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Original Research Article

A study to evaluate the efficacy and safety of intradermal and intralesional Purified Protein Derivative (PPD) for treatment of common warts in children

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ABSTRACT

Background: Viral warts are common dermatological diseases with wide range of treatment modalities. Utilization of various vaccines and skin test antigens has broadened the horizon of available immunotherapeutic agents for the treatment of warts. In this study, we compared efficacy and safety of intradermal and intralesional purified protein derivative (PPD) for treating common warts in children.

Objectives: To evaluate efficacy and safety of intradermal and intralesional PPD in treatment of common warts in children.

Materials and Methods: 180 children (aged 5-15 years) with common warts were randomly divided to receive intradermal (n=90) PPD 10 TU/0.1 ml at middle third of right forearm or intralesional PPD (n=90) 0.1 ml in the largest wart once in 2-weeks till there is complete clearance or maximum of five injections whichever is earlier. Patients were followed at 4 week after last injection for assessment of response, adverse effects, and recurrence of common warts.

Results: Complete, partial clearance and no response in 51.2%, 45.3% and 2.3% children was observed in intradermal group as compared to 54.2%, 42.5% and 1.1% response in intralesional group respectively. Recurrence of warts was observed in 1.2% and 2.2% children in intradermal and intralesional group respectively. Pain was the most common adverse effect in both groups followed by erythema lasting for 2-3 days not warranting for discontinuation of treatment in any patient.

Conclusion: Overall 96.5% and 96.7% patients in both intradermal and intralesional group responded to treatment respectively. We conclude that immunotherapy with PPD appears safe, effective, and acceptable treatment modality for common warts in children. Although intralesional group showed slightly higher efficacy for warts (0.2%), intradermal PPD has advantage of less pain, high patient satisfaction, less spillage of injection material onto surroundings and better compliance over intralesional group and hence can be considered as valuable first line treatment in children in resource poor developing countries.

1. Introduction

Viral warts are common cutaneous infection caused by different human papilloma viruses (HPVs).[1] The incidence increases during the school years to reach a peak in adolescence and early adulthood.[2] Over 100 HPV types have been recognized that have an affinity for different body sites. The prevalence of cutaneous warts is high in children aged between 12 and 16 years followed by a significant decline after the age of 20 years. Warts typically continue to increase in size and distribution and may become more resistant to treatment over time. Children with treatment resistant warts may

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be the potential reservoirs for HPV transmission.[3] Though apparently benign, they can have greater impact on patient's quality of life by causing embarrassment, fear of negative appraisal by others and frustration caused by persistence and/or recurrence. Moderate to extreme discomfort is reported in 51.7% of patients and social or leisure activities are affected to a moderate to extreme degree in 38.8%.[4] Since most warts in immunocompetent individuals are self limiting possibly due to suppression of viral transcription by intracellular mechanisms along with local and systemic immune responses which plays a pivotal role in spontaneous resolution of warts,a policy of no treatment is often advocated.[5] But they can recur even after complete resolution makes them frustrating both for the patient and the physician.[6] There is no single treatment option that has been proved 100% effective and hence many treatment modalities exist with variable cure rates. Destructive procedures such as cauterization with salicylic acid, podophyllotoxin, trichloroacetic acid (TCA), formaldehyde, 5-flurouracil, and photodynamic therapy, or surgical methods like cryosurgery, laser ablation, electrocautery, and excision are used invariably to treat warts. They are usually painful, often cause scarring and show inconsistent outcome with high frequency of relapse. Treatment with contact sensitizers, imiquimod, intralesional interferons and oral levamisole, cimitidine, or zinc sulfate has been tried with variable success.[7–10] The various skin test antigens and vaccines such as candida albicans, Bacillus Calmette Guerin (BCG), measles mumps rubella (MMR), PPD and Mycobacterium w vaccine have been tried for treatment of common warts with encouraging results.[11–17] PPD or tuberculin is a sterile protein extract from culture of mycobacterium tuberculosis.[18] It is used in skin testing to detect exposure to the bacillus and stimulates the cell-mediated immunity non specifically by activating natural killer (NK) cells, Th1 cells and cytokine production. An increase in IL-12 as a part of the enhanced cell mediated immunity contributes to its mechanism of action as an immunotherapeutic agent.[19]

This study was designed to compare the efficacy and safety of PPD (Figure 1) used intradermally (forearm) and intralesionally to treat common warts in children. There have been various studies available in literature showing efficacy of immunotherapy with PPD in cutaneous warts in adults; however, there are fewer studies showing their efficacy in children. Therefore we intended to carry out this study in children.

2. Materials and Methods

2.1. Inclusion criteria

Children of aged between 5-15 years clinically diagnosed with common warts presenting in the outdoor clinic of Dermatology, Venereology & Leprosy Department of Dr. R. P. Govt. Medical College, Kangra at Tanda, Himachal Pradesh between July 2019 and June 2020

were enrolled for the study after informed consent. Necessary approvals from Institutional Protocol review Committee and Institutional Ethics Committee and CTRI registration (CTRI/2019/07/020070) were obtained.

2.2. Exclusion criteria

Patients with immune suppression from any disease or drug therapy were excluded from the study.

Study design: The study was designed as an open-lebel, quasi-randomized, controlled, parallel group trial of intradermal and intralesional PPD carried out at a single centre.

Sampling technique: consequent, convenient sampling.

