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Original Research Article

Comparison of cryotherapy versus intralesional measles, mumps, rubella vaccine versus their combination therapy in Indian patients with cutaneous wart: a single centre prospective observational study

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ABSTRACT

Background: Need for more effective and less time consuming therapeutic method is current necessity for treatment of cutaneous warts. The objective of the study was to evaluate and compare the efficacy, safety of cryotherapy versus intralesional measles, mumps, rubella (MMR) vaccine versus combination of cryotherapy and intralesional MMR vaccine in Indian patients with cutaneous wart.
Methods: This prospective observational study was conducted in 60 patients of cutaneous warts. Patients were divided into three groups viz., group A, group B and group C. Group A was treated with cryotherapy alone, Group B received intralesional injection 0.1 to 0.3 ml of MMR vaccine alone and Group C received combination of group A and group B therapy. In each group treatment was repeated at 3 week interval for a maximum of 4 sittings. Percentage of improvement was evaluated using visual analogue scale (VAS) for local as well as distant (non-inoculated) warts. Follow-up was made every 2 months till 4 months to detect any recurrence.
Results: For local warts in second half of treatment (12^{th} week) patients of Group B and Group C showed significantly better response than patients in Group A. For distant warts in first half of treatment session patients showed significantly better response to Group C than as compared to Group B therapy ($p<0.039$).
Conclusions: Immunotherapy with MMR is superior treatment than cryotherapy for cutaneous warts with minimum side effects but the combination of cryotherapy with intralesional MMR has shown to have complementary effect in treatment response.

Keywords: MMR vaccine, Cutaneous wart, Cryotherapy

INTRODUCTION

Viral warts are benign proliferations caused by HPV virus affecting skin and mucous membrane.[1] Viral warts can be present with symptoms of pain, interface in day to day activity (specially in palmoplantar warts). Various modalities of therapy are available: such as cryotherapy, electrocautery, immunotherapy and various lasers; but with conventional therapies chances of permanent scarring and pigmentary changes are there.[1-3] Also treatment of recalcitrant wart is frustrating for both patient and physician. As viral infections are common in patients with reduced cell mediated immunity, thus improving cell mediate immunity of patient is the key factor in reducing recurrence. Immunotherapy for warts is a new modality of treatment; with intralesional immunotherapy delayed hypersensitivity reaction is stimulated which leads to increases ability of immune system to identify and clear HPV lesions.[2] We chose

measles, mumps, rubella (MMR) vaccine for immunotherapy as it is routinely administered in India in vaccination schedule and is readily available; also safety measures are already established for its use. Based on the above facts, we carried out this study aiming at the evaluation of the efficacy of intralesional MMR vaccine as an immunotherapy in combination with cryotherapy for recalcitrant viral and simple warts and its comparison to only cryotherapy and only immunotherapy groups.

METHODS

This prospective observational study was conducted in Department of Dermatology, Venereology and Leprosy of Vikhe Patil Institute of Medical Sciences, Ahmednagar from June 2017 to June 2018.

Inclusion criteria

Inclusion criteria were patients between 10-50 years of age, diagnosed to have single or multiple cutaneous warts on clinical features.

Exclusion criteria

Exclusion criteria were patients, prior allergic response to MMR vaccine, patients with acute febrile illness, pregnancy, infection with human immunodeficiency virus type 1, iatrogenic immunosuppression and primary immunosuppression.

After obtaining a written informed consent from all patients, detailed history regarding age, sex of patient, other co morbidities, duration of wart and any previous modality for treatment of wart was taken. Detailed clinical examination was done to note size, site, number of wart and rule out any systemic illness. Patients were advised not to use any other wart treatment during the study period.

Group A

In this group, all patients received cryotherapy every 3 weeks once a week until complete clearance of warts or for a maximum of 4 sessions. In each session, cryotherapy was done with liquid nitrogen using cryotherapy gun, each application was executed until a frozen halo of 2 mm around the base of the wart appeared (usually after 2–10 seconds). After thawing, the second cycle was also performed in the same way in each session. Any adverse reactions were recorded as well.

