Original Article

Immunotherapy For The Treatment Of Female Anogenital Wart With Purified Protein Derivative And Measles Mumps Rubella Vaccine: A Comparative Clinical And Immunological Study

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Abstract

Background External anogenital warts are considered the commonest viral sexually transmitted infection that has serious negative psychological effects. Various destructive modalities have been tried with variable results with high recurrence rates in contrast to intralesional immunotherapy. **Aim** to evaluate the efficacy, safety, and tolerability of intralesional Measles Mumps Rubella (MMR) vaccine versus intralesional and intradermal purified protein derivative (PPD) in treatment of female anogenital wart. **Methods** This randomized clinical trial included 69 female patients with anogenital warts above 18 years old divided into three equal groups. Group 1 received intralesional MMR at a dose of (0.2 ml) in the largest wart, group 2 received intralesional (IL)PPD (0.2 ml) in the largest wart, group 3 received intradermal(ID) PPD (0.2 ml) every 2 weeks till improvement or for a maximum five treatment sessions. The follow up period was 6 months after the last treatment session. **Results** Although it was not statistically significant, overall response was higher in the MMR group (78.3 %) versus IL PPD (69.6%) and ID PPD (56.5%).. The highest cure rates were after the 4th session in the MMR group and the 5th session in both IL PPD and ID PPD groups with slightly lower numbers of sessions needed for cure in the MMR group (4 sessions) versus both PPD group (5 sessions). IL PPD group showed non statistically significant higher rates of complications in comparison with ID PPD and MMR group. IL PPD showed higher rates of recurrence than MMR and ID PPD groups during the follow up period without significant difference. There was significant difference between level of IL12 before and after treatment in every group. In addition, there was significant difference between level of IL12 after treatment between IL PPD and other both groups. **Conclusion** MMR , intralesional PPD and intradermal PPD are effective in female anogenital warts with higher safety profile of MMR.

Key words: female anogenital warts, MMR , intralesional , intradermal, PPD and immunotherapy.

INTRODUCTION

Human papillomavirus (HPV) infections are the most common sexually transmitted infections worldwide.(1) It is transmitted mainly through sexual contact, however, autoinoculation and vertical transmission may be recorded.(2) Different subtypes of HPV are able to infect the genital mucosa; types 6 and 11 found in 90% of the affected patients.(3) Genital warts may spread and increase in size or resolve spontaneously with high recurrence rate within 3 months.(2) Persistent cervical infection with high-risk HPV types represents the most common risk factor for the evolution of cervical cancer and high-grade dysplasia. HPV-16, _18, _31, and _45 are found in approximately 80% of cervical cancer (4).

There is no single approved modality for the treatment of anogenital warts.Various modalities such as electro surgery, cryosurgery, and different physical or chemical modalities have been used with variable results but recurrences are common.(5) Intralesional antigen immunotherapy has been successfully used in the treatment of warts with the potential advantages of good efficacy, high safety profile, low recurrence

rate, and clearance of untreated distant warts unlike traditional wart therapies. It leads to production of Th-1 cytokines, which activate cytotoxic and natural killer cells to eradicate human papilloma virus infection. IL-12 is one of the proinflammatory cytokines characteristic of Th-1-based immune response (6).

Many studies have demonstrated the effectiveness of the MMR vaccine in the treatment of extragenital warts .In addition to, intralesional immunotherapy with the MMR vaccine can serve as an effective therapy for the treatment of anogenital warts.(7) Purified protein derivative seemed to be safe and effective in treatment of warts. Intradermal PPD was effective as well as intralesional PPD in wart treatment (8).

To our knowledge ,this is the first study to evaluate the efficacy, safety, and tolerability of intralesional Measles Mumps Rubella (MMR) vaccine versus intralesional and intradermal purified protein derivative (PPD) in treatment of female anogenital wart both clinically and immunologically.

Patients and Methods

This is a randomized clinical trial that included 69 female patients with anogenital warts above 18 years old diagnosed clinically and confirmed by dermoscopic examination. All patients were recruited from Dermatology Outpatient Clinic at Mansoura University Hospitals f-rom January 2021 to January 2022. The study was approved by research ethics committee in 2021 at Faculty of Medicine, Mansoura University, Egypt Number:MD.20.12.396.