2.3. Methodology

Clinical details regarding age, gender, duration of warts and previous treatments were recorded after written informed consent. The location, number, dimensions and clinical type of each wart selected for treatment were recorded. Pre procedure counseling included details of procedure, potential benefits and possible immediate injection site pain and swelling during first 24 to 72 hours.

Table 1: Grades of improvement & Likert scale for patient satisfaction score

Grades	**Definition**
Complete clearance	Complete disappearance of warts and skin texture at the site is restored to normal
Partial clearance	Residual wart still visible after 12 weeks
No change	No change in size and texture
Recurrence	Recurrence during the study period
Likert scale for patient satisfaction score	
Satisfaction level	**Score**
Very much satisfied	5
Somewhat satisfied	4
Undecided	3
Not really satisfied	2
Not at all satisfied	1

Table 2: Baseline characteristics

	Intradermal (n=86)	**Intralesional (n=87)**	**$P value**
Male	38 (44.2%)	42 (48.3%)	
Female	48 (55.8%)	45 (51.7%)	0.590
M:F Ratio	0.8:1	0.9:1	
Age (years) Mean±SD #	10.9±3.3	9.9±3.0	
Range	5-15 years	5-15 years	
5-8 years	22 (25.6%)	32 (38.6%)	0.078
9-12 years	35 (40.7%)	38 (43.7%)	
13-15 years	29 (33.7%)	17 (19.5%)	
Duration of warts Mean±SD #	4.8±7.1	9.8±9.5	
Range	0.25-60 months	0.3-36 months	
<6 month	38 (44.2%)	31 (35.6%)	0.52
6 months-1 year	43 (50%)	50 (57.5%)	
>1 year	5 (5.8%)	6 (6.9%)	
Number of warts Mean±SD #	13.2±7.5	9.7±7.4	
Range	2-42	3-30	
<10mm	774 (71.7%)	603 (71.2%)	0.571
10-20mm	228 (21.2%)	192 (22.6%)	
>20mm	77 (7.1%)	53 (6.2%)	
	Upper limb	13 (15.2%)	
	Lower limb	9 (10.5%)	
Site of warts	Hands	25 (29%)	
	Feet	22 (25.6%)	
	Multiple sites*	17 (19.7%)	
Past treatment			
Topical salicylic acid	7 (8.1%)	14 (16.1%)	
Electrocautery	1 (1.2%)	1 (1.1%)	
Indigenous	27 (31.4%)	21 (24.1%)	
Intralesional MMR	3 (3.5%)	2 (2.3%)	
Presence/Absence of risk factors			0.597
No	42 (48.9%)	39 (44.8%)	
Yes			
• Walking bare foot at home • Walking bare foot during	44 (51.1%) 22 (50%)	48 (55.2%) 27 (56.2%)	
• sports	13 (29.5%)	15 (31.2%)	
• Family member with warts/maid/servants	5 (11.4%)	3 (6.3%)	
• Use of public swimming pools	3 (6.8%)	3 (6.3%)	
• Mother with genital warts at time of delivery	1 (2.3%)	0	

*Includes warts on upper limb, lower limb, hands and feet

Table 3: Clearance of patients and number of warts with intradermal PPD at each visit and cure rate at the end of 12 weeks of study period

Site of warts	Number of patients / number of warts	After 1 dose (2 weeks)	After 2^{nd} dose (4weeks)	After 3^{rd} dose (6weeks)	After 4^{th} dose (8weeks)	After 5^{th} dose (12 weeks)	Complete clearance	Partial clearance			No Response	Recurrence
								No. of patients	Responded warts	Remaining warts		
Upper limb	13 /203 (15.2%)	0	0	4 /34 (30.7%)	3 /32 (23.1%)	2 /18 (15.4%)	8 / 84 (61.5%)	4 (30.8%)	90	26	0	1/3 (7.7%)
Lower limb	9 /139 (10.5%)	1/20 (11.1%)	0	1 /17 (11.1%)	4 /50 (44.4%)	0	6/87 (66.7%)	3 (33.3%)	36	16	0	0
Hands	25/330 (29%)	0	2 /22 (8%)	3 /38 (12%)	5 /109 (20%)	4 /60 (16%)	14/229 (56%)	11 (44%)	68	33	0	0
Feet	22/203 (25.6%)	0	3 /25 (13.6%)	3 /19 (13.6%)	2 /20 (9%)	2 /24 (9%)	10/88 (45.5%)	10 (45.5%)	78	21	2/16 (9%)	0
Multiple sites*	17 /204 (19.7%)	0	1/10 (5.8%)	3/38 (17.6%)	2 /24 (11.7%)	0	6/72 (35.3%)	11 (64.7%)	103	29	0	0
Total	86/1079	1/20 (1.1%)	6/57 (6.9%)	14/146 (16.2%)	16/235 (18.6%)	8/102 (9.3%)	44/560 (51.2%)	39 (45.4%)	375	125	2/16 (2.3%)	1/3 (1.1%)
						Size						
<10 mm	774	12	38	95	155	71	371 (47.9%)		313 (40.4%)	76 (9.8%)	11 (1.4%)	3 (0.4%)
10-20 mm	228	6	14	41	58	24	143 (62.7%)		41 (18%)	40 (17.5%)	4 (1.7%)	0
>20 mm	77	2	5	10	22	7	46 (59.7%)		21 (27.3%)	9 (11.7%)	1 (1.3%)	0

