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EFFEFT OF MMR - IMMUNOTHERAPY ON EXTRAGENITAL WARTS: A RANDAOMIZED CONTROLLED TRIAL

Dermatology

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ABSTRACT

Background/Aim: Immunotherapy is considered to be a useful modality for management of warts. In present study we compare the usefulness of Measles Mumps Rubella (MMR) Immunotherapy against normal saline for management of extragenital warts. **Methods:** A total of 50 patients aged 18-50 years presenting with extragenital warts were randomized into – MMR therapy (n=25 patients receiving 0.5 ml intralesional MMR) and Control group (n=25 patients receiving 0.5 ml intralesional 5% normal saline). All the patients were followed up after three weeks. Reduction in number and size of warts was recorded. Response to treatment was categorized as Complete response (100% reduction), marked response (75-99% reduction), moderate response (50-75% reduction) and inadequate response (<50% reduction). Data was analyzed using SPSS 21.0 version. Chi-square and independent samples 't'-tests were used. **Results:** In the MMR group, mean age of patients was 30.60±8.81 years; majority were males (64%), from rural areas (52%) and had an average of 7.44±4.41 warts with mean size 3.46±1.78 cm. No significant difference between MMR group and control group was observed for demographic profile, presenting complaints, number, size and distribution of warts. Post-injection adverse effects were seen in 48% of MMR and 20% of Control group but this difference was not significant statistically (p=0.060). After three weeks, mean % reduction in number and size of warts was 85.82±25.31 and 77.33±29.72 respectively in MMR group and 48.44±30.19 and 52.57±26.61 respectively in control group, thus showing a significant difference between two groups (p<0.05). Proportion of patients with complete and marked response was significantly higher in MMR group (68%) as compared to control group (20%) (p=0.003). **Conclusion:** Intralesional MMR immunotherapy was useful in complete to marked resolution of warts. Further studies with longer duration of follow-up to evaluate the recurrence are recommended.

KEYWORDS

Measles Mumps Rubella Immunotherapy, Extragenital warts, Intralesional, Normal saline, Complete resolution.

INTRODUCTION

Extragenital warts, despite being benign in nature are one of the most common reasons for visits to a dermatologist[1]. Warts are result of viral infection caused by human papillomaviruses (HPVs). They can affect both genital as well as extragenital sites. Till date more than 120 HPVs have been found to be associated with cutaneous warts, of these nearly 40 are associated with extragenital warts and malignancies[2]. There is an impact of location of warts on the severity of pain associated with it. Presence of warts in exposed areas of skin has cosmetic issues and could be socially unacceptable. Treatment of warts is often associated with recurrence. In effect warts place a huge burden on quality of life of affected patients[3].

A number of treatment options are available for treatment of cutaneous warts, that may include destructive therapies targeted to chemical or physical removal of diseased tissue trichloroacetic acid, salicylic acid, podophyllotoxin, and 5-fluorouracil, radio cautery, cryotherapy, surgical excision, carbon dioxide laser[1,4]. Non-destructive therapies such as antimitotic and antiviral agents are also used. Each therapeutic method is associated with its own advantages as well as disadvantages. The primary focus while planning a therapeutic intervention is on minimizing the side effects and recurrence. In the recent years, intralesional Measles, Mumps and Rubella (MMR) vaccine has emerged as an effective treatment modality for management of warts with early resolution of warts, low recurrence rates and almost negligible side effects[5-7]. However, most of these studies have been carried out as case-series and there is lack of case-control studies to establish the efficacy of intralesional MMR immunotherapy in relative terms. Hence, the present study was carried out as a case-control study to evaluate the efficacy of intralesional MMR in management of extragenital warts.

MATERIALAND METHOD

The present study was carried out at Department of Dermatology, Era' Lucknow Medical College, Lucknow after seeking approval from Institutional Ethics Committee and getting informed consent from the participating patients. A total of 50 patients with new onset (within three months of onset), treatment naïve adult patients aged 18-50 years presenting with extragenital warts were enrolled in the study. Pregnant and lactating women; patients with apparent infection or immune suppression, asthma, allergic skin disorders, meningitis, or convulsions; history of systemic/chronic illness, or who had received treatment for warts after the onset were excluded from the study.

Demographic and clinical details for presenting complaints, number and size of warts, sites involved, duration of illness, dietary and personal habits were recorded.

The patients were then randomized into – MMR therapy (n=25 patients receiving 0.5 ml intralesional MMR) (Group I) and Control group (n=25 patients receiving 0.5 ml intralesional 5% normal saline) (Group II). All enrolled patients received intralesional injection of 0.25 mL of reconstituted MMR vaccine/normal saline in largest wart with 30G insulin syringe (one dose).