Patients with immunosuppression, previous history of asthma or allergic skin diseases, any generalized dermatitis, previous history of tuberculosis, patients with a prior history of hypersensitivity to PPD or MMR, patients with proved COVID 19 infections within 2 months and patients who received any wart treatment 1 month before the start of the study were excluded.

Sample size calculation

Sample size calculation was based on Success rate of treatment of genital warts retrieved from previous research ***(Nofal et al., 2020).*** Using G power to calculate difference between 2 proportions using z test, 2 tailed, with α error =0.05 and power = 80.0% .The total calculated sample size will be 23 patients in each group to detect difference of 41%

Methods

Written informed consent was obtained from patients before inclusion into the study. All patients were subjected to complete history taking, general examination and dermatological examination to assess the number, size, and site of the warts; and to exclude patients with other skin diseases.History and dermatological examination of partner for presence of wart should be considered.

Digital photographs were taken for every patient at baseline, and every follow up visits by (Sony Cyber-shot DSC-W620).

Examination by dermoscopy (DermLite III; 3 Gen, USA) was done to diagnose warts before treatment

Patients were randomly divided into three groups by computer-generated random numbers inserted in opaque sealed envelope, 23 patients in each group. Topical anesthetic cream was applied at the injection site half an hour before the procedure.

Patients in group 1(G1) received intralesional (IL) MMR at a dose of (0.2 ml) in the largest wart. Patients in group 2 (G2) received intralesional (IL) PPD (0.2 ml) in the largest wart. Patients in group 3(G3) received intradermal (ID) PPD (0.2 ml) at the middle third of ventral aspect of forearm.

In the studied groups, Injections were repeated every 2 weeks until clearance or a maximum of 5 treatment sessions.

The response in target wart ,the distant warts and the overall response of all warts (including the treated and distant untreated warts) were also assessed and categorized as follows: complete response (disappearance of wart and returning of normal skin), partial response (50-99% reduction in the size/numbers of warts and poor response (0-50% reduction in the size/numbers of warts) ***(El Sayed et al., 2020)****(26)*

This was done by counting the number and evaluating the size of injected and distant warts documented by digital photographing under almost the same camera and lightening settings.

Sample collection

From each patient, 3 mL venous blood was collected before treatment and after last session from each patient into a serum separator tube . After clot formation, Samples was centrifuged at speed of 2000 x g for 10 minutes and sera was separated and stored at -20º C for further analysis. Measurement of IL-12 was carried out using enzyme-linked immunosorbent assay (ELISA) kits.

Safety assessment Local signs and symptoms (pain, erythema, edema, and scar) and flu-like symptoms within 12 hours of injection were recorded at each treatment session.

Follow up Follow up for clinical response was done every 2 weeks during sessions and for 6 months following the last treatment session.

Statistical analysis and data interpretation

Data were fed to the computer and analysed using IBM SPSS Statistics for Windows, (Version 22.0. Armonk, NY: IBM Corp). Qualitative data were described using number and percent and assessed by Chi-Square test, Monte Carlo, and Fisher exact tests as appropriate. Quantitative data were described using median (range) and compared by Mann Whitney test. Non-parametric data were expressed as mean and standard deviation. Significance of the obtained results was judged at the (0.05) level.

Results

We classified the included 69 female patients randomly into three groups. There was no statistically significant difference in the age, marital status, or the baseline clinical characteristics of the studied warts as regard duration , number and site between the studied groups except for perineum between Group (1) and Group (3) **(Table 1).**