Table 4: Clearance of patients and number of warts with intralesional PPD at each visit and cure rate at the end of 12 weeks of study period

Site of warts	Number of patients /number of warts	After 1 dose (2 weeks)	After 2^{nd} dose (4weeks)	After 3^{rd} dose (6weeks)	After 4^{th} dose (8weeks)	After 5^{th} dose (12 weeks)	Complete clearance	Partial clearance			No Response	Recurrence
								No. of patients	Responded warts	Remaining warts		
Upper limb	13 /118 (15%)	0	1 /10 (7.7%)	1 /6 (7.7%)	3 /31 (23.1%)	0	5 /47 (38.4%)	8 (61.6%)	58	13	0	0
Lower limb	10/76 (11.5%)	0	1 /4 (10%)	2 /14 (20%)	0	2 /18 (20%)	5 /36 (50%)	5 (50%)	33	7	0	0
Hands	25/251 (28.8%)	0	1 /6 (4%)	1/7 (4%)	8/75 (32%)	5/62 (20%)	14/150 (56%)	10 (40%)	79	19	0	1/3 (4%)
Feet	22/231 (25.3%)	0	2/8 (9.1%)	7/67 (31.8%)	1/8 (4.5%)	5/65 (22.7%)	14/148 (63.7%)	6 (27.3%)	56	13	1/11 (4.5%)	1/3 (4.5%)
Multiple sites*	17/172 (19.5%)	0	2/13 (11.7%)	4/50 (23.5%)	2/26 (11.7%)	1/12 (5.9%)	9 /101 (52.9%)	8 (47.1%)	59	12	0	0
Total	87/848	0	7/41 (8%)	15/144 (17.2%)	14/140 (16%)	13/157 (14.9%)	47/482 (54.2%)	37 (42.5%)	285	64	1/11 (1.1%)	2/6 (2.2%)
						Size						
<10 mm	603	0	30	104	106	110	350 (58.1%)		193 (32%)	48 (7.9%)	8 (1.3%)	4 (0.6%)
10-20 mm	192	0	8	32	29	36	105 (54.6%)		73 (38.1%)	10 (5.2%)	2 (1.2%)	2 (1.2%)
>20 mm	53	0	3	8	5	11	27 (51%)		19 (35.8%)	6 (11.3%)	1 (1.9%)	0

Table 5: Response to treatment at each visit in intradermal and intralesional group

		Intradermal (n=86)	Intralesional (n=87)	P value
After 1^{st} dose	Complete clearance	1 (1.2%)	0 (0%)	0.27
	Partial clearance	82 (95.4%)	80 (92%)	
	No response	3 (3.4%)	7 (8%)	
	Total patients	85	87	
After 2^{nd} dose	Complete clearance	6 (7.1%)	7 (8.1%)	0.92
	Partial clearance	75 (88.2%)	75 (86.2 %)	
	No response	4 (4.7%)	5 (5.7%)	
	Total patients	79	80	
After 3^{rd} dose	Complete clearance	14 (17.7%)	15 (18.7%)	0.75
	Partial clearance	62 (78.5%)	60 (75%)	
	No response	3 (3.8%)	5 (6.2%)	
	Total patients	65	65	
After 4^{th} dose	Complete clearance	16 (24.5%)	14 (21.5%)	0.92
	Partial clearance	47 (72.3%)	49 (75.4%)	
	No response	2 (3.2%)	2 (3.1%)	
	Total patients	49	51	
After 5^{th} dose	Complete clearance	8 (16.3%)	13 (25.5%)	0.46
	Partial clearance	39 (79.6%)	37 (72.5%)	
	No response	2 (4.1%)	1 (2%)	
Total	Complete	44 (51.2%)	47 (54.2%)	0.84
	Partial	39 (45.3%)	37 (42.5%)	
	No response	2 (2.3%)	1 (1.1%)	
	Recurrence	1 (1.2%)	2 (2.2%)	

Data were expressed as frequency (percentage) otherwise mentioned
Chi Square test

Table 6: Comparison of the number of warts in the intradermal and intralesional group

	Intradermal	Intralesional	$P value
Baseline	13.2±7.5	9.7±7.4	0.571
2 weeks	9.4±6.5	7.3±4.6	0.211
4 weeks	6.3±5.2	5.2±3.1	0.107
6 weeks	4.0±4.1	3.4±2.8	0.206
8 weeks	2.4±3.2	1.8±2.1	0.191
12 weeks	1.6±2.4	1.0±1.6	0.106
$$**P value**	<0.01	<0.01	

Table 7: Comparison between present study and other studies on purified protein derivative in viral warts