All the patients were followed up after three weeks. Reduction in number and size of warts was recorded. Response to treatment was categorized as Complete response (100% reduction), marked response (75-99% reduction), moderate response (50-75% reduction) and inadequate response (<50% reduction).

Data was analyzed using SPSS 21.0 version. Chi-square and independent samples 't'-tests were used to compare the data. 'p' value less than 0.05 was considered indicative of a statistically significant association.

RESULTS

Mean age of patients in Group I was 30.60±8.81 years whereas mean age of patients in Group II was 29.84±8.81 years. Majority of patients in Group I (64%) as well as Group II (72%) were males. There were 52% rural and 48% urban patients in Group I as compared to 48% and 52% respectively in Group II. Statistically, there was no significant difference between the two groups with respect to age, sex and place of residence (p>0.05). Pain, pruritus and discharge were the presenting complaints in 44%, 20% and 28% patients respectively in Group I and 32%, 20% and 24% patients respectively in Group II. There was no significant difference between the two groups with respect to presenting complaints (p>0.05). A total of 12 (48%) patients in Group I and 14 (56%) in Group II were asymptomatic (p=0.571). Mean time since onset was 7.96±8.12 weeks in Group I as compared to 6.64±6.17

weeks in Group II (p=0.520). There were 5 (20%) smokers, 3 (12%) alcohol users and 8 (32%) non-vegetarians in Group I compared to 6 (24%) smokers, no alcohol users and 10 (40%) non-vegetarians in Group II. Statistically, the two groups did not show a significant difference with respect to dietary and personal habits (p>0.05). Number of warts ranged from 1 to 16 with a mean value of 7.44±4.41 in Group I as compared to 6.96±2.99 in Group II. Size of warts ranged from 0.2 to 8 cm with a mean size of warts was 3.46±1.78 cm in Group I and 3.45±1.65 cm in Group II. Statistically, there was no significant difference between the two groups with respect to number and size of warts (p>0.05). With respect to distribution of warts, in both the groups face and hand were the most commonly involved site whereas forearm was the least commonly involved site. Statistically, there was no significant difference between the two groups with respect to distribution of warts (p=0.330) (Table 1).

Post-injection, a total of 48% patients experienced adverse reactions in Group I as compared to 20% in Group II. In group I, a total of 9 (36%) reported pain and 3 (12%) had swelling at injection site. In Group II, only 5 (20%) patients had pain at injection site and none had swelling. Statistically, there was no significant difference between two groups with respect to post-injection adverse reactions (p=0.060) (Table 2).

After three weeks, mean post-treatment number of warts and size was significantly lower in Group I as compared to that in Group II (p<0.001). Mean % reduction in number and size of warts was 85.82±25.31 and 77.33±29.72 respectively in MMR group and 48.44±30.19 and 52.57±26.61 respectively in control group, thus showing a significant difference between two groups (p<0.001 and p=0.003) (Table 3).

Proportion of patients with complete and marked response was significantly higher in MMR group (68%) as compared to control group (20%) (p=0.003) (Fig. 1).

DISCUSSION

The present study evaluated short-term outcome (three-weeks follow-up) of MMR immunotherapy in patients with extragenital warts and compared it against a placebo (normal saline). Adequate treatment response was noted in 92% of cases receiving MMR immunotherapy whereas marked/complete response was seen in 68% of cases as compared to only 20% of controls. Thus, we found MMR to be highly effective in management of extragenital warts. Although, MMR immunotherapy has been reported to be effective in a number of non-comparative case-series[5-7] yet there are few studies evaluating its performance against other drug regimens or placebo. In one recent study, Rezai *et al.*[8] reported complete clearance of warts in 65.2% of cases subjected to intralesional MMR immunotherapy as compared to 23.85% of placebo group (normal saline) patients in resistant-to-therapy palmoplantar warts. In the present study, we obtained marked to complete response in more than two-third of new onset, treatment naïve, extragenital warts cases subjected to MMR immunotherapy against 20% of placebo controls (normal saline) thereby showing results similar to those obtained by them. Intralesional immunotherapy seems to be an effective choice as it is known to stimulate cell-mediated and humoral immunity that helps to accelerate clearance of virus and viral infected cells which in turn effectively reduces the size of the wart[9-11].

In the present study, we found MMR immunotherapy to be more effective than placebo treatment with normal saline, however, it has been shown to be effective against other alternative treatments. In a recent study, Rajegowda *et al.*[7] found the response rate following MMR immunotherapy to be almost twice as compared to cryotherapy. It has also been shown to be effective against other innovative therapies too. In a recent study, Mohta *et al.*[12] reported complete clearance in 87.8% of intralesional MMR immunotherapy treated recalcitrant cutaneous warts as compared to 77.4% of those receiving intralesional vitamin D and only 12.5% of placebo (normal saline) group patients respectively. A relatively lower response rate in the present study could be owing to use of only one-dose of intralesional treatment as compared to 2 weekly repetitions in their study.

