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A Comparitive Study on the Efficacy and Safety of Intralesional Measles Mumps Rubella (MMR) Vaccine Versus Intralesional Vitamin D3 In The Management Of Multiple Verrucae Vulgaris Among Adults

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Abstract
Background *– Warts or Verrucae are the infection of skin and mucosae caused by human papilloma virus. Majority of therapeutic modalities for warts are unsatisfactory. Immunotherapy is an emerging and promising modality.*
Aims and Objectives*: To study the relative efficacy of intralesional MMR vaccine versus intralesional Vit D3 in the treatment of multiple verrucae vulgaris.*
Materials and Methods*: 50 patients with multiple(>6) common warts were enrolled and were randomly divided into two groups with 25 patients in each group. Group A was treated with intralesional 0.3ml Inj.MMR and Group B with intralesional 0.2ml of Inj Vitamin D3. Injections were repeated at 2 weeks interval until complete clearance or maximum of 4 sessions. Maximum of 2 large size warts were treated at each visit.*
Results*: In Group A complete to excellent response was seen in 92% of patients and in Group B it was 88%. The common complaint in both groups was injection site pain. No recurrence was seen in follow up period.*
Conclusion*: Both immunotherapies were effective in treatment of multiple common warts. Additional benefits associated were lesser time duration required and lesser side effects compared to destructive modalities*
Keyword*: Common warts, Immunotherapy, MMR vaccine, Vitamin D injections.*

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I. Introduction

Warts or verrucae vulgaris are the benign epidermal proliferation of skin and mucosae[1]. It is caused by Human papilloma virus (HPV), a non enveloped double stranded DNA virus. The virus infects both keratinized as well as non keratinized epithelium[2]. Warts are most common in childhood and in early 20's , however no age group is spared[3]. Warts are mostly asymptomatic . Occasionally it may be associated with itching and pain like the palmoplantar warts. Warts are very contagious resulting in spread to other parts in same individual or by direct contact to other individuals. Various destructive and ablative treatment options have been the mainstay of treatment for years. The shortcomings associated with these modalities are pain, scarring, secondary infection, frequent recurrences and inability to treat multiple warts[4]. Immunotherapy with agents such as zinc sulfate, imiquimod, intralesional candida antigen, BCG vaccine, MMR, PPD, Vitamin D is emerging as more popular and convenient modality for treating multiple and recurrent warts[5]. Immunotherapy manipulates the immune system to achieve an anti HPV immune reaction[6]. It has an additional benefit of clearing distant warts along with the treated lesion.

In this present study we have attempted to evaluate the relative efficacy and safety of two immunotherapeutic agents that is intralesional Measles Mumps Rubella(MMR) vaccine with that of intralesional Vitamin D3 in multiple verrucae vulgaris.

II. Aims And Objectives

1) To assess the relative efficacy of intralesional Measles Mumps Rubella vaccine to intralesional Vitamin D3 in the treatment of multilple verrucae vulgaris.
2) To assess the relative safety of intralesional Measles Mumps Rubella vaccine to intralesional Vitamin D3 in treatment of multiple verrucae vulgaris.

III. Materials And Methods

This study was single blinded, prospective comparative trial. The study was conducted among the patients with multiple warts attending the outpatient clinic of the Department of Dermatology, RIMS, Ranchi after the approval of the Ethics Committee.
The study population enrolled for the study were patients with multiple (>6) common wart. A total of 50 patients were included. The study period was form August 2021 to January 2022.
Patients fulfilling the inclusion and exclusion criterias only were enrolled in the study.

Inclusion criterias were

- Patients of both sexes belonging to age of between 18-60 years.
- Patients with multiple (>6) common wart.
- Patients who have not received any form of treatment 2 months prior to enrollment for the study.
- Patients willing for the treatment and follow ups.

Exclusion criterias were

- Patient with any known prior hypersensitivity to MMR vaccine or Injection Vitamin D.
- Pregnant and lactating women.
- Patients presenting with warts other than common warts.
- Patients with any evidence of immunosuppression including HIV.
- Patients with history of intake of immunotherapy drugs
- Patients with any systemic illness, secondary infection, acute febrile illness.
- Patient with allergic skin diseases, history of convulsion, meningitis , asthma
- Patients with keloidal tendency.

Post enrolment the procedure was explained to all the patients and informed consent was obtained.
The study population was then randomly divided into two groups. Group A and Group B with 25 patients in each group.
At the start of study a detailed history and clinical examination was done to assess and record the total number of lesions, duration and location of the warts.
Mandatory baseline investigations were done for all the enrolled patients such as Complete blood count, Bleeding time, Clotting time, Routine Viral serology , Fasting blood sugar.