	Patients	**Treatment schedule**	**Results**	**Follow up, Recurrences, Adverse events**
Present study	Intradermal group-86 Intralesional group-87	10 TU/0.1 ml of PPD given I/D group-at middle third of right forearm I/L group- in largest wart once in 2 weeks till clearance or for maximum 5 doses	Group I/D- overall response-96.5%, no response- 2.3% Group I/L-overall response- 96.7%, no response- 1.1%%	Follow up -1 month after last injection Recurrence- 3 patients Adverse effects-pain, erythema, itching and mild hyperpigmentation at injection site
Nimbalkar et al (2016)[13]	45 patients Viral warts	10 TU of tuberculin PPD in dose of 0.1 ml I/L at 2 weeks interval for a maximum of 6 injections	complete clearance in 62.2% patients, partial clearance in 17.8% patients and 20% patients with no improvement	Follow up-every 2 weekly till clearance of warts Recurrence- none Adverse effects-localized hair loss around injected viral wart over the scalp and pain and abscess at injection site in one patient
Saoji et al (2016)[14]	61 patients	2.5 TU/0.1ml intralesional PPD every 2 weeks for maximum of 4 sessions	Complete clearance in 76% and partial clearance in 24%	Follow up -6 months after last injection Recurrence- 1 patient Adverse effects-erythema, edema and pain at injection site
Sharquie et al(2016)[15]	30 out of 41 patients completed study	Amount of intralesional PPD that blanch each wart on right side needed versus I/L distilled water in each wart on left side every 2 weeks for maximum of 3 sessions	Complete cure in 23.33% patients PPDversus good response in6.66% patients in control group	Follow up -2 month after last injection Recurrence- none Adverse effects- pain at injection site in 1 patient
Chandra et al(2019)[16]	2 groups of 29 patients each	PPD-10TU/0.1 ml Mw vaccine-0.1 ml Every 2 weeks for maximum of 6 doses	Complete clearance PPD-50% Mw vaccine-68.8%	Follow up- 3 months after last injection Recurrence-none Adverse effects- pain, erythema and swelling at injection site

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Table 7 continued

Abo Elela et al(2011)[17]	Group 1-40 patients Group 2- 50 patients Group 3-20 patients(control)	Group 1-0.1 ml of I/L PPD Group 2- 0.1 ml I/D PPD Group 3-0.1 ml I/L saline Two weekly injections for 10 sessions or till complete clearance	Group 1- Complete response-96%, no response-4% Group 2- Complete response- 94.1%, no response- 5.9% Group 3- Complete response-15%, no response-85%	Follow up –every weekly for 10 weeks Recurrence- none Adverse effects-none
Abd-Elazeim et al (2013)[19]	PPD group-20 patients Placebo group-20 patients With recalcitrant multiple cutaneous warts	Intralesional PPD 0.1 ml I/L in largest wart and I/L saline 0.3 ml at weekly till clearance or for maximum of 6 doses	Complete response- 75% (PPD) and 10% (saline) at 6 months	Follow up- every 2 month for 6 month Recurrence-2 patients Adverse effects - pain and mild erythema in three patients during injection, swelling in one patient, and post-hypopigmentation in 2 patients
Wananukul etal. (2010)[20]	42 patients Palmoplantar and periungual warts	Intralesional PPD at a dose of 10 TU (0.1mL)in the largest wart once in 2 weeks till clearance or for maximum 6 doses	Complete response in 14%, 38%, 64%, 71%, 81%, and 93% after 1, 2, 3, 4, 5, and 6 treatments, respectively	Follow up-For 6 month after last dose Recurrence- 1 patient Adverse effects-edema and erythema on the injected site in 3 patients while three patients had painful purpura at the site of injection
Jaswal et al(2019)[21]	51 patients	0.1 ml of 5TU PPD I/L in largest wart at weekly interval till clearance or maximum of 6 weeks	Complete clearance-35(68.6%) patients Partial clearance- 6 (11.7%) patients No clearance-10(19.6%) patients	Follow up –3 month after last injection Recurrence- none Adverse effects-Pain , swelling at injection site
Lahti and Hannuksela (1982)[22]	Tuberculin group-14 patients Placebo patients-7 patients Common warts	tuberculin (PPD) as topical jelly vs. Patrolatum for maximum of 4 months	57% complete clearance in the tuberculin jelly group and 14.2% response in the petrolatum group	Follow up:4 months Recurrence- none Adverse effects-Slight itching or tingling sensations and redness at the site of application

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Table 7 continued

Shaheen et al (2015)[23]	3 groups of 10 patients each	MMR, PPD 0.1 ml as per wart size, or saline 0.3 ml,I/L once in 3 weeks till clearance or maximum of 3 doses	Cure rates – MMR group-80% (treated wart) and 40%(distant wart) PPD group-60% and Saline -0%	Follow up – every 3 weeks for 3 months after last dose Recurrence- none Adverse effects-erythema, edema and vasovagal attacks from MMR in 10% patients. Vasovagal attack in 10% controls
Podder et al (2017)[24]	60 patients	PPD group- 5TU/0.1 ml I/D and BCG group-0.1 ml I/D Over deltoid region at 4 weekly interval for maximum 3 sessions	PPD group- complete clearance in 18.5% patients BCG group- Complete clearance -48.5%	Follow up -3 follow ups at 4 weekly interval Recurrence-none Adverse effects- pain, abscess and scarring at injection site
Eassa et al. (2011)[25]	40 patients Anogenital warts in pregnant women	intradermal PPD 0.1 mL weekly for 12 weeks (group A) vs. 0.1 mL distilled water at similar site and repeated weekly for 4 weeks,and then shifted to (0.1 mL) PPD weekly for 12 weeks (group B).	Group A- complete resolution occurred in 50% patient, partial in 35% patients and no response in 5%. Group B-complete resolution in45% patients, partial in 40%,and No response in 10%patients .	Follow up- 6 months Recurrence-none Adverse effects –minimal pain at the site of injection, erythema, and tenderness, but no systemic side effects
Singh et al (2018)[26]	80 patients	Group 1-Intralesional PPD 10TU/0.1 ml I/L Group 2-Inj. VitD3 0.5ml I/L in maximum of 4 warts Every 2weeks for maximum of 4 sessions	PPD group- complete clearance in 80%% patients Vit D3 group- Complete clearance -72.5%	Follow up -3 month after last injection Recurrence- none Adverse effects- pain at injection site
Rajashekar et al (2018)[27]	30 patients	PPD group- 0.1 ml I/L at 2weekly interval for maximum 4 sessions BCG group-0.1 ml i/L at 2 weekly interval for maximum 4 sessions	PPD group- complete clearance in 35.3% patients BCG group- Complete clearance -30.8%%	Follow up -every month for 6 months after last injection Recurrence- none Adverse effects- tender nodule at injection site in BCG group
Fatima et al(2019)[28]	60 patients divided to 2 groups(30 each)	PPD Group-0.1 ml I/L in largest wart Cryotherapy Group-2 freeze thaw cycles 20 sec. duration Two weekly till clearance or maximum 6 sessions	PPD Group-21 (70%) cases reponded Cryotherapy Group-2- 9 (30%) casesv responded	Follow up- 3 months Recurrence- none Adverse effects-

