immunosuppressive therapy.

Sample size calculation: Using the data from Rajegowda HM et al., where 63.3% of patients in group A (MMR vaccine) and 33.3% of patients in group B (cryotherapy) showed Complete Clearance (CC) of warts after nine weeks, the sample size for comparing these proportions was calculated [1]. Assuming a 95% confidence level ($Z\alpha/2=1.96$) and 70% power ($Z\beta=0.52$), the minimum required sample size for the present study was computed to be 25 in each Group a total sample size of 50.

Study Procedure

Treatment protocol: Patients were then assigned to one of two treatment groups- Cryotherapy (Group CT) or MMR vaccine (Group MMR)- based on the clinical judgment of the treating dermatologist. A total of 50 patients diagnosed with multiple extragenital warts were enrolled in the study. Of these, 25 patients (50.0%) underwent cryotherapy (Group CT) and 25 patients (50.0%) received intralesional MMR vaccine therapy (Group MMR).

Group CT received cryotherapy with liquid nitrogen using a spray technique, maintaining a 1 cm distance and targeting a 5 mm margin around each wart. Each lesion was frozen for 10 seconds, thawed, and subjected to a second freeze-thaw cycle. This was repeated weekly for six sessions. Patients were observed for immediate adverse effects after each procedure.

Group MMR received intralesional immunotherapy with 0.5 mL of reconstituted live attenuated MMR vaccine injected into the largest wart using a 30G insulin syringe. This was administered every two weeks, up to a maximum of four doses or until CC.

Assessment of treatment: Patients were followed-up at each treatment visit and again at eight weeks post-treatment. The clinical improvement was evaluated based on the patient and physician global assessments, using the VAS score as seen in [Table/Fig-1] at each visit [1]. Likert Patient's satisfaction scores as seen in [Table/Fig-2] [6].

Grade	Type of clearance	VAS score	Description
Grade 4	Complete clearance	100%	Complete disappearance of treated warts and restoration of normal skin texture at the site
Grade 3	Excellent response	75-99%	Reduction in size and number of treated warts, with few residual warts still visible
Grade 2	Good response	50-74%	Some reduction in size only, but no decrease in the number of warts
Grade 1	Poor response	≤50%	No significant change in size or number of warts
Recurrence	Recurrence	N/A	Recurrence of warts during the study period

[Table/Fig-1]: Clinical improvement based on VAS [1].

Score	Patient satisfaction level
5	Very much
4	Somewhat satisfied
3	Undecided
2	Not really satisfied
1	Not at all satisfied

[Table/Fig-2]: Likert Patient's satisfaction scores [6].

STATISTICAL ANALYSIS

The statistical analysis for the study was performed using Statistical Package for Social Sciences (SPSS) v23. Descriptive statistics, including mean, median, standard deviation, and range, were calculated for continuous variables, while frequencies and percentages were determined for categorical variables. For continuous variables, comparisons between the two treatment groups were made using the independent t-test. For categorical variables, the Chi-square test was used to assess differences between the treatment groups. A p-value of less than 0.05 was considered statistically significant. All analyses were performed with a confidence level of 95%.

RESULTS

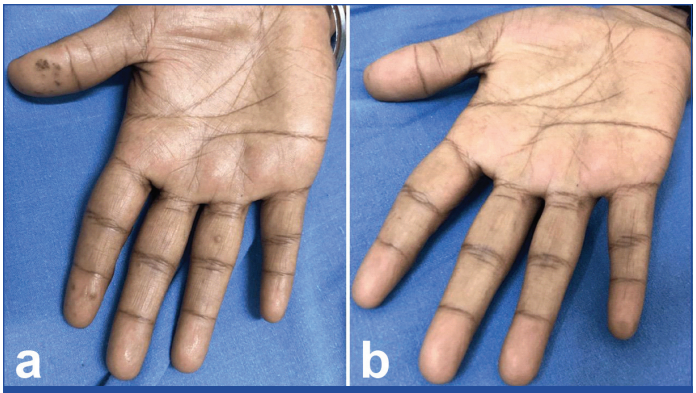
The mean age was 34.1±8.4 years in Group CT and 37.2±8.3 years in Group MMR, with no statistically significant difference (p=0.196). A higher proportion of patients in Group MMR were aged over 30 years (80%) compared to Group CT (60%), although this was not statistically significant (p=0.123). Both groups had a similar gender distribution, with males comprising 56% in Group CT and 52% in Group MMR (p=0.777) [Table/Fig-3].