Group B

In group B, cell mediated immunity of study subjects were tested by intradermal injection of MMR. In cases of multiple warts, only the largest warts were treated based on surface area. Injection of 0.1 ml of MMR vaccine (TRESIVAC 0.5 ml) was given into the skin of the forearm.[4] Determination of a positive reaction required erythema and induration of at least 5 mm in diameter within 48–72 h. Patients not reactive to the skin test were excluded from the study. Depending upon size of intradermal test reaction 0.1 to 0.3 ml of MMR vaccine was given in wart.[4] In patient with multiple warts, only the largest wart was treated based on surface area. Repeat injections at 3 week intervals until complete clearance was achieved or for a maximum of four treatments. Follow-up was made every 2 months till 4 months to detect any recurrence.

Group C

Group C, patients underwent similar procedure as group B subjects to check the status of cell mediated immunity. In treatment, cryotherapy (same as group A) was combined with intralesional injection of MMR vaccine (same as group B).[4] Treatment session was repeated at 3 week intervals until complete clearance was achieved or for a maximum of four treatment session. In cases of multiple warts, only the largest wart was treated. Follow-up was made every 2 months till 4 months to detect any recurrence.

Treatment evaluation

For each patient, a baseline photograph of the wart was taken in a fixed position at a fixed distance from the same camera at the beginning of treatment. Similar photographs of wart were taken on every follow up. Response to treatment was evaluated by the decrease in size of warts VAS (visual analogue scale) and photographic comparison. Scoring for VAS was noted as scoring for VAS was noted as 1: poor (<25%), 2: fair (25–50%), 3: good (51–75%), 4: excellent 76–95%), and 5: clear (>96%). Immediate and delayed side effects (if any) were recorded. The mean VAS score was taken for statistical evaluation.

Statistical analysis

Statistical testing will be conducted with SPSS Statistics 23.0 (SPSS Inc., Chicago, IL, USA). Results for quantitative variables like age; VAS local and distant was expressed as mean (±SD), median [range], IQR. Results for qualitative variables like percentage of gender, age groups, concomitant illness, previous treatment, smoking of were expressed as frequency and percentages. The one-sample Kolmogorov-Smirnov test is used to determine whether data sets differed from a normal distribution. Most of our data was ordinal and not normally distributed hence comparison between three treatment groups for VAS local be distant was done using Kruskal Wallis H test and two treatment groups was done using Mann Whitney U test. The difference between VAS local and distant at each visit was again compared using Kruskal Wallis H test for three treatment groups and Mann Whitney U test for two treatment groups. Nominal categorical data between the groups will be compared using the test or Fisher's exact test (for expected frequencies <5) as appropriate. P<0.05 was considered significant.

RESULTS

Demographic profile

Sixty patients were enrolled into the study. Demographic data and basic characteristics of wart in study group are described in Table 1.

Response to treatment

For local warts patients in group C therapy (cryotherapy and intralesional MMR) and patients in group A (cryotherapy alone) showed significantly better response than patients in patients with group B (intralesional MMR vaccine) in first half of treatment (i.e. at 6th week) ($p<0.002$) ($p<0.007$) respectively. Although response in group C patients was better than group A, it was not statistically significant. In second half of treatment (i.e. at 12th week) patients of group B and group C showed significantly better response than patients in group A ($p<0.016$) ($p<0.016$) respectively. Even though response in group C patients was better than group B, it was not statistically significant. Figure 1 depicts the mean VAS scale response in local warts from 1st to 4th visit at interval of 3 week in group A, B and C. Figures 2 (A-C) shows clinical photograph of patients with palmo-plantar wart treated with cryotherapy and intralesional MMR (group C).

Furthermore, in the immunotherapy groups (group B and group C) a complete remission was achieved in distant (non inoculated warts) for 62.5% and 100% respectively of the patients with more than one lesion. In first half of treatment (i.e. 6th week) patients with distant warts showed a significantly better response to group C than as compared to group B therapy ($p<0.039$). In second half of treatment session (i.e.12th week) despite of better response in group C as compared to group B patient, results were not statistically significant. Figure 3 depicts the VAS scale response in distant warts from 1st to 4th visit at interval of 3 week in group B and C.

Table 1: Demographic data and basic characteristics of wart in study group A, B and C.