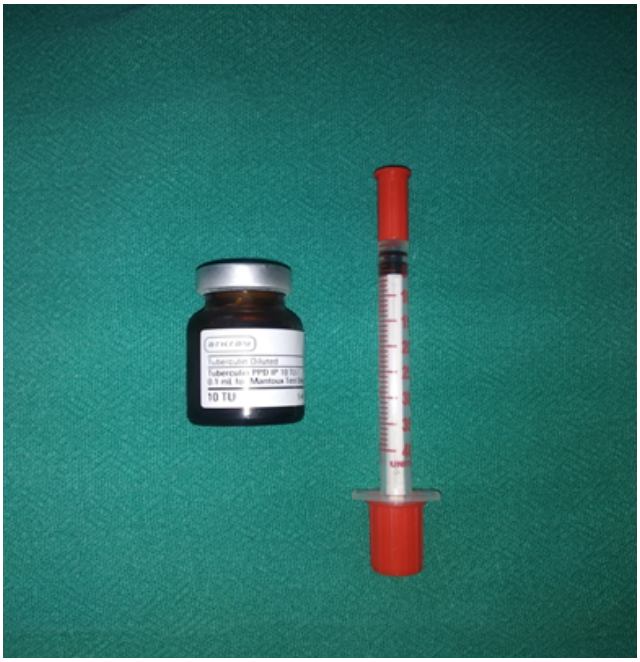

Fig. 1: Purified Protein Derivative [10TU] with insulin syringe.

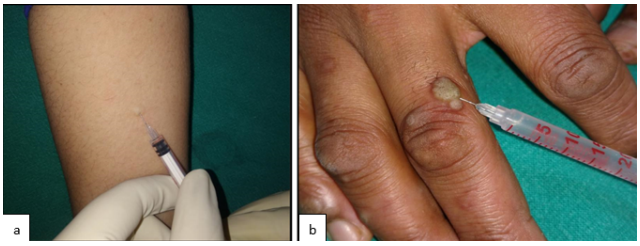

Fig. 2: a): Method of intradermal PPD injection at middle third of right forearm; **b):** Method of intralesional PPD injection. PPD is injected till the blanching of wart.

2.4. Treatment protocol

In this study, PPD was given in strength of 10TU/0.1ml with 30 G insulin syringe intradermally and intralesionally for comparative study.

Intradermal injection was given at middle third of right forearm after cleaning site with 70% alcohol or denatured spirit (Figure 2).

For intralesional injection, largest wart was injected with PPD using 30 G insulin syringe until blanching (Figure-3).

Patients were prescribed tablet diclofenac (50 mg sos) for post injection erythema and pain during first 2-3 days. The injection was given at period of 2 week interval until clearance or maximum of 5 doses whichever is earlier. No other treatment for warts was allowed for concurrent use.

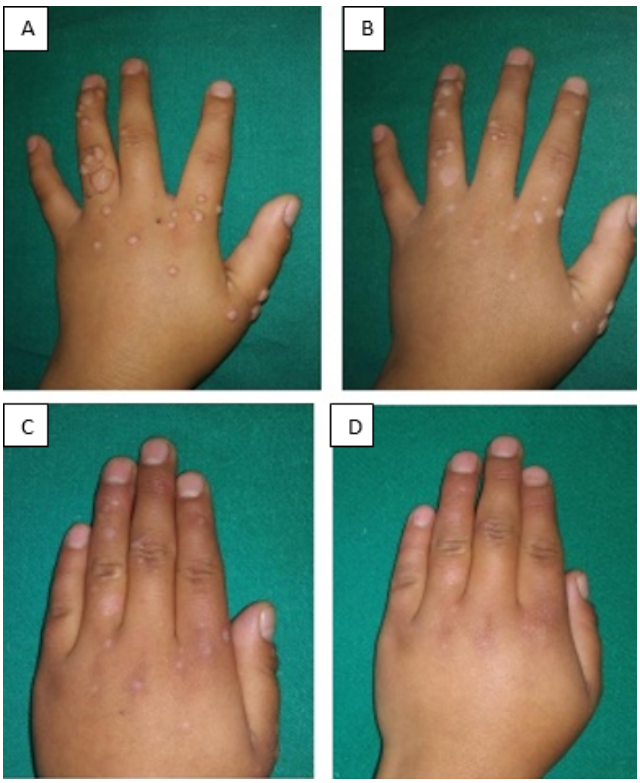

Fig. 3: Image-1: Multiple warts over dorsum of left hand and fingers; **A):** Baseline treated with intradermal PPD at middle third of right forearm; **B):** Two weeks after first dose; **C):** Clearance of warts at four weeks; **D):** Complete clearance of all warts at eight weeks after four doses with restoration of normal skin texture.