Table (1) Demographic data and Lesion characteristics of the studied groups

Demographic data and Lesion characteristics	**Group (1) MMR no=23**	**Group (2) IL PPD no=23**	**Group (3) ID PPD no=23**	**Test of significance**		
				P1	**P2**	**P3**
Age (Years) Mean ± SD Min-Max	 38.65± 7.57 30-51	 34.39± 8.13 20-47	 32.39± 12.44 18-60	0.07	0.06	0.52
Marital status Married Single	 21(91.3%) 2 (8.7%)	 22(95.7%) 1 (4.3%)	 21(91.3%) 2 (8.7%)	1.0	1.0	1.0
Duration/ m	2 (1-180)	4 (0.5-84)	3 (0.5-24)	0.19	0.64	0.07
No	18 (4-40)	10 (3-60)	18 (4-50)	0.64	0.77	0.26
Site Vulva Perinium Perianal Vaginal opening Mons pubic	 20(87.0%) 13(56.5%) 3 (13.0%) 2 (8.7%) 2 (8.7%)	 20(87.0%) 12(52.2%) 1 (4.3%) 0 (0%) 0 (0%)	 17(73.9%) 6 (26.1%) 3 (13.0%) 2 (8.7%) 4 (17.4%)	 1.0 0.76 0.61 0.48 0.48	 0.45 0.036* 1.0 1.0 0.66	 0.45 0.07 0.61 0.48 0.11
Previous treatments No Cryotherapy Aldara Aldara/podophilin Podophilin	 16(69.6%) 3 (13.0%) 1 (4.3%) 1 (4.3%) 2 (4.3%)	 14(60.9%) 7 (30.4%) 0 (0%) 0 (0%) 2 (4.3%)	 20(87.0%) 3 (13.0%) 0 (0%) 0 (0%) 0 (0%)	0.42	0.46	0.11

Although it was not statistically significant, overall complete response showed higher complete response rates in the MMR group with complete clearance of all warts in 78.3 % of patients. But in intralesional

injection of PPD complete responses was in 69.6% of patients and in intradermal injection of PPD complete clearance of all warts was in 56.5% of patients **(Table 2). (figure 1,2,3).**

Table (2) Response in injected wart, distant warts, and the overall response among the studied groups.

	Overall response	**Group (1) no=23**	**Group (2) no=23**	**Group (3) no=23**	**Test of significance**		
					P1	**P2**	**P3**
First session	Poor Partial	20 (87.0%) 3 (13.0%)	22 (95.7%) 1 (4.3%)	23 (100%) 0 (0%)	0.608	0.23	1.0
Second session	Poor Partial Complete	15 (65.2%) 6 (26.1%) 2 (8.7%)	17 (73.9%) 6 (26.1%) 0 (0%)	17 (73.9%) 6 (26.1%) 0 (0%)	0.531	0.53	1.0
Third session	Poor Partial Complete	6 (26.1%) 11 (47.8%) 6 (26.1%)	9 (39.1%) 12 (52.2%) 2 (8.7%)	12 (52.2%) 10 (43.5%) 1 (4.3%)	0.286	0.07	0.65
Fourth session	Poor Partial Complete	3 (13.0%) 7 (30.4%) 13 (56.5%)	3 (13.0%) 15 (65.2%) 5 (21.7%)	6 (26.1%) 14 (60.9%) 3 (13.0%)	0.039*	0.009*	0.49
Fifth session	Poor Partial Complete	1 (4.3%) 4 (17.4%) 18 (78.3%)	3 (13.0%) 4 (17.4%) 16 (69.6%)	6 (26.1%) 4 (17.4%) 13 (56.5%)	0.701	0.13	0.58

There was no relation between the age, number, size, the duration of warts and the response rate except in MMR group the median duration was significantly shorter in the complete responders (2 months) compared to partial and poor responders (23 months) .In addition to, in ID PPD group , the median size of largest wart was significantly smaller in the complete responders (1mm) compared to partial and poor responders (3 mm). **(Table 3).**

Table (3) Factors affecting the response in studied groups.

		Complete responder	**Partial and poor responder**	**P value**
Group (1) no=23	Age (Years) Mean ± SD	**38.17±7.28**	**40.00±8.94**	0.624
	Duration/m	2 (1-12)	23 (1-180)	0.02*
	Number	16 (4-40)	21 (5-40)	0.379
	Size in mm	5 (1-20)	6.5 (2-20)	0.180
Group (2) no=23	Age (Years) Mean ± SD	**34.13±8.87**	**34.87±7.08**	0.841
	Onset duration	4 (0.5-84)	5.5 (1-84)	0.720
	Number	10 (3-60)	14 (3-60)	0.721
	Size in mm	2 (1-5)	2 (0.5-5)	0.838
Group (3) no=23	Age (Years) Mean ± SD	**36.15±13.52**	**27.50±9.36**	0.099
	Onset duration	3 (0.5-24)	3 (0.5-24)	0.950
	Number	20 (5-25)	16.5 (4-50)	0.575
	Size in mm	1 (1-3)	3 (1-5)	0.016*

MMR treated patients required lower number of sessions to achieve complete cure versus PPD (intralesional and intradermal), without significant difference except between Group (1) MMR and Group (3) ID-PPD. The median number of sessions till complete cure was 4 in MMR group versus 5 in both PPD groups **(Table 4).**

Table (4) The number of sessions among cured cases.