Parameters		Group CT n=25	Group MMR n=25
Age (in years), Mean±SD		34.1±8.4	37.2±8.3
Age (in years)	<30	10±40.0	5±20.0
	>30	15±60.0	20±80.0
Gender	Male	14±56.0	13±52.0
	Female	11±44.0	12±48.0
Duration of lesions (in months) (Mean±SD)		3.5±1.7	3.0±2
Site of lesion	Upper limb	18±72.0	14±56.0
	Lower limb	7±28.0	7±28.0
	Face	0	4±16.0
Symptoms	Pain	12±48.0	12±48.0
	Itching	7±28.0	10±40.0
	No symptoms	6±24.0	3±12.0
Type of Wart	Plantar	5±20.0	6±24.0
	Palmar	7±28.0	7±28.0
	Verruca vulgaris	11±44.0	10±40.0
	Verruca plana (Plane warts)	2±8.0	2±8.0

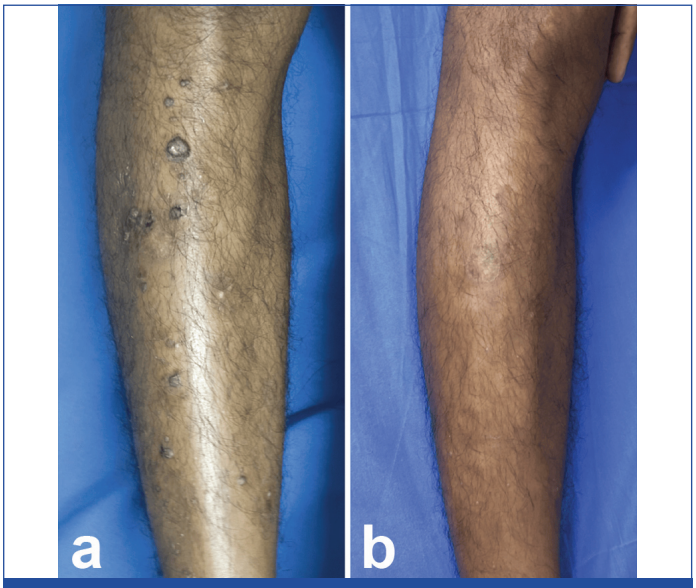
[Table/Fig-3]: Comparing the study groups and distribution of patients depending on various factors (N=50).

The mean duration of lesions was 3.5±1.7 months in Group CT and 3.0±2.0 months in Group MMR, with no significant difference (p=0.288). With regards to symptoms, pain was reported by 12 (48%) of patients in both groups, while itching was noted in 7 (28%) of Group CT and 10 (40%) of Group MMR patients (p=0.370). The mean number of lesions was 6.7±3.2 in Group CT and 7.2±2.8 in Group MMR (p=0.513), with most patients having between 3 to 11 lesions. The average size of the lesions was 1.3±0.6 cm in Group CT and 1.2±0.6 cm in Group MMR (p=0.510).

At the final follow-up at eight weeks, CC (Grade 4) was achieved in 24 (96%) of patients in MMR group compared to 23(92%) of patients in cryotherapy group [Table/Fig-4-6].



[Table/Fig-4]: Clinical image of patient in group A (Cryotherapy): a) Baseline presentation - Week 0; b) Response at the end of final week - Week 8.



[Table/Fig-5]: Clinical image of patient in Group MMR (Intralesional MMR): a) Baseline presentation - Week 0; b) Response at the end of final week - Week 8.

Clinical improvement evaluated using patient and physician global assessments - VAS score#		Group CT n=25 n (%)	Group MMR n=25 n (%)	p-value
At 2 weeks	Grade 1	20 (80.0)	10 (40.0)	0.003*
	Grade 2	5 (20.0)	7 (28.0)	
	Grade 4	0 (0.0)	8 (32.0)	
At 4 weeks	Grade 2	5 (20.0)	6 (24.0)	0.009*
	Grade 3	10 (40.0)	0 (0.0)	
	Grade 4	10 (40.0)	19 (76.0)	
At 6 weeks	Grade 3	7 (28.0)	1 (4.0)	0.147
	Grade 4	18 (72.0)	24 (96.0)	
At 8 weeks	Grade 3	2 (8.0)	1 (4.0)	0.949
	Grade 4	23 (92.0)	24 (96.0)	