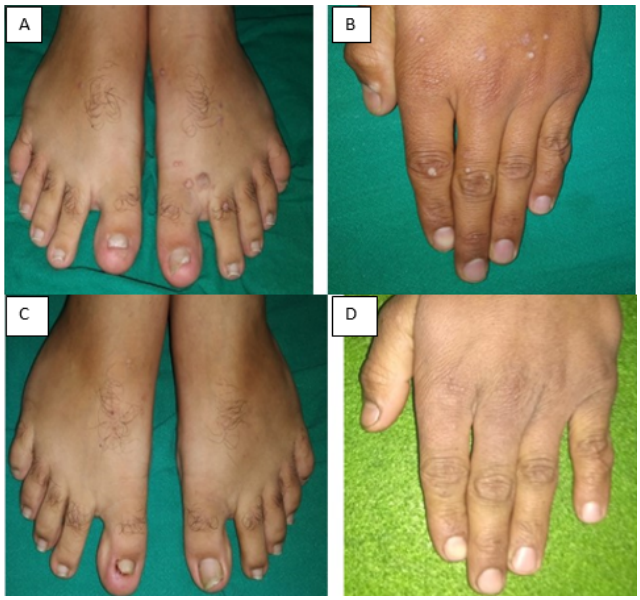

Fig. 4: Multiple warts over bilateral dorsum of feet, dorsum of left hand, left index and middle finger; **A,B):** Baseline treated with intralesional PPD in largest wart until blanching; **C,D):** complete clearance at eight weeks after four doses with restoration of normal skin texture

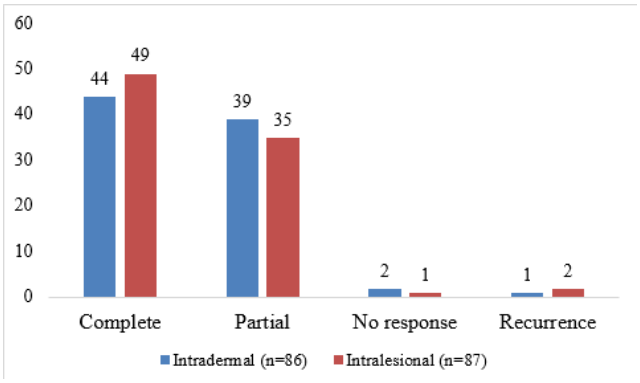

Fig. 5: Response to treatment in both intradermal and intralesional group

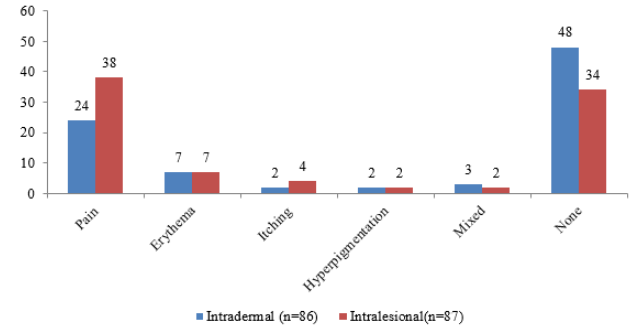

Fig. 6: Side effects observed in intradermal and intralesional group

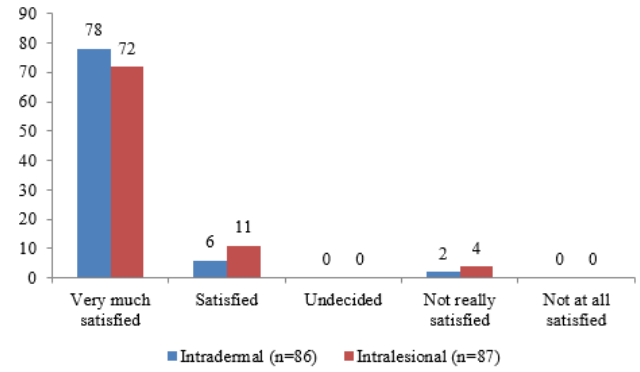

Fig. 7: Patient satisfaction score at end of study in both intradermal and intralesional group.

2.5. Evaluation for therapeutic outcome

All patients were evaluated for therapeutic outcome measured as the reduction in number or size of warts during follow-up visits at 2, 4, 6, 8 and 12 weeks. Pre and post treatment photographic comparison were also made to assess and corroborate the therapeutic response. Subsequently patients were advised to report anytime in case of recurrence. At each visit, patients were enquired about the occurrence of any systemic or local adverse reactions such as pain during and after treatment, erythema or swelling at injection site, pigmentary changes and any other associated complaints. Patient response and satisfaction score was assessed as shown in (Table 1) at end of 12-week study period.

2.6. Statistical analysis

Data were recorded into Microsoft® Excel Workbook 2019. Quantitative data were expressed as mean±SD, and compared using Student t-test. Categorical variables were expressed as frequency and percentages, and compared using Chi square test. P value<0.05 was considered significant. Statistical analysis was performed using SPSS v21.0 (IBM, USA).