No of session	Group (1) no=18	Group (2) no=16	Group (3) no=13	Test of significance		
				P1	P2	P3
2	2 (11.1%)	0 (0%)	0 (0%)	0.075	0.014*	0.74
3	4 (22.2%)	2 (12.5%)	1 (7.6%)			
4	7 (38.8%)	3 (18.7%)	2 (15.3%)			
5	5(27.7%)	11 (68.7%)	10 (76.9%)			

Side effects were higher in IL PPD group in the form of 30.4 % of patients reported erythema , (13.3%) pain, (21.7%) injection site itching, (8.7 %) edema and (13%) burning sensation in comparison with ID PPD and MMR group, but there was no significance between them **(Table 5).**

Table (5) Side effects among the studied groups

Side effects	Group (1) no=23	Group (2) no=23	Group (3) no=23	Test of significance		
				P1	P2	P3
Pain	4 (17.4%)	3 (13.0%)	0 (0.0%)	1.0	0.11	0.23
Erythema	4 (17.4%)	7 (30.4%)	4 (17.4%)	0.30	1.0	0.30
Edema	1 (4.3%)	2 (8.7%)	1 (4.3%)	1.0	1.0	0.55
Itching	3 (13.0%)	5 (21.7%)	3 (13.0%)	0.69	1.0	0.43
Burning sensation	4 (17.4%)	3 (13.0%)	0 (0.0%)	1.0	0.11	0.23

At the end of 6 months follow up, higher rate of recurrence (4.3%) was observed in the IL PPD group versus (0 %) in both MMR and ID PPD group among the cured cases, but it was not statistically significant. Among partial and poor responders, there was higher progression rate in ID PPD group (17.4%) versus (8.7 %) in both MMR and IL PPD group without statistical significance **(Table 6).**

Table (6) follow up results after 6 months among studied groups.

follow up results		Group (1) no=23	Group (2) no=23	Group (3) no=23	Test of significance		
					P1	P2	P3
Complete responders	No recurrence	18(78.3%)	15(65.2%)	13(56.5%)	0.781	0.35	0.76
	Recurrence	0 (0%)	1 (4.3%)	0 (0%)			
Partial & poor responders	Stationary	3 (13%)	5(21.7%)	6 (26.1%)			
	Progression	2 (8.7%)	2 (8.7%)	4 (17.4%)			

IL12 serum level demonstrate that there was statistically significance between level of IL12 before and after treatment in every group. In addition, there was significance between level of IL12 after treatment between G1 versus G2 and G2 versus G3 **(Table 7).**

Table (7) IL12 pg/ml before and after treatment among the studied groups

IL12 pg/ml	Group (1) no=23	Group (2) no=23	Group (3) no=23	Test of significance		
				P1	P2	P3
IL12 before	7.25 (3.12- 92.75)	7.05 (2.39- 13.18)	8.15 (0.08- 15.68)	0.65	0.85	0.32
IL12 after	15.30 (5.33- 170.99)	10.08 (1.86- 109.54)	14.09 (4.82- 30.44)	0.036*	0.52	0.03*
P value	≤0.001*	0.003*	≤0.001*	-	-	-

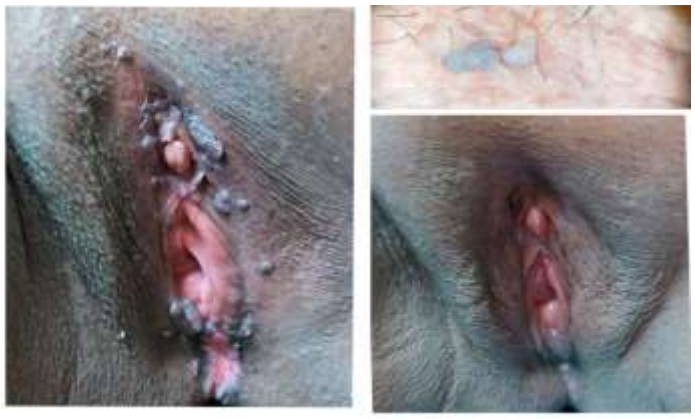

Figure (1) female patient 33 y old in the MMR group with multiple genital warts. a, Before treatment. B Dermoscopic picture before treatment, C After 5 sessions of IL MMR with complete response.