[Table/Fig-6]: Comparison of study groups by clinical improvement evaluated using patient and physician global assessments - VAS score N=50.
*Statistically significant at p<0.05; Chi-square test; #Grade 4, which represents Complete Clearance (CC) with a VAS score of 100%; Grade 3 indicates an excellent response with a VAS score of 75%-99%; Grade 2 reflects a good response with a VAS score of 50%-74%; Grade 1 signifies a poor response with a VAS score of ≤50%

Assessment of the single largest wart revealed significant differences in clearance rates between the two groups over time. At two weeks of treatment, 8 (32%) of Group MMR patients achieved CC compared to none in Group CT, with all Group CT patients showing only Partial Clearance (PC) (p=0.003). At the final assessment at eight weeks, CC was observed in 24 (96%) of patients in MMR group and 23 (92%) of patients in cryotherapy group (p=0.949) [Table/Fig-7].

At the final eight-week assessment, 24 (96%) of patients in MMR group and 23 (92%) of patients in cryotherapy group achieved complete satisfaction (score 5) (p=1.000) [Table/Fig-8].

Assessment in the single largest wart#		Group CT n=25 n (%)	Group MMR n=25 n (%)	p-value
At 2 weeks	PC	25 (100)	17 (68.0)	0.003*
	CC	0 (0.0)	8 (32.0)	
At 4 weeks	PC	15 (60.0)	6 (24.0)	0.022*
	CC	10 (40.0)	19 (76.0)	
At 6 weeks	PC	8 (32.0)	1 (4.0)	0.027*
	CC	17 (68.0)	24 (96.0)	
At 8 weeks	PC	2 (8.0)	1 (4.0)	0.949
	CC	23 (92.0)	24 (96.0)	

[Table/Fig-7]: Comparison of study groups by assessment in the single largest wart N=50.
*Statistically significant at p<0.05; Chi-square test; #Complete Clearance (CC) (100% clearance of the lesion) scored as 3; Partial Clearance (PC) (50-99% reduction in size) scored as 2; No Response (less than 50% reduction in size) scored as 1

Patient satisfaction#		Group CT n=25 n (%)	Group MMR n=25 n (%)	p-value
At 2 weeks	2	5 (20.0)	0 (0.0)	<0.001*
	3	20 (80.0)	10 (40.0)	
	4	0 (0.0)	7 (28.0)	
	5	0 (0.0)	8 (32.0)	
At 4 weeks	3	10 (40.0)	1 (4.0)	0.017*
	4	5 (20.0)	5(20.0)	
	5	10 (40.0)	19 (76.0)	
At 6 weeks	3	0 (0.0)	1 (4.0)	0.027*
	4	6 (24.0)	0 (0.0)	
	5	19 (76.0)	24 (96.0)	
At 8 weeks	3	0 (0.0)	1 (4.0)	1.000
	4	2 (8.0)	0 (0.0)	
	5	23 (92.0)	24 (96.0)	

[Table/Fig-8]: Comparison of study groups by patient satisfaction N=50.
*Statistically significant at p<0.05; Chi-square test; #Patient satisfaction was assessed using a Likert scale, with scores ranging from 1 to 5. A score of 5 indicated being very much satisfied, 4 represented somewhat satisfied, 3 indicated undecided, 2 reflected not really satisfied, and 1 corresponded to not at all satisfied

With regards to treatment, both groups Group CT and Group MMR had 100% of patients reporting pain at baseline, with no significant difference between the groups (p=1.000). However, by two weeks, a significantly higher percentage of patients in Group CT 15 (60.0%) reported pain compared to Group MMR 6 (24.0%) (p=0.010), with similar trends observed at four and six weeks. By eight weeks, neither group reported any pain nor there was no significant difference between them (p=1.000). Blisters were noted in 10 (40%) of patients in CT group mainly at 2-4 weeks of therapy and Post-inflammatory hypopigmentation was noted in 5 (20%) of patients in CT group, mainly at 6-8 weeks of therapy.

Participants in CT group required 7.64±0.95 weeks for CC of lesions, while patients in MMR group required only 5.76±1.56 weeks for CC of lesions [Table/Fig-9].