3. Results

A total of 180 children having common warts were enrolled for study and divided into intradermal and intralesional group on alternate basis. The data were analyzed for various parameters before and after treatment. A total of 90 children received intradermal and 90 received intralesional PPD. However, 4 children in intradermal and 3 children in intralesional group did not complete study and were excluded from final analysis. A total of 86 children in intradermal and 87 children in intralesional group completed study.

Both groups were comparable at baseline regarding gender, age, duration, number of warts and site of warts (Table 2). In intradermal group, the number of warts was 13.2 ±7.5 and the majority, 774 (71.7%) warts were noted to be of <10mm size while in intralesional group it was 9.7±7.4 and the majority, 603 (71.2%) warts were of <10 mm size.

Thirty eight patients (44.2% versus 43.7%) in intradermal and intralesional group respectively had received treatment in the past with topical salicylic acid, electrocautery, indigenous methods and intralesional MMR immunotherapy for variable periods without benefit.

In the study, environmental risk factors for warts like walking and doing sports activities with barefoot, family member with warts, use of public swimming pools and presence of genital warts in mother at delivery were present in 44 (51.1%) and 48 (55.2%) children in intradermal and intralesional group respectively. Warts on hands was most common site seen in each of 25 (29% versus 28.8%) patients followed by warts on feet in 22 (22.6%) and 22 (25.3) % patients in both intradermal and intralesional group respectively.

At the end of 12-week study period, in intradermal group, 44 (51.2%) patients with 560 warts were cleared and in remaining 39 (45.3%) patients 375 warts responded to treatment. In intralesional group, at the end of 12 weeks

study period, 47 (54.2%) patients with 482 warts were cleared and in remaining 37 (45.5%) patients 285 warts responded to treatment (Figures 3 and 4)). In the present study, maximum response in terms of clearance of warts with patients was observed after 3^{rd} and 4^{th} dose of PPD and statistically significant reduction in number of warts was found from first follow up onwards with non significant p value in both intradermal and intralesional group respectively (Tables 3, 4, 5 and 6 and Figure 5).

Pain was the most common side effect observed in 24 (27.9%) children in intradermal and 38 (43.7%) children in intralesional group, followed by erythema, itching and mild hyperpigmentation in each of 8.1%, 2.3% and 2.3% patients of intradermal and 8.1%, 4.6% and 2.2% patients of intralesional group respectively (Figure 6). Pain was the most common side effect noted and was more in intralesional than intradermal group (p= 0.002). No other systemic adverse effects occurred in any patient.

At end of study, when patient satisfaction score was noted, 78 (90.7%) patients in intradermal group were very much satisfied (satisfaction score 5) as compared to 72 (82.7%) patients in intralesional group respectively with overall comparable results (p= 0.305), (Figure 7).

4. Discussion

In children and young adults, viral warts are one of the most common dermatological condition caused by HPV of various types. These viruses can remain latent for long period of time and later can reactivate or persist without becoming clinically apparent. The HPV virus can survive at low temperature which leads to its persistence in environment for longer period of time. This explains why patient walking barefoot can develop warts on feet. The virus spread can occur to other sites of body including face and hands. Trauma, scratching, nail biting and sucking of nails are some of other common predisposing factors in children.[29,30]

Local destructive and surgical therapies which are conventional methods in the treatment of warts in children can be more painful, inconvenient and can cause permanent scarring in future. Immunotherapy has gained popularity for the treatment of multiple warts and difficult to treat areas in recent times. An antigen when injected to the wart to activate cell mediated immunity that not only acts against the antigen but also HPV, resulting in clearance of warts.[20] Considering the high prevalence of tuberculosis infection in our country, it is easy to induce a positive cell mediated immune response with PPD which was the reason for selecting this antigen for immunomodulation as well as easy availability in our study.

The exact mechanism of action of PPD is not very well established but injection into the wart tissue induces the release of various pro-inflammatory chemicals which further cause activation of APC (antigen presenting cell), which recognize and then process the HPV at the local site.[17]This leads to the development of robust adaptive immune reaction mediated by Th1 cytokines such as interleukin-4, 5,8, IFN-ý and TNF-α against mycobacterium tuberculosis as well as against HPV infection with further increase in IL-12 as a process in boosting the cell mediated immunity also contributes to the mechanism of action.[21]

In our study, prevalence of warts in both sexes was comparable but female children were affected predominantly as compared to previous studies who showed either equal or male predominance.[29,30] More participation in most of household as well as other physical activities by females in this region may be attributed to female predominance as compared to males in our study.

We noted the peak prevalence of warts in age-group of 9-12 years (40.7% and 43.7%) in both intradermal and intralesional group respectively which was comparable to previous studies.[29,31] The most common environmental risk factors associated with warts in children as reported in our study were walking and playing barefoot followed by family member infected with warts. These findings were more or less similar to previous studies.[30,32,33] This also concludes that presence of these environmental factors may serve as important risk factor for development of warts in children.