PROCEDURE

Group A: Under all aseptic precautions, intralesional MMR vaccine 0.3ml was given using an insulin syringe.
Group B: Under all aseptic precautions intralesional injection Vitamin D3 0.2ml (60,000 IU/ml) was given using an insulin syringe
The base of 2 large sized warts were considered for injection in each patient.
Same warts were treated at each session
Injections were reported at 2 week interval until complete clearance or for a maximum of 4 injections.
At each visit clinical examination was done for size and number of lesions
Photographs were taken before starting the treatment and at each subsequent visit and after 3 months
Post treatment, patients were advised not to use any topical or oral medication.

EVALUATION AND ASSESSMENT

Efficacy parameter – The clinical improvement was rated as complete clearance, excellent response, good response or poor response by the physician's global assessment using a visual analogue scale score [Table 1] at each visit taking into account baseline clinical photographs[7].
Safety parameter- Pain, swelling, burning, erythema at injection site, Flu like symptoms post injection and scarring.

TABLE No 1: Visual Analog Scale Score

GRADES OF CLINICAL IMPROVEMENT	DEFINITION
COMPLETE CLEARANCE (VAS score-100%)	Complete disappearance of warts including distant warts
EXCELLENT RESPONSE (VAS score 75-90%)	Reduction in number with few residual warts still visible
GOOD RESPONSE (VAS Score 50-74%)	Some reduction in size but no decrease in number

POOR RESPONSE (VAS Score <50%)	No significant change in size and number of warts.

The statistical analysis was done using SPSS . The statistical tests used in this study was paired t-test. P<0.05 was considered to be statistically significant.

IV. Results

All 50 patients completed the study . The mean age of patients in Group A was 28.76 ± 7.084 years and in Group B was 26.56 ± 4.538 years. Duration of the warts in Group A ranged from 4 months to 60 months whereas in Group B it ranged from 3 months to 78 months. The number of warts in Group A was from 8 to 40 with mean of 20.48 ± 6.887 whereas in Group B the range was from 10 to 38 with mean of 21.48 ± 6.165 [Table 2]

In Group A, complete clearance of wart was seen in 16 (64%), excellent response was noted in 7 (28%), good response in 2 (8%) and poor response in 0 (0%) patients [Table 3].

Complications reported were minimal that is almost all patients reported of pain at injection site which persisited for few hours. Only 2 (8%) patients developed flu like symptoms which subsided within 2-3 days . No recurrences were noted during follow up period.

In Group B, that is injection vitamin D3 group complete clearance of warts was noted in 10 (40%) , excellent response was seen in 12 (48%) , Good response in 2(8%) patients and 1 patient(4%) had poor response.

Most common side effect reported was injection site pain by 25 patients(100%).

No recurrences were noted after the complete clearance in follow up period.

TABLE No 2: Demographic details of study population

	GROUP A	GROUP B
AGE Mean ± SD	28.76 ± 7.084	26.56 ± 4.538
DURATION OF DISEASE Min- Max	4-60	3-78
NO. OF WARTS Min-Max (Mean)	8-40 (20.48 ± 6.887)	10-38 (21.48 ± 6.165)
SIZE OF WART(cm) Min- Max	0.2-1.5	0.3-1.3

TABLE No 3 : Clinical improvement noted in Group A and B

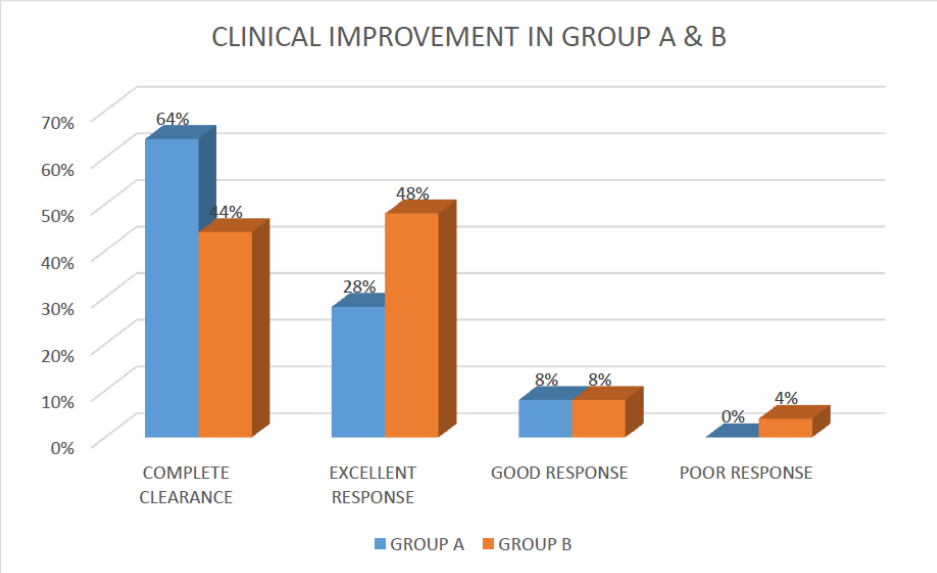
	GROUP A		GROUP B	
GRADING OF IMPROVEMENT	Number	Percentage (%)	Number	Percentage (%)
COMPLETE CLEARANCE	16	64	10	40
EXCELLENT RESPONSE	7	28	12	48
GOOD RESPONSE	2	8	2	08
POOR RESPONSE	0	0	1	04