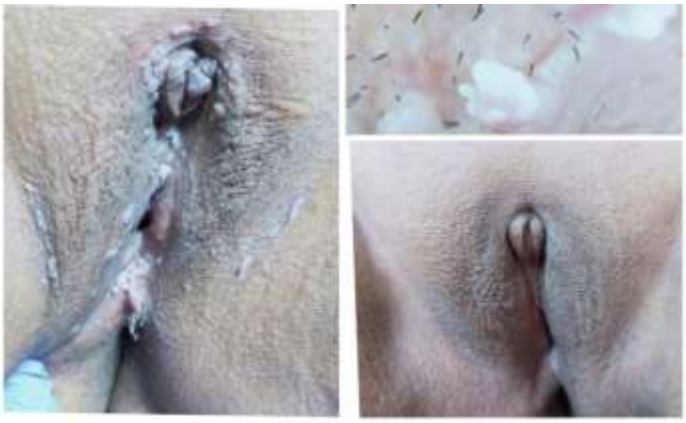

Figure (2) female patient 35 y old in the IL PPD group with multiple genital warts .A , before treatment .B, Dermoscopic picture.C, After 5 sessions of IL PPD with complete response

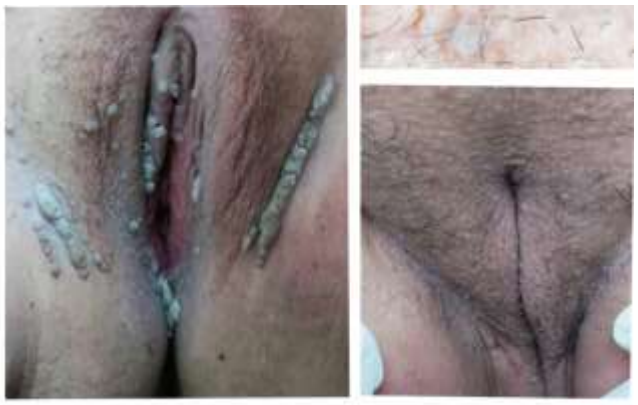

Figure (3) female patient 48 y old in the ID PPD group with multiple genital warts. a, Before treatment. B Dermoscopic picture before treatment,C After 5 sessions of ID PPD with complete response

Discussion

Anogenital warts (AGWs) are the most frequent sexually transmitted infections worldwide and have a detrimental impact on the quality of life.(9) AGWs may spread and increase in size or resolve spontaneously with high recurrence rate within 3 months.(2) Persistent cervical infection with high-risk HPV types represents the most common risk factor for the evolution of cervical cancer and high-grade dysplasia .(4)

Treatment of genital warts is unsatisfactory in most of cases as they depend on destruction of the involved tissue with different physical or chemical modalities with variable results, however, normal skin may harbour the virus which may cause high incidence of recurrence (10) **.** Intralesional immunotherapy increases recognition of the virus by the patient's immune system by stimulating cell-mediated immune response(11).

In the present study, IL injection of MMR was associated with complete clearance of all warts in 78.3 % of patients. These results came in parallel with ***Nofel et al, 2022*** (12) who stated that 73% of pediatric patients with genital warts yielded complete clearance. On contrast to our results, ***Sharma et al, 2020*** (7) reported that (63.6%) of adult patients with genital warts had reached complete clearance. These contradictory results could be explained by differences in the studied population and lesser number of sessions. ***Zamanian et al., 2021*** (13)reported higher response than the present study with complete clearance in 92% of pediatric patients with non genital warts after IL MMR injection. This may be attributed to the differences in the studied population and in the type of the treated warts.