Group	Mean	SD	p-value
Cryotherapy	7.64	0.95	<0.001*
MMR vaccine	5.76	1.56	

[Table/Fig-9]: Comparison of study groups by time (in weeks) for Complete Clearance (CC) of warts.
Independent t-test was used; *Statistically significant at p <0.05; SD: Standard deviation

DISCUSSION

The mean age of patients in the cryotherapy group (34.1 years) was slightly lower than in the MMR vaccine group (37.2 years), though the difference was not statistically significant. This similarity in age distribution is important, as age has been reported to influence

immune response and the efficacy of treatments such as cryotherapy and immunotherapy, as demonstrated by Vanarase MU et al., [5]. Gender distribution was also comparable between the two groups, with no significant differences in the number of male and female patients (p=0.777) [4]. This is in line with other studies, such as those by Mohta A et al., (2021), which demonstrated no gender-based differences in the effectiveness of intralesional immunotherapy or cryotherapy for treating warts [9].

In both groups, the most common types of warts were verruca vulgaris, followed by plantar warts, and palmar warts. This was in contrast to a study by Awal G and Kaur S., where palmoplantar warts were the common presentation and responded well to MMR in comparison to other types of warts [10].

Clinical improvement, as assessed by VAS revealed a significantly faster response in the MMR group predominantly in two weeks and four weeks. These findings are consistent with previous studies, such as Rajegowda HM et al., who reported a 63.3% CC rate for MMR therapy at nine weeks compared to only 33.3% with cryotherapy [1]. Similarly, Dhope A et al., observed a 65% CC rate in the MMR group versus a 5% clearance rate in the control group using normal saline [4].

Analysis based on the size of single largest wart in each patient showed better resolution of warts in Group MMR at weeks two, four and six compared to Group CT. In spite of intralesional MMR being injected only into the single largest wart, patients' demonstrated clearance of warts at distant sites as well. This highlights the immunotherapeutic potential of the MMR vaccine, which stimulates a delayed-type hypersensitivity response, enhances cell-mediated immunity, and promotes systemic clearance of warts, not just localised destruction [1,4].

Patient satisfaction also significantly favoured the MMR group. By two weeks, more than half of the MMR patients reported high satisfaction scores, whereas most cryotherapy patients remained undecided about their treatment outcomes (p<0.001). Higher patient satisfaction scores were obtained in MMR group compared to cryotherapy group at four and six weeks of treatment. The higher satisfaction rates likely reflect the superior efficacy, fewer sessions needed, and minimal side-effects experienced by MMR-treated patients. This was in contrast to a study by Chauhan PS et al., where 59 patients out of a total of 100 patients dropped out of the study citing dissatisfaction with treatment response. But in the same study, out of the 51 patients who completed treatment, 42 patients were very satisfied [11].

With regards to treatment side effects, Blisters and post-inflammatory hypopigmentation was exclusively found in 10 (40%) and 5 (20%) patients in the CT group. Similarly, Chauhan PS et al., reported minimal discomfort with MMR vaccine injections compared to cryotherapy or other destructive treatments [11].

Clinically, intralesional MMR may serve as an effective alternative to cryotherapy, particularly in patients with multiple warts, where administering the vaccine to a single lesion may cause clearance of warts at distant sites.

Limitation(s)

Firstly, the study was conducted at a single tertiary care centre which may limit the generalisability of the findings to the broader population. Secondly, the study duration was limited to eight weeks, which may not be sufficient to assess long-term recurrence rates or delayed adverse effects. The absence of blinding for patients and clinicians could also have introduced observer or performance bias, particularly in subjective assessments such as pain, satisfaction, and cosmetic concern. Furthermore, immunological parameters such as cytokine levels or T-cell responses were not evaluated, which could have provided a deeper understanding of the mechanisms underlying the therapeutic effects of the MMR vaccine.

CONCLUSION(S)

A major advantage of intralesional MMR immunotherapy is that administration of the vaccine into a single largest wart results in significant clinical improvement not only at the injected site but also leads to clearance of warts at distant sites. The present study demonstrates that while cryotherapy and intralesional MMR vaccine are effective treatment modalities for multiple extragenital warts, intralesional MMR can be considered as a superior alternative to cryotherapy.

Authors' contributions: All authors contributed equally to the study conception, design and data acquisition. In addition, while Dr. SS and DD contributed to the definition of intellectual content and literature search, Dr. NB ,SS and GD contributed to data and statistical analysis as well as manuscript preparation. Dr. DM and SG also contributed to the definition of intellectual content, manuscript reading and review. All the authors have read and approved the final manuscript and take up responsibility for the integrity of the work as a whole from inception to the published article.

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