The findings of the present study, thus are in agreement with most of the previous studies supporting highly efficient role of intralesional MMR immunotherapy in management of extragenital warts. The present study had certain limitations, such as smaller sample size, outcome assessment at a shorter interval and lack of follow-up in order to assess recurrence. Further studies on a larger sample size, a longer duration of outcome and recurrence assessment, ability to repeat intervention and inclusion of other comparative intralesional therapies are recommended.

CONCLUSION

Intralesional MMR immunotherapy is highly effective in management of extragenital warts in short duration. Studies to evaluate its effectiveness in prevention of recurrence are recommended with a longer follow-up period.

Table 1: General Profile and Baseline characteristics of Patients in two groups

SN	Characteristic	Group I (MMR) (n=25)	Group II (Normal saline) (n=25)	Statistical significance
1.	Mean age±SD (Range) in years	30.60±8.01 (18-50)	29.84±8.81 (18-49)	't'=0.319; p=0.780
2.	Sex Male Female	 16 (64%) 9 (36%)	 18 (72%) 7 (28%)	 2=0.368; p=0.544
3.	Place of residence Rural Urban	 13 (52%) 12 (48%)	 12 (48%) 13 (52%)	 2=0.080; p=0.777
4.	Presenting complaints			
	Pain	11 (44%)	8 (32%)	2=0.764; p=0.382
	Pruritus	5 (20%)	5 (20%)	2=0; p=1
	Discharge	7 (28%)	6 (24%)	2=0.104; p=0.747
	Cosmetic/Asymptomatic	12 (48%)	14 (56%)	2=0.321; p=0.571
5.	Mean Duration of Onset±SD (Weeks)	7.96±8.12	6.64±6.17	t=0.647; p=0.520
6.	Smoking	5 (20%)	6 (24%)	2=0.117; p=0.733
7.	Alcohol use	3 (12%)	0	2=3.191; p=0.074
8.	Non-vegetarian diet	8 (32%)	10 (40%)	2=0.347; p=0.556
9.	Family history	0	0	-
10.	Mean Number of warts±SD (Range)	7.44±4.41 (2-16)	6.96±2.99 (3-14)	t=0.451; p=0.654
11.	Mean size±SD (Range) cm	3.46±1.78 (1-8)	3.45±1.65 (0.2-8)	t=0.016; p=0.987
12.	Distribution Face Hands Feet Forehead Forearm	 8 (32.0%) 7 (28%) 5 (20%) 4 (16%) 1 (4%)	 13 (52%) 7 (28%) 2 (8%) 1 (4%) 2 (8%)	2=4.610; p=0.330

Table 2: Post-injection adverse reactions

SN	Characteristic	Group I (MMR) (n=25)	Group II (Normal saline) (n=25)	Statistical significance
1.	No	13 (52%)	20 (80%)	$\chi 2$=5.628; p=0.060
2.	Pain	9 (36%)	5 (20%)	
3.	Swelling	3 (12%)	0	

Table 3: Response to treatment (After 3 weeks of follow-up)

SN	Characteristic	Group I (MMR) (n=25)	Group II (Normal saline) (n=25)	Statistical significance
1.	Mean Post-treatment number±SD	1.16±1.38	3.52±2.54	t=4.092; p<0.001
2.	Mean Post-treatment size±SD (cm)	0.38±0.68	1.72±1.28	t=4.623; p<0.001
3.	Mean post-treatment reduction in number±SD (%)	85.82±25.31	48.44±30.19	t=4.744; p<0.001
4.	Mean post-treatment reduction in size±SD (%)	77.33±29.72	52.57±26.61	t=3.105; p=0.003

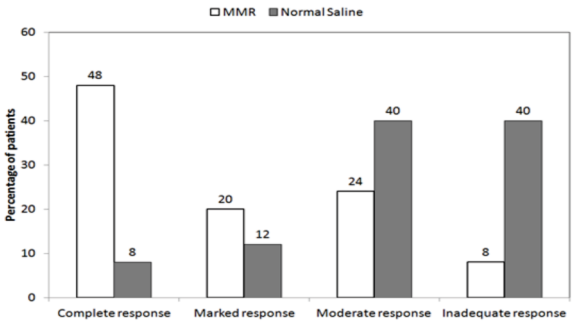

Fig. 1: Outcome of treatment in MMR and Normal saline groups (2=13.976; p=0.003)

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