In the present study, IL injection of PPD was associated with complete clearance of all warts in 69.6% of patients . These results came in parallel with ***Nada et al,2020*** (14) who reported that 69.5% of patients showed complete recovery from genital warts treated with IL PPD injection**.** In addition to, the results of the present study were in concordance with ***Tawfik et al,2022*** (15) who stated that 65% of patients with genital warts yielded complete clearance after IL PPD injection. In the same line, ***Azab et al,2022*** (16) reported complete clearance in 58.7% of patients with genital warts treated with IL PPD. In contrast to our results in this group , ***Moubasher et al., 2021*** (17) reported that only (13. 3%) of patients with genital warts had reached complete clearance after IL PPD. These contradictory results could be explained by small sample size. ***Nofel et al, 2020*** (18) stated that 32.1% of patients with recalcitrant genital warts yielded complete clearance of all warts after IL PPD. This may be attributed to the differences in the number of the studied patients and in the nature of the treated warts. The therapeutic response seen in the present study was lower than the study by ***Awad et al., 2022*** (19) who reported complete clearance in 81.7% of pediatric patients with non-genital warts after IL PPD injection. This may be attributed to the differences in the number of the studied patients, in the studied population, and in the type of the treated warts.

On the other hand, ID PPD in the present study was associated with complete clearance of all warts in 56.5% of patients. These results came in parallel with ***Eassa et al,2011*** (20) who stated that 50% of pregnant women with genital warts patients yielded complete clearance. On contrast to our results, ***Elela et al,2011*** (21)reported higher response as they stated that was complete cure in 96% cases with non-genital warts treated with ID PPD**.** This may be attributed to the type of the treated warts and higher number of sessions. ***Podder, et al., 2020*** (22) reported lower response as they reported that only (18.5 %) of patients with genital warts had reached complete clearance of their wart after ID PPD every month for 3 sessions. These contradictory results could be explained by differences in the nature of the treated warts, less number of sessions and long interval between the sessions.

We also noticed that patients who did not respond in the first four sessions did not show any response later Table (2), this came in parallel with ***Tawfik et al,2022*** (15) who observed that patients who did not response in the first three sessions are less likely to respond after the third session as well. In the present study, we noticed that there was significant difference between MMR versus IL PPD and between MMR versus ID PPD during the fourth session showing that PPD treatment needed more number of sessions than MMR treatment to reach complete clearance.This come in parallel with ***Eassa et al,2011*** (20) and ***Elela et al,2011*** (22) who reported clearance of most of the patients after the 12 sessions with and 10 sessions respectively.

Intralesional MMR and PPD can attract antigen presenting cells leading to elevation of serum interleukin-12 (IL-12) and the production of Th1 cytokines like interleukin-4 (IL-4), interleukin-5 (IL-5), IL-8, interferon (IFN)-gamma, and TNF-alpha. The immune response is generalized, which helps in clearing distant warts as well. PPD is devoid of any viable organisms; therefore, its use is considered safe in children and in pregnant women (23). BCG vaccination is a part of our childhood immunization program. So, it was expected that subsequent exposure to tuberculin injection led to inflammatory immune response.

To our knowledge, this is the first study to compare between intralesional MMR,,intralesional PPD and intradermal PPD in the treatment of female anogenital warts. The results of the present study demonstrated a higher rate of complete clearance in the MMR group (78.3%) followed by IL PPD group (69.6%) and lastly ID PPD group (56.5%), with no significant difference between the three studied groups. Combination of three antigens in MMR vaccine produces better immunostimulant effect than PPD vaccine alone, which could-explain slight better response with MMR vaccine. Also,***Mohammed et al., 2021*** (24) were the only authors to compare between between intralesional MMR and intralesional PPD in different type of warts (common ,genital ,palmar or planter warts) warts .They reported no significant difference in the over all response with slightly higher complete response rates in MMR (80%) than IL PPD (60%). They studied

different age group (both adults and pediatrics) and different type of warts. ***Elela et al, 2011*** (21) who compared between ID PPD versus IL PPD in patients with non genital warts stated that complete cure in 96% in ID PPD group versus 94% in IL PPD group. This may be attributed to the the type of the treated warts and higher number of sessions (ten session).

In MMR group, there was no significant relation between the response to MMR and the age, number or size in our study . But, there was significant relation between the response to MMR and duration which was the same as reported by ***Sharma et al,2020*** [7] that found that patients with a shorter duration of disease have a higher chance of seeing complete clearance of their warts.

In IL PPD group, there was no significant relation between the response and the age, duration, number or size in our study. These results are not matched to that obtained by ***Awad et al., 2022*** [19] who reported better response to PPD in older age group which is statistically significance.