Demographic data		Group A	Group B	Group C
		N (%)	N (%)	N (%)
Gender	Male	10 (50)	10 (50)	12 (60)
	Female	10 (50)	10 (50)	8 (40)
Number	Single	4 (20)	4 (20)	4 (20)
	Multiple	16 (80)	16 (80)	16 (80)
Site	Face	2 (10)	4 (20)	2 (10)
	Genital	4 (20)	2(10)	2(10)
	Palmo-plantar	6 (30)	4 (20)	2 (10)
	Palmo- plantar and verruca vulgaris on rest of body	0 (0.0)	4 (20)	6 (30)
	Verruca vulgaris on rest of body	8 (40)	6 (30)	8 (40)
Smoking	Yes	8 (40)	6 (30)	6 (30)
	No	12 (60)	14 (70)	14 (70)
Concomitant illness	Yes	6 (30)	2 (10)	4 (20)
	No	14 (70)	18 (90)	18 (80)

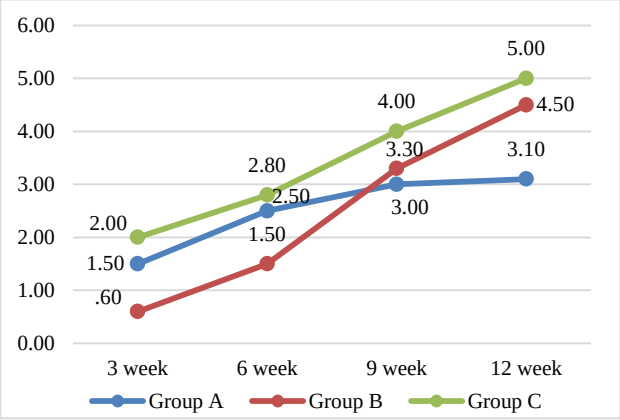

Figure 1: Comparison of mean VAS scale for local warts from 1st to 4th visit at interval of 3 week in group A, B and C.

Recurrence was observed in 12 patients (60%) patients of the group A and 4 patients (20%) of group B; while no recurrence was observed in group C after the 6-month follow-up period. Figure 4 depict the recurrence rate in group A, B and C after 6 months of follow up.

Factors affecting wart removal

Group B and C patients showed a statistically significant relationship between the therapeutic response and patient age (>30 years) and smoking ($p<0.02$) ($p<0.039$) respectively; on other hand no significant correlation was observed between age, smoking and the therapeutic response in the group A. Patients with wart on facial and palmoplantar area showed poor therapeutic response in group A ($p<0.02$); however site of wart didn't show any significant difference in therapeutic response was found in group B and C. No significant correlation was found

between gender, duration of wart, concomitant illness and the therapeutic response in any of the groups.

Figure 2: (A) Baseline photograph of a patient with palmplantar wart (Group C); (B) grade 3 response by VAS seen at 9 weeks; (C) grade 5 responses by VAS seen at 12 week one month after the last sitting baseline.

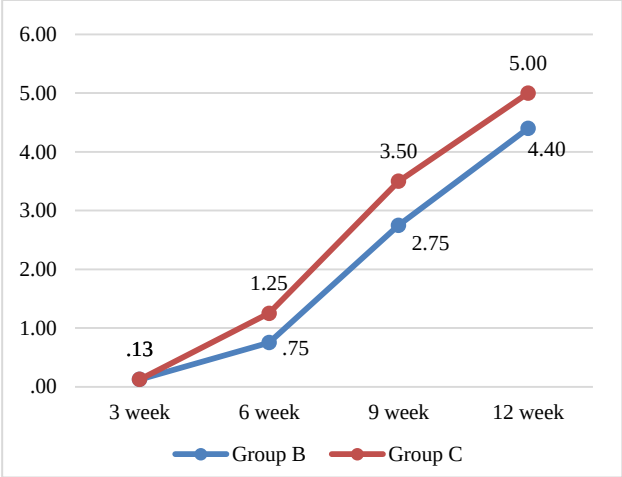

Figure 3: Comparison of mean VAS scale for distant warts from 1st to 4th visit at interval of 3 week in group B and C.