Complete to complete response noted in Group A was 23 (92%) patients and in Group B was 22(88%) patients and the difference was statistically insignificant with p >0.05

TABLE No 4 : Side Effects observed in Group A and B

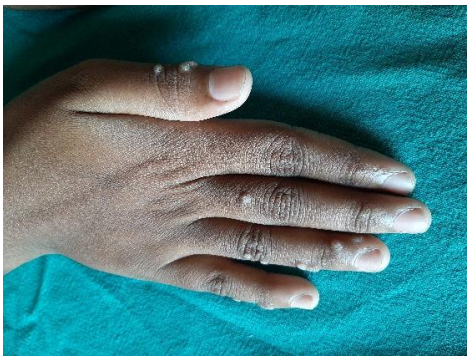
	GROUP A		GROUP B	
SIDE EFFECT	NUMBER	PERCENTAGE(%)	NUMBER	PERCENTAGE(%)
Pain at injection site	25	100	25	100
Flu like symptoms	2	8	0	0
Erythema	0	0	0	0
Burning	0	0	0	0
Scarring	0	0	0	0
Swelling	0	0	0	0

GRAPH No 1: Graphical representation of clinical improvement in Group A and Group B



GROUP A- INTRALESIONAL MMR VACCINE

A: At baseline



B: At 12 weeks

GROUP B- INTRALESIONAL VITAMIN D

A: At baseline

B: At 12weeks

V. Discussion

Warts are notorious owing to their recurrent and resistant nature. Overtime diverse therapeutic modalities have been developed to treat warts. However none of them are 100% satisfactory. This void for up to mark treatment for multiple verrucae has kept the search for improving our armamentarium of wart treatment. Immunotherapy is emerging as novel treatment using biological substance which clears local as well as distant warts by increasing immune response against the pathogen. Researchers have tried number of antigens and in the present study , two of such treatment options have been evaluated.

MMR vaccine mounts an TH1 immune response , this in turn increases TNF α, IL-2, Il-4 , IL-5 and IFN-γ and propagates a delayed hypersensitivity reaction against both MMR viral antigens and HPV [8].

However Vitamin D3 regulates epidermal proliferation and cytokine production. It activates the toll like receptors of the macrophages and downregulates IL-1a, IL-6 which in turn induces anti-microbial peptide formation in injected and distant warts[9].

Dhope A et al[10] conducted a case control study on a sample size of 40 patients using Inj MMR and placebo. 20 patients were treated with Inj MMR and 65% patients had complete clearance of lesions.

In our study Group A, complete response was observed among 64% of patients and complete to excellent response among 92% of the patients. The findings of our present study is consistent with other studies.

Raju J et al[11] conducted an open label prospective study. In his study he included 30 patients with extragenital warts and treated them with Inj. MMR for maximum of 5 times at 2 week interval. At the end of his study period he observed complete clearance of warts among 70% of patients which was similar to our study.

The efficacy of MMR vaccine in warts was further strengthened by reports of Ofat et al[12], Shah et al[13] who reported complete clearance in 63% and 72% of patients respectively.

In our study Group B, complete to excellent response was noted among 88% of patients. These findings were relatable to other studies. Aktas et al[14] conducted a study on 20 patients of plantar wart with Inj. Vitamin D3. He noted excellent response among 80% of patients.

Similar results were observed by Banoth et al[15], Kavya et al[16] who reported complete response in 76.92% and 78.57% of patients respectively.

In the present study. Patients reported pain at injection site as predominant complaint similar to findings of Aktas et al who made similar observation in his study and noted mild to moderate pain as chief complaint among the study population.

VI. Conclusion

Both the intralesional immunotherapeutic treatment modalities are economical, safe , promising for multiple common wart. Both the treatment have shown good tolerability and safety and can also treat distant warts. Both therapies have shown similar efficacy , however clinical improvement was marginally more for intralesional MMR. Hence, Immunotherapy can be first line of treatment for multiple warts.

LIMITATION

- Small number of patients
- Study included only patientys with verrucae vulgaris
- Short follow up period.

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