On the other hand, In ID PPD group, the mean age of the responders (36.15 years) was older than the mean age of non responders (27.5 years), but without statistical significance. So it seems that the response is better with older age group. This may be explained by well established immune system in the responders group . In addition to, The results of the present study revealed significant relation between the response to ID PPD and size of wart as patients with a smaller size of wart have a higher chance of seeing complete clearance of their warts.

In this study 17.4% of patients injected with MMR experienced pain, erythema(17.4%), injection site itching (13%), edema(4.3%)and burning sensation (17.4%). Pain during injection was in all patients and Flu-like symptoms were reported in 4 patients (27%) of the MMR group reported by ***Nofel et al,2022***. (12)

In the IL PPD group, 30.4 % of patients experienced erythema ,(13.3%) pain, ,injection site itching (21.7%), edema(8.7 %)and burning sensation (13%) . This goes with the reports of ***Tawfik et al,2022*** (15) who stated that the side effects associated with the injection were mild, transient and nonsignificant. Mild pain and burning sensation few minutes after the procedure were observed in all the patients and, only two patients of 40 had itching and erythema lasting for 2 days.

In the ID PPD group, 17.4 % of patients experienced erythema ,(13.3%), ,injection site itching (13%), edema(4.3)and no patients reported pain or burning sensation . This goes with the reports of ***Podder et al., 2020*** (22) who reported only pain in 40.74% and scaring in 14.8% of patients.

One of the most frustrating aspects of wart treatment is disease recurrence. As most of the conventional destructive modalities are not directly antiviral, recurrence of the lesions is a major problem, particularly in the genital area. Recurrences can be expected in about 25% of cases, with the interval varying from 2 months to 23 years .(25) In the present study, at the end of 6 months follow up, only IL PPD group showed recurrence of one case (4.3%) in contrast to two other groups with no recurrence which is statistically non-significant. This is the same as previous reports by ***Tawfik et al,2022*** (15) who reported 1 relapsed case out of 40 injected cases by IL PPD. Also***, Nofel et al, 2022*** (12) reported no recurrence after 6 months in patients injected by MMR. These absent/low recurrence rates compared to traditional treatments may be attributed to the development of a long-term HPV-directed immunity.

It has also been proposed that the antigen injection is associated with proliferation of peripheral blood mononuclear cell(PBMCs) that promotes Th1 cytokine responses further activating cytotoxic T-cells and natural killer cells to eradicate HPV-infected cells**.**(26) That is why we investigated the serum levels of IL-12 (a Th1 cytokine) before and after treatment with PPD and MMR

To our knowledge, this is the first study to assess serum level of IL-12 in female patients with anogenital warts before and after MMR and PPD injection.In the present study, we found that the serum level of IL -12 were significantly elevated after treatment in MMR,IL PPD and ID PPD treated groups than before treatment denoting significant stimulation of Th1 immune responses by three types of treatments. In addition , The median level of serum IL-12 in IL PPD group was lower than MMR group and ID PPD group after treatment with statistical significance between level of IL12 after treatment between MMR versus IL PPD and IL PPD versus ID PPD. This may explain why one patient (13.3%) of IL PPD group had recurrence of their lesion after 6 months in contrast to MMR and ID PPD that had no recurrence after 6 months. This was the same as reported by ***Shaheen et al,2015*** (26) who compare the efficacy of IL MMR and IL PPD in treatment of multiple warts and investigate their effect on serum interleukin IL-4 and IL-12. They concluded that Serum ILs-4 and-12 increase following antigen injection but MMR resulted in a significantly higher serum IL-12 than PPD. That might be attributed to the inclusion of more than one antigen in this form of immunotherapy.

Conclusion

Both intralesional MMR, intralesional PPD and intradermal PPD are effective in treatment of anogenital warts with lower recurrence rates and higher safety profile of MMR. Intradermal injection of PPD in the forearms instead of intralesional injection in the treatment of anogenital warts in women is an acceptable and safe modality and is a promising therapy especially in countries where vaccination against tuberculosis is performed routinely and mandatorily

Recommendations

More studies on MMR and PPD are needed to show whether results will be improved after injection of higher doses and multiple numbers of warts. However, this study was limited by the small sample size and the relatively short follow-up period. Further randomized, double-blinded, and vehicle-controlled studies with larger sample sizes, are required to support our findings.

Funding Information

All costs of this study were provided by the researchers.

Conflict of Interest

There is no conflict of interest.

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