PPD for treatment of warts has been used intradermally, topically as well as intralesionally. In our study, overall 96.5% and 96.7% patients in both intradermal and intralesional group responded to treatment at end of study period out of which complete clearance was observed in 44 (51.2%) and 47 (54.2%) patients and partial clearance was observed in 39 (45.3%) and 37 (42.5%) patients of intradermal and intralesional group respectively. No response was seen in 2 (2.3%) in intradermal and 1 (1.1%) patients in intralesional group respectively. Response was seen as early as two weeks after first injection in one of patient in intradermal group and six patients in intradermal and seven patients in intralesional group after second dose of PPD. Lahti and Hannuksela[22] in their study observed a low clearance rate of 57% with topical tuberculin jelly at 3-4 months. In comparison to PPD immunotherapy, the major disadvantage of topical tuberculin jelly was the longer duration of treatment. Therefore they repoerted that intradermal PPD is a better mode of treatment for multiple warts for earlier and higher clearance. Wananukul et al[20]studied 42 patients out of which 50% patients aged below 15 years were treated with tuberculin PPD and observed complete clearance in 93% of the cases . However, cure rate in children aged <15 years had not been defined separately in their study. Nimbalkar et al[13] in their study of 45 patients aged >12 years having viral warts observed that 62.2% of their patients showed complete clearance at injected and distant warts while 17.8% showed partial clearance when treated with 10TU PPD (0.1ml). Shaheen

et al[23] demonstrated that with PPD immunotherapy, rate of clearance of target and distant warts was 60% while with MMR vaccine, it was 80%. In our study, injected and distant warts in intralesional group were cleared in similar frequency in majority of patients. Abo Elela et al[17] reported a complete clearance rate of 96% after ten injections of intradermal PPD as compared to 94.1% when PPD was used intralesionally. Saoji et al[14] in their study injected 2.5 TU of PPD intralesionally in a few warts with a total of four sessions at 2 weekly intervals and observed a complete disappearance of warts in 76% of patients with thirteen (24%) patients as non responders to treatment respectively. On other hand, Podder et al[24] in their study used intradermal PPD to treat 27 patients and observed a complete clearance in only 18.52% while others had partial response at 12 weeks.

Immunotherapy has overcome the limitations of surgical or destructive therapies. It enhances the cell mediated immune response that clears the virus infective tissue irrespective of whether it is visible or not. So, there are lesser chances of recurrence. It also targets warts situated away from the site of the immunotherapeutic injection and therefore help in treating warts on inaccessible sites and on cosmetically important areas where ablative therapy cannot be done due to patients' apprehension or chances of scarring.[24]

The efficacy with PPD immunotherapy in warts has been found superior when compared with placebo, inj vit.D3, BCG vaccine and cryotherapy.[25–28]

The intradermal and intralesional PPD was also highly effective in our patients who were treated earlier with various different treatment modalities reflecting its superiority. Also majority of cured patients were highly satisfied (satisfaction score 5 on Likert scale) with treatment.

In our study, recurrence was observed in 1.2% children with intradermal and 2.3% children with intralesional PPD which was comparable to previous studies.[20] It was also observed that the patients with recurrence of warts had longer duration of warts in comparison to those patients who were treated completely or partially with intradermal or intralesional PPD.

Partial clearance and recurrence in patients of intradermal and intralesional groups respectively, at the end of 12 week period was probably either due to inadequate infilteration of lesion, (due to spillage of injection material in the intralesional group) or shorter follow up period which require further studies with large sample size and long duration follow up to validate these findings. However it may be possible that some of PPD treated warts may show late clearance even after 12 weeks. It has also been reported in a study by Abd Elazeim et al.[19] We also observed that irrespective of site of warts, maximum therapeutic effect was noted in terms of clearance of warts and patients after third and fourth dose of both intradermal and intralesional PPD with statistical significant reduction in number of warts after first follow up visit was observed compared to baseline similar to previous study.[24] But in another study done by Chandra et al,[16] significant reduction in warts was observed after third and fourth dose of Mw vaccine and PPD. Further reduction in wart numbers continued even after completion of five doses as evident by follow up visit 4 weeks after last injection.

PPD immunotherapy is well tolerated by our patients. The most common side effects were pain in both groups followed by erythema and itching which required no treatment and subsided within 2-3 days and patients continued their treatment. In our study recurrence of wart was noted during follow up, which occurred in three patients out of which two develop new lesions on different site and one had developed warts on same sites. Longer duration of disease, having more viral load which further may require either more treatment sessions or large volume of drug per session to cause stimulation of immune system.

Immunotherapy with PPD can be given through any approach and appears one of possible and safe treatment option for common warts in children besides other modalities used in adult patients. It is equally effective over injected as well as distant sites. Regression of untreated distant warts after single lesion infilteration, no scarring or pigmentation as from destructive wart treatments, and possible low recurrence are another additional benefits. It is simple to perform, easy available, inexpensive, easy to use, better compliance and has minimal side effects and can be considered a luecrative treatment option to treat common warts in children in developing countries.

5. Conclusion

Immunotherapy with PPD can be given through any approach and appears one of possible and safe treatment option for common warts in children besides other modalities used in adult patients. It is equally effective over injected as well as distant sites. Regression of untreated distant warts after single lesion infilteration, no scarring or pigmentation compared to destructive wart treatments, and possible low recurrence are another additional benefits. It is simple to perform, easy available, inexpensive, easy to use, better compliance and has minimal side effects and can be considered a luecrative treatment option to treat common warts in children in developing countries.

6. Limitations

Lack of control arm, short follow up period and small number of patients in each group are some of limitations in this study.

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8. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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None.

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