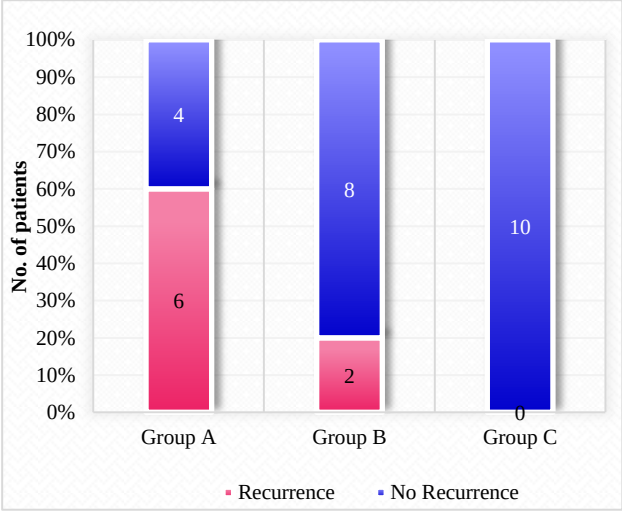

Figure 4: Recurrence of warts after the 6-month follow-up period in group A, B and C.

Side effects

The most common side effect noted in the patients treated with cryotherapy (group A) was post-inflammatory hypo pigmentation (Figure 5); which was seen in 6 (30%) patients and other side effects noted were blister formation (10%), pain during procedure (10%) and scarring (5%). In group B, the only side effect observed was pain during injection in 17 patients (85%). The side effects noted in group C were hypo pigmentation in 2 patients (10%) and blister formation in 1 patient (5%), only 4 patients (20%) had pain at the time of injection. However, there was no statistically significant difference in the side effect profile of group B and C.

Figure 5: Hypopigmentation and recurrence observed in a patient treated with cryotherapy alone (group A).

DISCUSSION

Viral warts are a common problem affecting approximately 10% of the population.[5] Warts are usually common in paediatric age group and immunosuppressed patients, although it can affect anyone and can present at

any age. Treatment of patient with multiple warts is very disappointing for both patients and dermatologist due to recurrence. Especially patients with palmoplantar warts and facial warts in beard region are most difficult to treat; as shaving and nail biting as habit tic disorder in children causes continuous auto- inoculation of warts in adjacent area which results in koebner phenomenon and hence responsible for recurrence.[6]

Various factors can affect the outcome of wart removal. These are duration of wart, site of wart, size of wart, type of wart, previous treatment, age of the patient, concomitant illness and smoking.[7] In this study, we found that patients with more than 30 years of age and chronic smokers have reduced the clearance rate of wart in group B and C. Similar to our study Horn et al has found significant correlation between age and clearance of wart.[8] On the contrary Gamil et al and Fahime Khozeimeh et al stated that age had no effect on the therapeutic response in immunotherapy treated warts.[9,10] To the best of our knowledge correlation Smoking and clearance of wart has not been done previously. Patients with wart on facial and palmoplantar area showed poor therapeutic response in group A ($p<0.02$). In the present study, no statistically significant association was found between the therapeutic response in either of the group A, B or C and the different clinical variables including gender, number and duration of the warts. Similarly Nofal et al did not find any correlation between gender, number and duration of wart.[11]

Both humoral and cell mediated responses are stimulated during HPV infection, but warts are mostly cleared by cell mediated immunity (CMI); in which dendritic cells (DC), CD4+ T helper cells and CD8+ T cells play predominant roles.[9] Patients with florid warts have defective Th1 profile increase of the permissive Th2 profile.[12] Intralesional immunotherapy induces delayed hypersensitivity reaction; leading to activation of Th1 profile and in turn activation of CD8 cytotoxic cells and NK cells. Attributing to fact that increasing age is associated with decreased capabilities of individual to mount of cell-mediated immunologic response, poor response for immunotherapy is observed in group B and C.[13,14] Smoking probably influences clinical responses through their effect on cytokines and also interferes with phagocytosis and neutrophil chemo taxis. Smoking also has long-term chronic effect on many important aspects of inflammation and immune responses.[15] Reason for poor therapeutic response in group A for facial and palmoplantar wart was Koebner response (as mentioned previously) and unlike immunotherapy cryotherapy can't build an immune response hence acts only on those lesions which are treated and have no effect on distant lesions. Hence, patients seeking wart removal should be subjected to detailed history and physical examination for assessment of associated poor prognostic factors such as systemic illness, chronic addictions, any element of continuous friction on wart etc. and treatment should be individualized for each patient.

It is known fact that mechanism of action of group A therapy is by physical destruction of wart, in group B principle is to develop immunity against viral antigen and group C is a combination of physical destruction along with immunotherapy. And as it is a gradual process to develop immunity against any particular antigen; because of these fact results of our study revealed during first half of treatment local warts responded best in group C followed by group A and response of group B patients was lowest. For distant warts maximum response was achieved in second half of treatment session, group C response was better than group B. In this study we found that, in the immunotherapy groups (group B and group C) complete remission was achieved in distant (non-inoculated warts) for 62.5% and 100%respectively of the patients with more than one lesion. Similar to our study Nofal et al found complete remission for distant warts in 74.5% of the patients who received immunotherapy (MMR vaccine).[16] By this observation we can conclude that, the clearance distant warts is by the development of a widespread cell-mediated immunity against HPV virus as a response to antigen injection; which suggest use of intralesional immunotherapy for cases with multiples and treatment resistant warts.

Substantial number of patients of group A suffered from side effects such as post inflammatory hypopigmentation in 6 (30%) patients, blister formation, pain during procedure, hypopigmentation and scarring. Fortunately we did not encounter any major significant side effects in our patients of immunotherapy (group B and group C). Majority of group B patients 17 (85%) reported pain during injection as a side effect and in group C only 4 (20%) suffered from pain during injection which was much lesser as compared to group B. However, there was no statistically significant difference in the side effect profile of group B and group C. Additionally very few patients of group C suffered from side effects such as hypopigmentation and blister formation but it was significantly less as compared with group A, as group C cryotherapy application was limited only for single wart in contrast with group A in which it was administered in every wart.

Cryotherapy acts by complex mechanism; freeze and thaw cycles produce intracellular ice and extracellular ice formation and cellular destruction, which ultimately result in apoptosis of virus infected cell.[17] But rapid freeze thaw cycles in widespread area are most destructive as it produces ischemic necrosis, which can lead to side effects such as blister formation and hypopigmentation.[17] Therefore cryotherapy as alone as a treatment modality is not advisable in patients with multiple warts. In our study, group C showed the best response amongest all three groups. Principal behind combing cryotherapy and MMR vaccine wart was; it improves the tolerance to injection by numbing the area and makes tissue softer that helps in administration of the injection with minimal resistance. In addition combining two modalities of treatments gives added advantage in

outcome of treatment. Fortunately we observed very mild and insignificant side-effects of cryotherapy in patients of group C as we targeted only single wart. In past the same principal is used for treatment of keloid, hypertrophic scar, lesihmaniasis, Pancreatic cancer.[18-20]

Many agents are tried for immunotherapy BCG, Candida, Trichophyton.[21] We choose MMR as its safety is already established due to vaccination schedule in India. Also MMR has three different antigens, hence chances of induction of delayed hypersensitivity is highest with this agent. According to literature MMR and PPD (purified protein derivative) are the most effective agents in immunotherapy.[22] MMR vaccine is cost effective treatment over conventional treatment; as it helps to clear distant warts and total cost of treatment is also less considering less number of sessions and low cost of MMR vaccine.

There is no gold standard treatment for wart which can give complete clearance hence combination different types of treatment is often needed. Also therapeutic approach differs according to type and site of the wart. The combination of cryotherapy with intralesional injections of MMR vaccine, which is much more effective than the use of MMR alone, should be promoted.

To the best of our knowledge there are no previous studies quoting combination of cryotherapy and intralesional immunotherapy in treatment of cutaneous warts.

Study limitation

Larger sample size is required to validate our results.

CONCLUSION

Although cryotherapy of wart is one of the most commonly used treatment modality; it invariably requires multiple sittings and the results might be slow and inadequate.

Although immunotherapy with intralesional MMR vaccine works in both local and distant warts; combination of cryotherapy with MMR vaccine improves the response especially for clearance of local warts. Based on our study, combination of cryotherapy with MMR vaccine should be considered in treatment-resistant patients, as it is more efficacious in removing wart, reduces the total number of treatment sessions and chances of recurrence.

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Ethical approval: The study was approved by the institutional ethics committee

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